Journal of Affective Disorders 320 (2023) 353–359

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Effect of brexanolone on depressive symptoms, anxiety, and insomnia in women with postpartum depression: Pooled analyses from 3 double-blind, randomized, placebo-controlled clinical trials in the HUMMINGBIRD clinical program

C. Neill Epperson [a,*], David R. Rubinow [b], Samantha Meltzer-Brody [b], Kristina M. Deligiannidis [c,d], Robert Riesenberg [e], Andrew D. Krystal [f], Kemi Bankole [g], Ming-Yi Huang [g], Haihong Li [g], Colville Brown [g], Stephen J. Kanes [g], Robert Lasser [g]

[a] Department of Psychiatry, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, United States of America
[b] Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill, NC, United States of America
[c] Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, United States of America
[d] Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, United States of America
[e] Atlanta Center for Medical Research, Atlanta, GA, United States of America
[f] Department of Psychiatry, University of California, San Francisco, San Francisco, CA, United States of America
[g] Sage Therapeutics, Inc., Cambridge, MA, United States of America

ARTICLE INFO

Keywords:
Postpartum depression
Anxiety
Antidepressant
Neuroactive steroid
Brexanolone

ABSTRACT

Background: Brexanolone is currently the only treatment specifically approved for postpartum depression (PPD) in the United States, based on the results from one Phase 2 and two Phase 3 double-blind, randomized, controlled trials in the HUMMINGBIRD program.
Methods: Adults with PPD randomized to a 60-h infusion of brexanolone 90 μg/kg/h (BRX90) or placebo from the 3 trials were included in these post hoc analyses. Data on change from baseline (CFB) in the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score, HAMD-17 Anxiety/Somatization and Insomnia subscales, and Clinical Global Impression of Improvement (CGI-I) scale were pooled. Response rates for HAMD-17 (≥50 % reduction from baseline) and CGI-I (score of 1 or 2) scales and time to response were analyzed.
Results: Patients receiving BRX90 ($n = 102$) versus placebo ($n = 107$) achieved a more rapid HAMD-17 response (median, 24 vs 36 h; $p = 0.0265$), with an Hour-60 cumulative response rate of 81.4 % versus 67.3 %; results were similar for time to CGI-I response (median, 24 vs 36 h; $p = 0.0058$), with an Hour-60 cumulative response rate of 81.4 % versus 61.7 %. CFB in HAMD-17 Anxiety/Somatization and Insomnia subscales also favored BRX90 versus placebo, starting at Hour 24 through Day 30 (all $p < 0.05$), and response rates for both subscales were higher with BRX90.
Limitations: The study was not powered to assess exploratory outcomes.
Conclusions: Brexanolone was associated with rapid improvement in depressive symptoms and symptoms of anxiety and insomnia compared with placebo in women with PPD. These data continue to support the use of brexanolone to treat adults with PPD.

1. Introduction

Postpartum depression (PPD) is defined by the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) as a major depressive episode (MDE) with onset during pregnancy or within 4 weeks following delivery (American Psychiatric Association, 2013). Postpartum depression is one of the most common medical complications associated with pregnancy, with an overall prevalence of approximately 13 % among

* Corresponding author at: University of Colorado School of Medicine, Anschutz Medical Campus, 1890 N Revere Court, Rm C2000E, Aurora, CO 80045, United States of America.
E-mail address: neill.epperson@cuanschutz.edu (C.N. Epperson).

https://doi.org/10.1016/j.jad.2022.09.143
Received 9 May 2022; Received in revised form 26 August 2022; Accepted 27 September 2022
Available online 30 September 2022
0165-0327/© 2022 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

postpartum women in the United States (Bauman et al., 2020), similar to that of preterm birth (Martin et al., 2018), gestational diabetes (DeSisto et al., 2014), and hypertensive disorders of pregnancy (Centers for Disease Control and Prevention, 2019). Multiple psychosocial and biological factors are associated with increased risk of PPD, and a history of mood and anxiety disorders is recognized as one of the strongest predictors of PPD (Biaggi et al., 2016; Moses-Kolko and Roth, 2004; Robertson et al., 2004; Yim et al., 2015).

