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REVIEW

Clinical Utility of Zuranolone for Postpartum Depression: A Narrative Review

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Abstract: Peripartum depression (PPD) affects approximately one in every eight birthing individuals. Despite a high prevalence, PPD is underdiagnosed and undertreated. Several PPD treatment options exist including psychotherapies, conventional serotonergic-based antidepressants and alternative and integrative medicine approaches. Rapid-acting neuroactive steroid-based antidepressants have been studied and approved in the United States (US) for the treatment of adult females with PPD. Zuranolone is the first US Food and Drug Administration approved oral antidepressant for adult females with PPD. This narrative review reports on the evidence for the clinical utility of zuranolone in PPD treatment. In double-blind, randomized, placebo-controlled, clinical trials, zuranolone demonstrated rapid, statistically significant and clinically meaningful improvements in depressive symptoms. Most common adverse events reported with zuranolone use were somnolence, dizziness, sedation, and headache. No clinically significant changes in vital signs, electrocardiogram or clinical lab parameters were observed. No loss of consciousness and no increase in suicidal ideation from baseline or deaths were seen in the studies. Secondary analyses demonstrated that zuranolone improves comorbid symptoms of anxiety and insomnia and some measures of health-related quality of life. Zuranolone relevant infant dose lactation data suggest that its use is compatible with breastfeeding, though future research is needed to measure potential adverse effects on the breastfed infant. Key aspects of clinical decision-making in patients with PPD are discussed.

Keywords: zuranolone, postpartum depression, neuroactive steroid, GABA, insomnia, anxiety

Introduction

Peripartum depression (PPD) is a major depressive episode with onset during gestation or within four weeks following delivery as defined in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition.[1] Women remain at significantly increased risk of depression and other psychiatric disorders through twelve months postpartum.[2] PPD affects approximately one in every eight birthing individuals.[3] A previous diagnosis of a Major Depressive Disorder (MDD) and being less than 24 years of age are common risk factors associated with PPD development.[3,4] In recent years, the prevalence of PPD increased by 24% for the general population within developed countries as compared to pre-pandemic times.[5] Despite being one of the most common complications of childbirth, more than 60% of women with PPD do not receive a diagnosis or formal care and treatment.[6] Untreated or undertreated PPD is associated with short-term and long-term detrimental effects on the patient and family. PPD is associated with poor maternal functioning, partner conflict, an increased risk of depression in the partner, poor breast-feeding initiation, and disruption of mother–infant bonding affecting cognitive, emotional and social functioning of the child.[7–10] If left untreated, PPD can persist for years.[11] Severe PPD symptomatology is correlated with suicidal ideation, poor sleep quality.[12,13] Anxiety may be present in approximately 70% of women with PPD.[14] PPD significantly increases risk of completed suicide, a known leading cause of maternal mortality in the first postpartum year.[15]

In 2022, the World Health Organization released its guide for integration of perinatal mental health in maternal and child health services. The guide, which has been endorsed by the United Nations, recommends maternal mental health screening starting at grass roots levels by trained community health workers[16] and stepped care, which is a less resource–intensive evidence–based intervention for most patients.[16] Evidence-based psychotherapies including cognitive behavior

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therapy (CBT), and interpersonal therapy (IPT) are effective and are often recommended as first-line treatments for mild-to-moderate PPD.[17–19] Evidence-based Reach Out, Stay Strong, Essentials protocol[19–21] and Practical Resources for Effective Postpartum Parenting protocol[22] may be cost-effective preventative interventions.[23] There is increasing evidence for alternative and complementary therapies, with modalities including bright light therapy,[24] physical activity,[25] and yoga,[26] having the most safety and efficacy evidence in PPD.

Historically, serotonergic-based antidepressants have been the most common pharmacotherapy for PPD, with selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) recommended for moderate-to-severe illness.[23] In the US, serotonergic and other conventional antidepressants are not approved by the Food and Drug Administration (FDA) for use in PPD, thus their use is considered off-label. Several randomized, controlled trials (RCTs) studied antidepressant effectiveness in the postpartum period.[27] The majority of RCTs have studied SSRIs and demonstrate low certainty of evidence that they may be more effective in treating PPD versus placebo.[28] A recent meta-analysis of controlled trials of SSRIs in PPD concluded that the strength of evidence was low and inconclusive of whether SSRIs are more effective than psychosocial interventions, however showed higher response and remission than placebo.[28] Other commonly used antidepressants like SNRIs, noradrenergic and specific serotonergic antidepressants (NASSA), such as mirtazapine, and tricyclic antidepressants (TCAs) are also used in clinical practice. Amitriptyline was found to be inferior to group problem solving therapy[29] and in a separate RCT, nortriptyline did not show any difference in response, time to response or remission as compared to sertraline.[30] Hence, the use of conventional antidepressants remains mainly empiric rather than evidence-based. Conventional antidepressants have limitations including delayed treatment response,[31,32] a need for dose titration and common adverse effects like weight gain, sexual dysfunction and sleep disturbances which often result in poor adherence. Patients often fail to achieve remission, with only 37% achieving remission with their first antidepressant trial.[33] Patients may have to try several antidepressants before finding the medication with an acceptable balance of efficacy and side effects. Delayed onset of treatment efficacy may be detrimental in postpartum individuals whose symptoms occur during an important period for parent–child bonding and managing increased responsibilities affecting the wellbeing of the whole family, thus there is a recognized need for rapid-acting, safe and efficacious treatment options.