Early and effective treatment of core depressive symptoms of PPD is vital, considering that these symptoms are associated with adverse maternal and infant outcomes (Bauman et al., 2020), impaired maternal functioning (Barkin et al., 2016; Bobo and Yawn, 2014), reduced initiation of breastfeeding (Gagliardi et al., 2012; Wouk et al., 2017), and unfavorable parenting practices (Balbierz et al., 2015; McLearn et al., 2006). At the same time, managing residual symptoms such as anxiety and insomnia, which are commonly associated with PPD, is also necessary to improve patients' quality of life (Da Costa et al., 2006); moreover, in major depressive disorder, residual symptoms have been associated with a greater risk of relapse (Nierenberg et al., 2010; Sakurai et al., 2017). Prominent symptoms of anxiety, which can be present in up to 70 % of women with PPD (Hendrick et al., 2000; Nakic Rados et al., 2018; Ross et al., 2003), are themselves associated with more severe PPD, making its treatment more difficult (Hendrick et al., 2000; Postpartum Depression: Action Towards Causes and Treatment Consortium, 2015). Similarly, altered sleep states, including insomnia, have been shown to be both a risk factor for and a symptom of PPD (Dorheim et al., 2014; Marques et al., 2011; Okun, 2015; Wolfson et al., 2003). In addition, reduced sleep quality may be predictive of increased depressive symptomology (Emamian et al., 2019; Marques et al., 2011; Park et al., 2013). Further, a recent study suggested that treating insomnia during pregnancy may improve symptoms of depression and anxiety during pregnancy and postpartum, and decrease the rate of depression at 3 months postpartum (Felder et al., 2022).

Brexanolone (Zulresso® [brexanolone] injection, Sage Therapeutics, Inc., Cambridge, MA) is an intravenous formulation of allopregnanolone, a neuroactive steroid and positive allosteric modulator (PAM) of gamma-aminobutyric acid type A ($GABA_A$) receptors (Kanes et al., 2017a; Sage Therapeutics Inc., 2022). Brexanolone can directly interact with $GABA_A$ receptors (Reddy and Estes, 2016) and is hypothesized to help restore normal signaling in neuronal networks, thereby maintaining the excitatory-inhibitory neuronal balance (Edinoff et al., 2021), which is important for functional connectivity within neuronal networks (Fogaca and Duman, 2019; Northoff and Sibille, 2014; Roux and Buzsaki, 2015). Neuronal network dysregulation has been implicated as a key mechanism underlying depression (Duman et al., 2019; Fogaca and Duman, 2019; Lener et al., 2017; Luscher and Mohler, 2019). In PPD, a potential mechanism involving GABAergic deficit has been suggested based on results from preclinical research; GABA signaling is thought to be impaired and, as a result, the key neuronal networks that allow the brain to appropriately respond to stimuli such as stress are dysregulated (Gunduz-Bruce et al., 2021; Maguire and Mody, 2008). Unlike benzodiazepines, which target synaptic $GABA_A$ receptors (Rudolph and Knoflach, 2011), the neuroactive steroid brexanolone can target a large population of $GABA_A$ (synaptic and extrasynaptic) receptors, resulting in increased phasic and tonic activity of GABAergic neurons, respectively (Reddy and Estes, 2016). This activity is thought to restore the function of key neuronal networks (Edinoff et al., 2021; Luscher and Mohler, 2019). Although benzodiazepines are highly effective therapies for anxiety and insomnia, they do not exhibit long-term antidepressant activity, and their use is limited by side effects, withdrawal symptoms that can last for months, and potential for abuse (Department of Health and Human Services, 2020; Duman et al., 2019).