Over the past several years, neuroactive steroids have been developed as rapid-acting, acute treatments for PPD. The term neuroactive steroid includes both neurosteroids (molecules derived from cholesterol and synthesized in the brain) as well as steroids synthesized in the periphery, including the adrenal glands, ovaries and placenta, that act on the brain. Many neuroactive steroids are positive allosteric modulators (PAMs) of inhibitory $GABA_A$ receptors (R), the ligand-gated and membrane-bound ion channels that facilitate or prevent passage of negatively-charged chloride ions into the post-synaptic membrane.[34–36] Synaptic $GABA_ARs$ contribute to low-affinity phasic inhibition while extrasynaptic $GABA_ARs$ contribute to high affinity tonic inhibition.[37,38] $GABA_ARs$ can bind alcohol, barbiturates, benzodiazepines, general anesthetics and neuroactive steroids depending on their subunit arrangement, composition, and location.[39] The binding of neuroactive steroids to $GABA_ARs$ typically potentiates both synaptic and extrasynaptic receptors[40,41] leading to changes in the excitatory–inhibitory balance of those neural networks.[42] Neuroactive steroids are essential to the regulation of the hypothalamic–pituitary–adrenal (HPA) axis during acute and chronic stress as well as nonstress conditions.[43,44] In addition to integral action in the HPA axis, neuroactive steroids have been shown to have anti-inflammatory and neurotrophic effects within the central nervous system (CNS).[45,46] Well-established research indicates that PPD involves a differential response of the stress steroid system as well as a differential (epi)genetic risk in serotonergic and GABAergic signaling which act as moderators or mediators between changes in the reproductive steroid system and clinical symptomatology.[47] Consequently, synthetic neuroactive steroids and their analogs became a target of research as PPD therapeutics.

This narrative review focuses on the clinical utility of zuranolone (see Table 1), the first US FDA-approved oral neuroactive steroid-based antidepressant for PPD, and then discusses key aspects of clinical decision making in patients with PPD.

Methods

We searched PubMed through December 2024, using the following keywords (Zuranolone OR SAGE217) AND (Postpartum) AND (Depression). We included controlled clinical trials with the following criteria: human patients

Table 1 Studies Examining the Clinical Utility of Zuranolone in Adult Females with Postpartum Depression

First Author, Year	Study Design	Sample Size		MeanAge (in years)	Postpartum Time Frame	Inclusion Criteria	Active Intervention	Primary Outcomes Measures
		Active intervention	Control					
Zhang et al 2022[48]	Systematic review and meta-analysis	156 brexanolone, 75 Fluoxetine, 148 sertraline, 32 saffron, 54 nortriptyline, 35 paroxetine, 6 estradiol, 76 zuranolone	362, placebo	25.2–32.1	6 weeks to 12 months	Randomized controlled parallel - group trials involving more than 10 participants, aimed to investigate the efficacy and tolerability of antidepressant agents for the treatment of women diagnosed with PPD, detailed data on changes in the severity of depressive symptoms	Brexanolone (30–90ug/kg/h), fluoxetine (N/A), sertraline (25–200mg), saffron (N/A), nortriptyline (10–150mg), paroxetine (10–40mg), estradiol (5mg), zuranolone (30 mg)	11 studies with 944 participants were included in this meta-analysis comparing 8 antidepressants. In all RCTs, active antidepressants were superior to placebo in reducing depression with SMD ranging from −1.70 (95% CI −4.72 to 1.33) to −9.59 (95% CI −15.78 to −3.4). Estradiol, paroxetine and zuranolone were considered superior to the others.
Deligiannidis et al 2021[49] and 2023[50]	Phase 3 double-blind, randomized, placebo-controlled clinical trial (51) and secondary analysis of study data (75)	77, zuranolone	76, placebo	29.3 in active intervention and 27.4 in placebo	≤ 6 months	Baseline $HAMD_{17}$ ≥ 26; current MDE with onset during the third trimester of pregnancy or ≤ 4 weeks postpartum	Zuranolone 30 mg x 14 days	Significantly greater reduction from baseline in $HAMD_{17}$ with zuranolone compared to placebo at day 15 (least square means, −17.8 points vs −13.6; 95% CI, −6.9 to −1.5; p=0.003).[49] At day 15 and 45 the rate of sustained concurrent remission of depressive and anxiety symptoms was higher with zuranolone versus placebo using the criteria of either the combined $HAMD_{17}$ /HAMA (p < 0.001; odds ratio [OR; 95% CI], 6.2 [2.2 to 17.4]) or the combined MADRS/HAMA (p=0.003; OR [95% CI], 3.7 [1.5 to 8.9][50]
Deligiannidis et al 2023[51]	Phase 3, double-blind, randomized, placebo-controlled clinical trial	98, zuranolone	98, placebo	30.0 in active intervention and 31.0 in placebo	≤ 12 months	Baseline $HAMD_{17}$ ≥ 26; current MDE with onset during the third trimester of pregnancy or ≤ 4 weeks postpartum	Zuranolone 50 mg x 14 days	Statistically significant improvements in depressive symptoms and a change from baseline score of $HAMD_{17}$ at day 15 in the zuranolone group compared with the placebo group (LSM = −15.6, SE = 0.82, vs LSM = 11.6, SE = 0.82; LSM difference = −4.0, 95% CI = −6.3, −1.7; p = 0.001)

(*Continued*)

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Table 1 (Continued).

First Author, Year	Study Design	Sample Size		MeanAge (in years)	Postpartum Time Frame	Inclusion Criteria	Active Intervention	Primary Outcomes Measures
		Active intervention	Control					
Deligiannidis et al 2024[52]	Phase 1 open label study	15, zuranolone	N/A	30.1	≥ 12 weeks	Healthy, postpartum females actively pumping breast milk or breastfeeding ≥ 3 times daily, weighed ≥ 50 kg and had a body mass index of between 18 and 40 kg/m2 at screening	Zuranolone 30 mg x 5 days and a 15-day breastmilk collection from day 3–12	Relative Infant Dose (RID) at day 5 was estimated to be 0.00125 (0.000827) mg/kg per day with 30 mg of zuranolone; estimated mean for RID was 0.357% of maternal weight-adjusted dose. 14 days of daily administration of 50 mg zuranolone estimated RID was approximately 0.74% and 0.98% for a milk intake of 150 and 200 mL/kg per day.
Meltzer-Brody et al 2024[53]	Unanchored matching-adjusted indirect treatment comparison (MAIC), Bucher indirect treatment comparisons (ITC), and network meta-analysis (NMA)	99 zuranolone, 17 sertraline, 35 paroxetine, 43 fluoxetine and counseling, 19 paroxetine and CBT, 16 paroxetine, 56 sertraline-CM, 129 antidepressants (fluoxetine, sertraline, paroxetine, citalopram, escitalopram, lofepramine or reboxetine)	208 placebo, 23 placebo and counseling, 125 listening visits	23.1–31.7	6 weeks to 12 months	Randomized controlled trials of oral pharmacologic agents or studies of pharmacologic agents in combination with non-pharmacologic interventions for PPD in females ages ≥ 15 years, that reported a $HAMD_{17}$ or EPDS score as an outcome and did not include hormone treatments.	Zuranolone (50 mg), sertraline (25–200mg), paroxetine (10 −40mg), fluoxetine (N/A)	7 studies were identified for comparison of effectiveness of zuranolone, SSRIs (fluoxetine, sertraline, paroxetine, citalopram, or escitalopram), placebo, and combination treatments (SSRIs + non-pharmacologic interventions), using EPDS CFB as a measure of patient outcomes. Larger EPDS CFB was observed among zuranolone-treated vs SSRI-treated patients from day 15 onward. Zuranolone-treated (vs SSRI-treated) patients exhibited 4.22-point larger reduction in EPDS by day 15 (95% CI: −6.16, −2.28) and 7.43-point larger reduction at Day 45 (−9.84,−5.02) with Bucher ITC. NMA showed EPDS reduction for zuranolone was 4.52 (−6.40, −2.65) points larger than SSRIs by day 15 and 7.16 (−9.47, −4.85) larger at day 45.