Brexanolone was approved in 2019 by the US Food and Drug Administration (FDA) for the treatment of adult women with PPD (Sage Therapeutics Inc., 2022) based on efficacy and safety data from 3 pivotal (one Phase 2 and two Phase 3) double-blind, randomized, controlled trials (RCTs; NCT02614547, NCT02942004, NCT02942017) (Kanes et al., 2017a; Meltzer-Brody et al., 2018) and 1 open-label proof-of-concept study in women with PPD (Kanes et al., 2017b). Treatment with brexanolone is currently available only through the FDA-approved inpatient Risk Evaluation and Mitigation Strategy (REMS) program due to the potential risk of excessive sedation or sudden loss of consciousness in patients during infusion. Although patients with PPD are commonly treated with selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants (Kroska and Stowe, 2020), brexanolone is the first and currently the only FDA-approved drug specifically indicated for PPD in patients 15 years and older (Sage Therapeutics Inc., 2022). The rapid response (by Hour 60) after the initiation of brexanolone treatment (Kanes et al., 2017a; Meltzer-Brody et al., 2018) sharply contrasts with SSRIs, which typically take 4 to 6 weeks to achieve optimal improvement (De Crescenzo et al., 2014). Brexanolone is also generally well tolerated in women with PPD, with no deaths or unexpected adverse events reported in the 3 pivotal trials (Kanes et al., 2017a; Meltzer-Brody et al., 2018).

Previous post hoc analyses of pooled data from the 3 pivotal brexanolone trials showed that a significantly higher proportion of patients receiving brexanolone 90 μg/kg/h (BRX90) versus placebo achieved rapid (by Hour 60) and sustained (through Day 30) reduction in symptoms of PPD as assessed by change from baseline (CFB) in 17-item Hamilton Rating Scale for Depression (HAMD-17) total score and rates of HAMD-17 response, HAMD-17 remission, and Clinical Global Impression of Improvement (CGI-I) response (Gerbasi et al., 2021). The current post hoc analyses assessed the effect of BRX90 on time to onset of HAMD-17 response and CGI-I response, and on reduction in symptoms of anxiety and insomnia in adults with PPD. Our interest in these assessments was motivated by the perspective that brexanolone is likely to have potent therapeutic effects on anxiety and insomnia such as is seen with benzodiazepines that are also $GABA_A$ receptor PAMs (Department of Health and Human Services, 2020; Holbrook et al., 2000; Mitte et al., 2005), but with a better safety profile and accompanying antidepressant effects.

2. Methods

2.1. Study design and participants

This is a post hoc evaluation of pooled data from clinician-reported outcomes in the 3 pivotal double-blind RCTs of brexanolone from the HUMMINGBIRD clinical program, referred to as Studies A (NCT02614547; Phase 2), B (NCT02942004; Phase 3), and C (NCT02942017; Phase 3) (Kanes et al., 2017a; Meltzer-Brody et al., 2018), that examined the safety and efficacy of brexanolone injection compared with placebo in patients with moderate to severe PPD. All 3 studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Study protocols were reviewed and approved by the relevant institutional review boards or independent ethics committees. All patients provided written informed consent.

Full descriptions of the trial designs and inclusion and exclusion criteria have been published previously (Kanes et al., 2017a; Meltzer-Brody et al., 2018). Briefly, the studies included women aged 18 to 45 years <6 months postpartum with PPD (MDE with onset in the third trimester or <4 weeks postpartum) and a qualifying HAMD-17 total score of ≥26 for Studies A and B or 20 to 25 for Study C. Studies A and C used 1:1 randomization to BRX90 or placebo, whereas Study B used 1:1:1 randomization to brexanolone 60 μg/kg/h, BRX90, or placebo. Patients received a 60-h continuous infusion of brexanolone or placebo in a monitored setting followed by 12 h of monitoring for completion of assessments. Patients were followed up until Day 30 with clinical and safety assessments performed at Days 7 and 30.