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Winslow et al 2024[54]	Double-blind, Randomized controlled trial	996 zuranolone 45 SAGE-217	762 Placebo	46.5	≤ 6 months	Peer reviewed, English languages of adults ≥ 18 years old, randomized, placebo-controlled trials. Diagnosis of either postpartum depression or major depressive disorder defined by the DSM-5.	Zuranolone (20–50 mg) - 14 days SAGE-217 (30 mg) - 14 days	6 studies were identified. 2 focused on efficacy of zuranolone in treatment of PPD while the other 4 RCT focused on zuranolone in treating MDD. Significant decrease in HAMD score verse placebo (Mean Difference –4.06, 95% CI-4.25 to –3.87 p<0.001)
Raja et al 2024[55]	Randomized Controlled Trials Identified by systematic review	1,154 zuranolone	877 Placebo	30.0–45	N/A	The literature retrieved was based on participant age (18–75) diagnosed with Major Depressive Disorder or Postpartum with or without insomnia and intervention with zuranolone for treatment compared to a control group.	Zuranolone 20mg–50 mg	Subgroup analysis revealed significant impact of zuranolone on HAMD17 score at Day 15. (Mean difference – 4.08; 95% CI = -[5.82–2.35] p,0.00001).

Abbreviations: PPD, postpartum depression; RCT, randomized controlled trial; SMD, standard mean deviation; CI, confidence interval; $HAMD_{17}$, Hamilton rating scale for depression; HAMA, Hamilton anxiety rating scale; OR, odd ratio; MADRS, Montgomery-Åsburg depression rating scale; MDE, major depressive episode; LSM, least square means; SE, standard error; RID, relative infant dose; MAIC, matching-adjusted indirect treatment comparison; ITCs, indirect treatment comparisons; CBT, cognitive behavioral therapy; CM, contingency management; EPDS, Edinburgh postnatal depression scale; SSRI, selective serotonin reuptake inhibitor; CFB, change from baseline; NMA, network meta-analysis.

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with postpartum depression and an intervention of zuranolone and a control using placebo. We excluded all studies of zuranolone in major depressive disorder. We included meta-analyses of controlled clinical trials when postpartum data was reported separately from trial data in major depressive disorder. Two authors (A.G. and K.M.D) independently carried out the selection process, screening titles and abstracts of retrieved records then full texts were assessed for inclusion in this narrative review. We identified and screened 21 records with our search of which 8 were included (see Figure 1 for reasons why articles were excluded).

Zuranolone, the First US FDA-Approved Oral Neuroactive Steroid-Based Antidepressant for PPD

Zuranolone is a synthetic analog of allopregnanolone which is a potent PAM of extrasynaptic and synaptic $GABA_AR$s and a neuroactive steroid. It is the only oral medication approved by the US FDA for treatment of PPD in adult females. It is distinct from brexanolone because of the presence of a cyanopyrazole ring at carbon 21. Zuranolone has the advantage of being orally bioavailable and hence offers the ease of once daily, evening dosing at home.

The ROBIN study was the first phase 3 randomized, double-blind, placebo-controlled outpatient trial in females with PPD.[49],153 females (ages18–45 years), six months or less postpartum with severe (ie Hamilton Rating Scale for Depression[56] ($HAMD_{17} \geq 26$)) PPD were randomized 1:1 to receive zuranolone 30 mg or placebo, once daily for fourteen days. Participants with a history of bipolar disorder, psychotic disorders or active substance use disorders were excluded from the study. Participants could enter the study if they were taking a stable antidepressant dose for 30 days before starting the trial (and maintained that dose for the duration of the trial) or not taking an antidepressant at study entry. Zuranolone showed rapid (by day 3), clinically meaningful and sustained response as compared to placebo. There was a significantly greater reduction from baseline in $HAMD_{17}$ total score with zuranolone compared with placebo at day 15 (least squares mean (LSM), −17.8 vs −13.6: difference, −4.2; 95% CI, −6.9, −1.5; $p = 0.003$). Sustained differences in $HAMD_{17}$ scores favoring zuranolone were

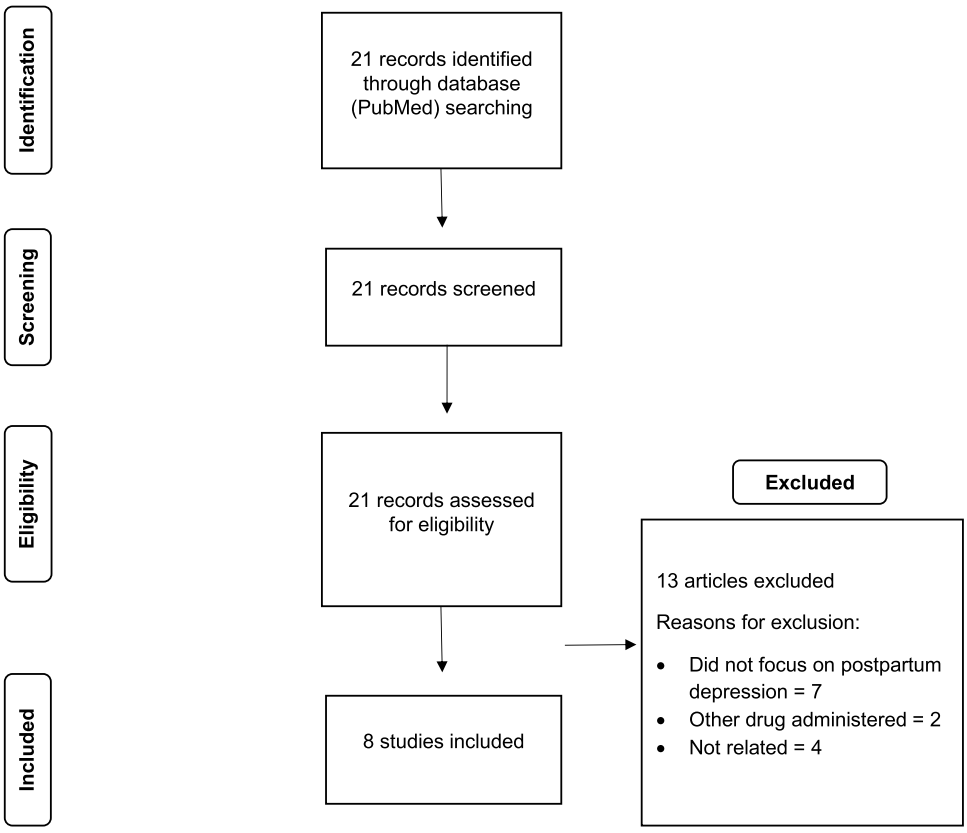

Figure 1 Flow chart of literature review.

observed from Day 3 (LSM difference, −2.7; 95% CI, −5.1, −0.3; p = 0.025) through day 45 (LSM difference, −4.1; 95% CI −6.7, −1.4; p = 0.003). A greater proportion of participants achieved $HAMD_{17}$ response (reduction of ≥50% in HAM-D_{17} score from baseline) and remission ($HAMD_{17}$ score ≤7) at day 15. The response rate was 72% in zuranolone group vs 48% in placebo group; (odds ratio (OR), 2.63; 95% CI, 1.34, 5.16; p = 0.005) at day 15. $HAMD_{17}$ remission at day 15 was 45% in those receiving zuranolone versus 23% receiving placebo (OR, 2.53; 95% CI, 1.24, 5.17; p = 0.011). There was a sustained larger reduction from baseline for Montgomery-Åsberg Depression Rating Scale[57] (MADRS) score with zuranolone at day 15 (difference −4.6; 95% CI, −8.3, −0.8; p = 0.02). A sustained larger reduction in Hamilton Anxiety Rating Scale[58] (HAMA) score also favored zuranolone at day 15 (difference, −3.9; 95% CI, −6.7, −1.1; p = 0.006), hence demonstrating rapid and sustained improvements in anxiety. Clinical Global Impression Improvement[59] response and the Barkin Index of Maternal Functioning[60] measure demonstrated improved global and maternal functioning compared with placebo despite a high placebo response. Zuranolone was generally well tolerated. Most common treatment emergent adverse events in the zuranolone group (≥5%) were somnolence (15%), headache (9%) dizziness (8%), upper respiratory tract infection (8%), diarrhea (6%) and sedation (5%).