2.2. Study outcomes

The primary endpoint in all three studies was CFB in HAMD-17 total score at Hour 60 (Kanes et al., 2017a; Meltzer-Brody et al., 2018). Secondary endpoints included CFB in HAMD-17 total score at all other timepoints, and proportions of patients achieving CGI-I response (defined as CGI-I score of 1 [very much improved] or 2 [much improved]), HAMD-17 response (defined as ≥50 % reduction from baseline in HAMD-17 total score), and HAMD-17 remission (defined as HAMD-17 total score of ≤7) at Hour 60 (Kanes et al., 2017a; Meltzer-Brody et al., 2018). The safety and tolerability of brexanolone have been previously evaluated (Kanes et al., 2017a; Meltzer-Brody et al., 2018).

The post hoc analyses included (1) time to onset of treatment response (the first time a patient achieves HAMD-17 or CGI-I response); (2) CFB in the HAMD-17 Anxiety/Somatization (A/S) subscale (including 6 items: anxiety [psychic], anxiety [somatic], somatic symptoms [gastrointestinal], somatic symptoms [general], hypochondriasis, and insight); (3) proportion of patients achieving HAMD-17 A/S response (≥50 % reduction from baseline in HAMD-17 A/S subscale score); (4) CFB in the HAMD-17 insomnia subscale (sum of individual item scores rating difficulty falling asleep and staying asleep at 3 periods during the night: early, middle, late); and (5) proportion of patients achieving HAMD-17 insomnia response (≥50 % reduction from baseline in HAMD-17 insomnia subscale score) (Bobo et al., 2016). The HAMD-17 insomnia response rate was also assessed in an exploratory analysis using the definition of ≥70 % reduction from baseline in order to apply a stricter criterion. Subgroups of patients with symptoms of insomnia (HAMD-17 insomnia subscale score ≥ 1) or severe insomnia (HAMD-17 insomnia subscale score ≥ 4) (Montgomery et al., 2009) at baseline were assessed for a categoric response of HAMD-17 insomnia subscale score <1 or <4, respectively, as exploratory outcomes. The criteria used here for assessing HAMD-17 insomnia response have not been validated.

2.3. Statistical analyses

The post hoc analyses were conducted on the combined efficacy dataset, which included all randomized patients who started BRX90 or placebo infusion and had a valid baseline and at least 1 postbaseline HAMD-17 total score. Time to onset was assessed by Kaplan-Meier analysis. Change from baseline in HAMD-17 total scores or subscale scores was analyzed using a mixed-effect model for repeated measures. A generalized estimating equation (GEE) or logistic regression approach was used for response assessments (excluding patients with a baseline score of 0 in GEE method for HAMD-17 insomnia subscale analyses). Post hoc analyses were not adjusted for multiplicity and all p values are nominal, with a value of <0.05 indicating significance. All statistical analyses were performed using SAS software (Version 9.4; SAS Institute, Cary, NC, USA) unless otherwise noted.

3. Results

The combined efficacy dataset included 209 women with PPD (N = 102 for BRX90; N = 107 for placebo). Baseline demographics and clinical characteristics were well balanced across treatment groups (Table 1).

3.1. Time to onset of HAMD-17 response

The cumulative percentage of patients achieving a HAMD-17 response over time was higher in the BRX90 group compared with the placebo group at Hour 60 (81.4 % vs 67.3 %) through Day 30 (88.2 % vs 75.7 %) (Fig. 1). Patients receiving BRX90 achieved a significantly more rapid HAMD-17 response than those receiving placebo; the median (95 % confidence interval [CI]) time to HAMD-17 response was 24 h (24 to 36 h) with BRX90 versus 36 h (24 to 48 h) with placebo (p = 0.0265) (Fig. 1).

Table 1
Baseline patient demographics and clinical characteristics.