The SKYLARK study was an additional phase 3 randomized, double-blind placebo-controlled outpatient trial.[51],196 females (ages 18–45 years) with severe PPD ($HAMD_{17}$≥26) were randomized in a 1:1 ratio to receive zuranolone 50 mg or placebo once daily for fourteen days. The inclusion and exclusion criteria were like the ROBIN study, though this study enrolled participants up to twelve months postpartum. The antidepressant effects of zuranolone were rapid, starting at day 3 (change from baseline (CFB) in $HAMD_{17}$ score (LSM −9.5 vs −6.1; LSM difference =−3.4, 95% CI=−5.4, −1.4; p=0.001). Treatment with zuranolone compared with placebo resulted in statistically significant improvement in depressive symptoms at day 15 (LSM CFB) in $HAMD_{17}$ score −15.6, vs −11.6; LSM difference, −4.0, 95% CI= −6.3, −1.7); significant improvement in depressive symptoms was also reported at days 28 and 45. Similarly, the CFB in Clinical Global Impression Severity[59] score at day 15 was also significantly greater in zuranolone group as compared with placebo (LSM =−2.2 vs −1.6, LSM difference = - 0.6, 95% CI=−0.9, - 0.2; p = 0.005). Response to zuranolone was rapid, with median time to first $HAMD_{17}$ response of 9 days in zuranolone group as opposed to 43 days in the placebo group. The $HAMD_{17}$ response rate at day 15 was significantly greater in the zuranolone group compared with placebo (57% vs 38.9% OR = 2.02, 95% CI=1.11,3.67; p = 0.021). The $HAMD_{17}$ remission rate was greater for zuranolone at day 45 (44.0% vs 29.4%; OR = 2.08, 95% CI = 1.11, 3.92; p = 0.023). Improvement in depressive symptoms as assessed by CFB in MADRS score was also significantly greater in the zuranolone group compared with the placebo group at day 15 (LSM difference =−5.1, 95% CI = −8.4, −1.7; p = 0.003). Improvements in anxiety as assessed by CFB in HAMA score at day 15 were also significantly greater in the zuranolone group compared with the placebo group (LSM difference= −2.2, 95% CI=−4.2, −0.3; p = 0.024). Patient reported outcomes as measured by the Edinburgh Postnatal Depression Scale[61] (EPDS) and Patient Health Questionnaire-9[62] correlated well with the overall $HAMD_{17}$ score, indicating stability over time and may allow opportunity for comparison of treatment effects between studies in the future.

Zuranolone at 50 mg was generally well tolerated. Most participants who experienced side effects reported mild-to-moderate treatment emergent adverse events. Most common adverse events (≥ 5%) reported were somnolence (zuranolone 26.5%; placebo 5.1%), dizziness (zuranolone 13.3%; placebo 10.2%), sedation (zuranolone 11.2%; placebo 1%) and headache (zuranolone 9.2%; placebo 13.3%). No clinically significant changes in vital signs, electrocardiogram or clinical lab parameters were observed. No loss of consciousness and no increase in suicidal ideation from baseline or deaths were seen in the study. Although this study successfully enrolled ethnically and racially diverse patient population, there was low representation from females outside the US. Since participants were only evaluated through day 45, the long-term efficacy and safety of zuranolone is unknown.

In a systematic review and meta-analysis on efficacy of zuranolone versus placebo in PPD and MDD, Winslow et al[54] included 6 double-blind, randomized controlled trials comprised of 1707 participants. Two RCT's[49,51] focused on efficacy of zuranolone in treatment of PPD, while the other 4 RCT[63–66] focused on zuranolone in treating MDD. In PPD, there was an overall significant decrease in $HAMD_{17}$ score vs placebo (mean difference −4.06, 95% CI-4.25 to −3.87; p < 0.001).

In another systematic review and meta-analysis by Raja et al[55] included 8 RCT comprising of 2031 participants enrolled in MDD and PPD clinical trials. The PPD subgroup analysis revealed a significant impact of zuranolone on HAMD17 score at Day 15 (mean difference-4.08; 95% CI=[5.82,-2.35] p < 0.00001). Additionally, the PPD subgroup

analysis revealed significant impact of zuranolone on MADRS scores at Day 15 (mean difference = −4.86; 95% CI = [−7.35, −2.36]; p = 0.0001) and Day 15 hAM-A scores (mean difference = −2.75; 95% CI = [−4.33, −1.16], p = 0.0007).

Zuranolone Use During Lactation

The safety of antidepressants during lactation is of paramount importance for individuals with PPD who choose to breastfeed. 83% of postpartum individuals initiate breastfeeding and 60% continue to breastfeed until six months postpartum, even if not exclusively, making antidepressant safety during lactation a leading concern.[67] Most professional organizations consider medications with a relative infant dose (RID) <10 to be generally compatible with breastfeeding[23] A RID is the weight-adjusted proportion of the maternal dose consumed by the infant in breast milk over a 24-hour period.[68] A medication's RID should not be the only factor taken into consideration when deciding about the safety of medication use while continuing breastfeeding as medications with low RIDs could still be associated with infant adverse effects, though they are less likely to be. The phase 1 open label study by Deligiannidis et al[52] assessed the extent of five doses of zuranolone 30 mg transfer into the breastmilk of 15 healthy, non-pregnant, lactating adult females.[69] The RID at day 5 of 30 mg dose was 0.357%. The estimated mean RID of once daily administration of 50 mg of zuranolone for fourteen days was estimated using a simulation approach across a range of infant ages and weights. The estimated mean RID for 50 mg zuranolone was 0.74% and 0.98% with daily milk intake of 150 and 200 mg/kg per day, respectively. These RIDs are each below 1% and well below the 10% RID threshold generally considered compatible with breastfeeding. The RIDs measured for zuranolone were like or lower to commonly prescribed serotonergic, conventional antidepressants and other central nervous system agents.[52] There was a mean decrease of 8.3% in breast milk volume collected at steady state over 3–5 days compared with the 3-day periods at baseline, considered to be due to uncontrolled factors like infant demand, maternal stress, sleep, or expression technique.

Additional Zuranolone Data: Efficacy Comparisons and Effects on Health-Related Quality of Life, Anxiety and Insomnia

There are a couple of studies that compared the efficacy of serotonergic antidepressants with neuroactive steroid-based antidepressants in PPD. Although efficacy is not the only deciding factor when considering treatment options, it can aid in clinical decision-making. Zuranolone was shown to demonstrate a larger improvement in depressive symptoms (measured as CFB in EPDS) as compared to SSRIs (fluoxetine, sertraline, paroxetine, citalopram and escitalopram). Participants showed significantly greater CFB in EPDS even after a sufficient window for SSRI onset of efficacy and 30 days after cessation of zuranolone treatment.[53] In another comparison study, zuranolone, estradiol and paroxetine were found to be superior to other antidepressants (ie, sertraline, nortriptyline, fluoxetine and saffron). The investigators advised that the results of these meta-analysis should be regarded with caution as the overall quality of evidence is low.[48,53]

In a study using the 36-item short form health survey,[70] zuranolone showed early improvements (day 15) in health-related quality of life across most functioning and wellbeing domains.[71] Benefits continued to accrue even after improvement in depressive symptoms reached a relative maximum CFB. Most importantly, participants showed improvement in the vitality domain, which is an indicator of improvement in energy, fatigue and subjective wellbeing, as early as day 15. This could indicate early improvement in maternal functioning. The vitality domain is related to functional outcomes and is also shown to be correlated with a reduction in healthcare resource use. This contrasts with serotonergic antidepressant use where up to 23% patients can experience reduced energy as a treatment-emergent side effect.[72]

75.5% of participants in the SKYLARK study had moderate to severe anxiety (HAMA score ≥ 20) and those receiving zuranolone showed both early (day 3) and sustained improvement in anxiety symptoms.[49] A greater proportion of women receiving zuranolone achieved concurrent remission of depressive and anxiety symptoms compared with those receiving placebo as early as day 3 (18.9% vs 2.7%; p = .003) and at day 15 (40.5% vs 19.2%; p = .007) and day 45 (52.1% vs 23.2%; p <.001).[50] Beneficial effects on insomnia were also observed.[50] Anxiety and insomnia are common comorbidities of PPD and are associated with more severe depression,[73] and increased risk of self-harm.[13] Although more research is needed to demonstrate if these results are consistently achievable, this could indicate that zuranolone may reduce the need for polypharmacy which is often needed to manage these concurrent/comorbid symptoms.

Conclusion

PPD is one of the most common perinatal psychiatric disorders. Untreated, PPD affects maternal functioning, is associated with adverse effects on the cognitive, emotional and social functioning of the child and increases the risk of maternal morbidity. Early recognition and treatment of PPD is critical to avoid short-term and long-term sequalae for the peripartum individual, child and family. Every patient deserves an individualized treatment plan considering their unique needs and challenges including psychological and social factors affecting symptoms, social support and access to care. Efforts should be made to optimize sleep, nutrition, social support and maximize use of behavioral and somatic treatments. The choice of pharmacological treatment offered should involve considerations of severity of illness, comorbid medical illness, and adherence to treatment, previous response to treatment and side effects to prior antidepressant trials.[23]

CBT and IPT are recommended first line treatments for mild-to-moderate depression. They are effective as alternatives and in conjunction with antidepressants. Patients with a prior positive experience and response to psychotherapy may prefer psychotherapeutic to psychopharmacologic approaches. Despite efficacy, psychotherapeutic interventions can have their limitations. In the US, access to care, including insurance, cost, and time are common barriers for many patients.[74]

Patients with moderate or severe PPD or those who are at increased risk for suicide should receive antidepressant treatment in combination with other therapeutic approaches. Given the short, acute treatment course and rapid antidepressant effects of neuroactive-steroid based antidepressants, we clinically recommend the use of brexanolone IV or oral zuranolone as a first line treatment in postpartum adult females with moderate or severe unipolar PPD. Neurosteroid-based antidepressants such as zuranolone may be an effective choice in patients who have failed conventional antidepressants or are unable to tolerate them due to side effects. Zuranolone can be used as an adjunct to other antidepressants for patients who either have a partial response to conventional antidepressants or experience relapse despite their use at adequate doses. Zuranolone has been studied in adult females who are up to twelve months postpartum and is associated with the clinical improvement of anxiety and insomnia symptoms and some measures of health-related quality of life.