	Placebo N = 107	BRX90 N = 102
Age, mean ± SD, years	27.4 ± 5.9	27.8 ± 6.0
Race, n (%)		
White	65 (60.7)	61 (59.8)
Black/African American	40 (37.4)	37 (36.3)
Other	2 (1.9)	4 (3.9)
Ethnicity, n (%)		
Hispanic/Latino	21 (19.6)	17 (16.7)
BMI, mean ± SD, kg/m^2	31.2 ± 8.2	31.3 ± 8.1
Antidepressant use, n (%)	25 (23.4)	22 (21.6)
History of MDD, n (%)	3 (2.8)	2 (2.0)
Duration between delivery and treatment, mean ± SD, months	3.4 ± 1.7	3.6 ± 1.6
HAMD-17 total score, mean ± SD	25.7 ± 3.6	25.5 ± 3.5
HAMD-17 A/S score, mean ± SD	8.1 ± 2.1	7. 8 ± 2.0
HAMD-17 insomnia subscale score, mean ± SD	4.6 ± 1.5	4.4 ± 1.5

Abbreviations: BMI = body mass index; BRX90 = brexanolone 90 μg/kg/h; HAMD-17 = 17-item Hamilton Rating Scale for Depression; HAMD-17 A/S = HAMD-17 Anxiety/Somatization subscale; MDD = major depressive disorder; SD = standard deviation.

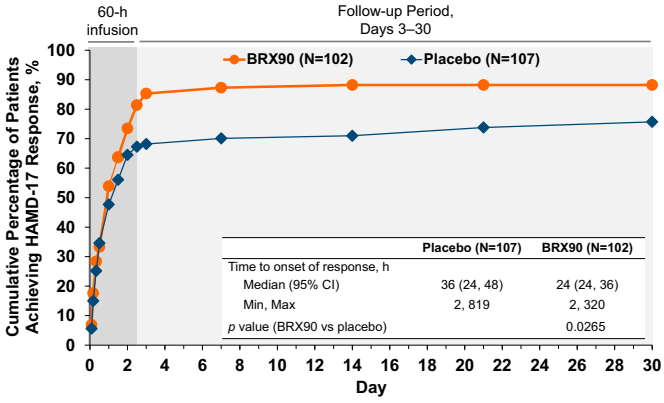

Fig. 1. Cumulative percentage of patients achieving HAMD-17 response over time.
p value was based on the log-rank test from the Kaplan-Meier analysis. Results were not adjusted for multiplicity. Abbreviations: BRX90 = brexanolone 90 μg/kg/h; CI = confidence interval; HAMD-17 = 17-item Hamilton Rating Scale for Depression.

3.2. Time to onset of CGI-I response

The cumulative percentage of patients achieving a CGI-I response over time was higher with BRX90 than with placebo at Hour 60 (81.4 % vs 61.7 %) through Day 30 (88.2 % vs 78.5 %) (Fig. 2). Patients achieved a significantly more rapid CGI-I response with BRX90 than with placebo, with a median (95 % CI) time to onset of 24 h (24 to 36 h) in the BRX90 group compared with 36 h (24 to 60 h) in the placebo group (p = 0.0058) (Fig. 2).

3.3. Anxiety symptoms

Change from baseline in HAMD-17 A/S score was significantly greater in the BRX90 group versus the placebo group starting at Hour 24 (p = 0.0030) and was sustained through Day 30 (all p < 0.05) (Fig. 3A). A significantly greater proportion of patients receiving BRX90 versus placebo achieved HAMD-17 A/S response at Hour 24 through Day 30 (all p < 0.05) (Fig. 3B).