Patients with a prior adequate response, minimal and tolerable side effects to serotonergic or other conventional antidepressants may prefer to use them over neurosteroid-based antidepressants. Patients with active alcohol, opioid, sedative, hypnotic or anxiolytic use disorder may be better candidates for serotonergic or other antidepressants than neurosteroid-based antidepressants due to the additive risk of sedation or somnolence. Postpartum individuals who choose not to use contraception or have a contraindication for its use are better suited to use serotonergic antidepressants since zuranolone has not been studied during pregnancy and may be associated with fetal risk. Lactating individuals may use serotonergic-based or neuroactive steroid-based antidepressants when clinically warranted. SSRIs are a well-studied class of medication in lactation and are considered relatively safe.[75,76] Recent data from brexanolone and zuranolone lactation studies indicate that the RID for both medications are very low.[52,77] There is no data on effects of zuranolone on a breastfed infant and limited data on effects on milk production. If zuranolone is required by the patient, it is not a reason to discontinue breastfeeding.[78] Until more data are available, zuranolone should be used with careful infant monitoring for excessive sedation during breastfeeding in newborn and preterm infants.[78]

Zuranolone should be taken with fat containing food (eg, 400 to 1000 calories, 25% to 50% fat) for better absorption. If a dose is missed, the next dose should be taken at the regular time the following evening. Patients should not take an extra dose on the same day to make up for missed dose. The remainder of the 14-day course should be completed. Patients unable to tolerate the 50 mg daily dose may have their dose reduced to 40 mg daily for the remainder of the treatment course. Zuranolone has an FDA boxed warning regarding the impaired ability to drive or engage in potentially hazardous activities due to its central nervous system depressant effects. Patients should be advised not to drive or engage in other potentially hazardous activities until at least 12 hours after zuranolone administration for the duration of the 14-day treatment course.

Patients of reproductive potential should use effective contraception during treatment and for one week after the final dose. Zuranolone is approved under schedule IV of the Controlled Substance Act. Although identified as a drug with low potential for abuse and dependence, zuranolone has not been studied in patients with an active substance use disorder.

Timely and adequate treatment of PPD is essential considering its growing prevalence and association with adverse maternal and infant outcomes. Zuranolone has the potential to become the first-step treatment for moderate-severe PPD due to its rapid-onset, clinically meaningful improvement in depressive symptoms and generally favorable side effect profile. However, not all individuals with PPD prefer pharmacotherapeutic approaches, thus there is a need for continued therapeutic development.

Abbreviations

PPD, peripartum depression; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; MDD, major depressive disorder; US, United States; CBT, cognitive behavioral therapy; IPT, interpersonal therapy; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; FDA, food and drug administration; RCTs, randomized, controlled trials; NASSA, noradrenergic and specific serotonergic antidepressant; TCAs, tricyclic antidepressants; PAMs, positive allosteric modulators; HPA, hypothalamic-pituitary-adrenal; CNS, Central Nervous System; HAMD, Hamilton rating scale for depression; LSM, least square means; CI, confidence interval; OR, odds ratio; HAMA, Hamilton anxiety rating scale; OR, odds ratio; LSM, least square means; MADRS, Montgomery-Åsberg depression rating scale; HAMA, Hamilton anxiety rating scale; CFB, change from baseline; EPDS, Edinburgh postnatal depression scale; RID, relative infant dose.

Ethics Approval

Ethics approval was not required, as all data were gathered from previously published studies.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Dr Deligiannidis serves as a consultant to Sage Therapeutics, Brii Biosciences, Gerbera Therapeutics, GH Research, Neuroscience Software and Reunion Neuroscience. Dr. Deligiannidis served as a study principal investigator for contracted research awarded to the Feinstein Institutes for Medical Research from Sage Therapeutics, Gerbera Therapeutics, Woebot Health and Premier Healthcare. She also receives grants from the National Institutes of Health (NIH) and royalties from an NIH employee invention. Ms. Giannopoulos and Dr. Singh report no disclosures or conflicts of interest in this work.

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