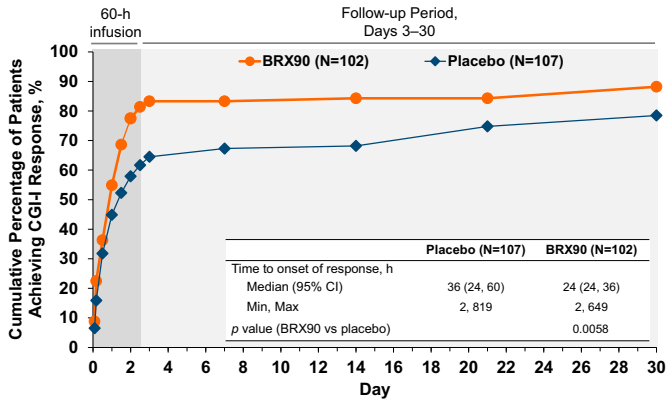

Fig. 2. Cumulative percentage of patients achieving CGI-I response over time. *p* value was based on the log-rank test from the Kaplan-Meier analysis. Results were not adjusted for multiplicity. Abbreviations: BRX90 = brexanolone 90 μg/kg/h; CGI-I = Clinical Global Impression of Improvement; CI = confidence interval.

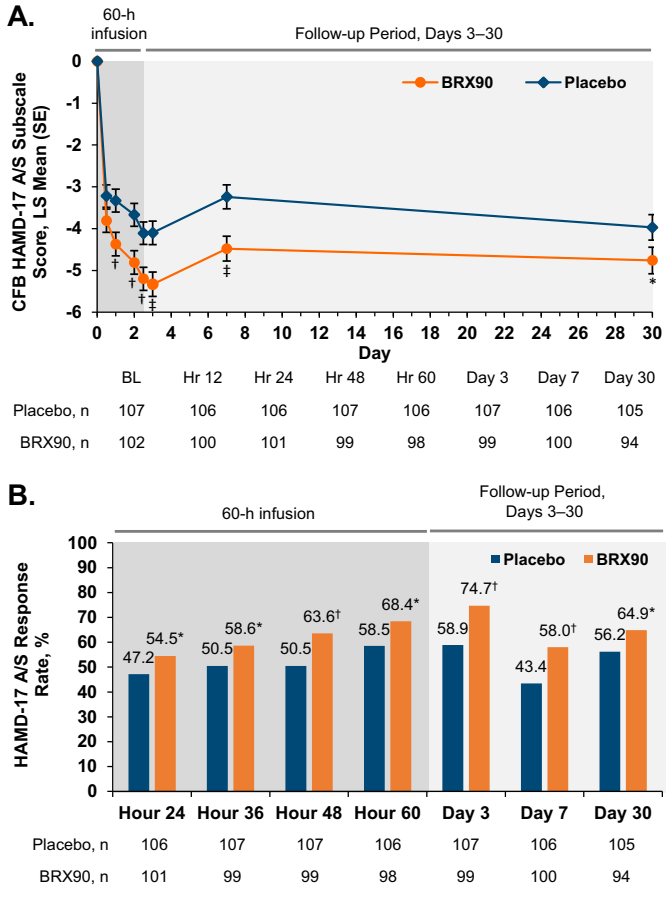

Fig. 3. Improvement in anxiety-related symptoms over time. (A) Change from baseline (CFB) in HAMD-17 A/S subscale score through Day 30. (B) Proportion of patients achieving HAMD-17 A/S response through Day 30.
*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ versus placebo. Abbreviations: BL = baseline; BRX90 = brexanolone 90 μg/kg/h; HAMD-17 A/S = 17-item Hamilton Rating Scale for Depression Anxiety/Somatization subscale; LS = least squares; SE = standard error.

3.4. Insomnia symptoms

Change from baseline in HAMD-17 insomnia subscale score was significantly greater with BRX90 versus placebo at all timepoints starting at Hour 24 through Day 30 (all $p < 0.05$) (Fig. 4A). The proportion of patients achieving a HAMD-17 insomnia response (≥50 % reduction from baseline) was greater with BRX90 versus placebo at Hour 24 through Day 30 ($p < 0.05$ at all timepoints except at Day 30) (Fig. 4B). Furthermore, a significantly greater proportion of patients achieved a ≥70 % reduction from baseline in HAMD-17 insomnia subscale score with BRX90 versus placebo at all timepoints measured (all $p < 0.05$),

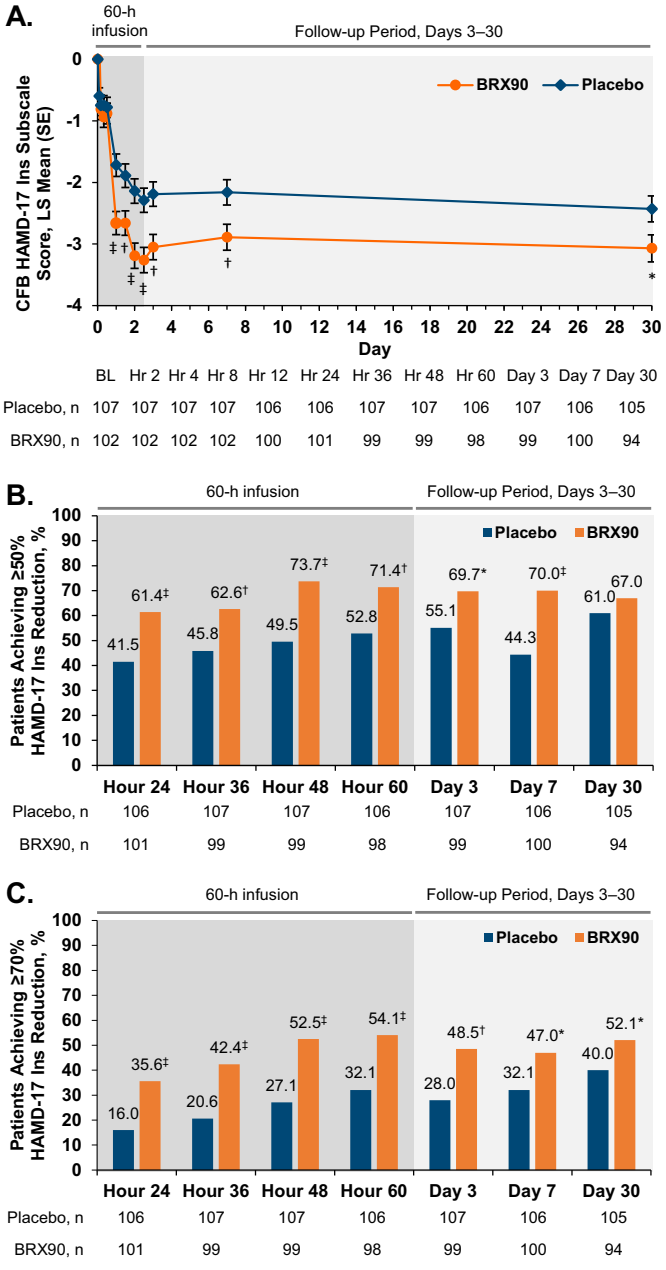

Fig. 4. Improvement in insomnia-related symptoms over time. (A) Change from baseline (CFB) in HAMD-17 insomnia subscale through Day 30. (B) Proportion of patients achieving HAMD-17 insomnia response defined by ≥50 % reduction from baseline. (C) Proportion of patients achieving HAMD-17 insomnia response defined by ≥70 % reduction from baseline.
*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ versus placebo. Abbreviations: BRX90 = brexanolone 90 μg/kg/h; HAMD-17 Ins = 17-item Hamilton Rating Scale for Depression Insomnia subscale; LS = least squares; SE = standard error.

ranging from 35.6 % to 54.1 % for BRX90 and 16.0 % to 40.0 % for placebo (Fig. 4C).

In the subgroup of patients with baseline insomnia symptoms (HAMD-17 insomnia subscale score $\geq$ 1), a significantly greater proportion of patients receiving BRX90 versus placebo reported a complete absence of symptoms of insomnia (HAMD-17 insomnia subscale score $<$ 1) at Hour 24 through Day 30 ($p < 0.05$ for all timepoints except Day 7) (Supplementary Fig. 1A). Similarly, in the subgroup of patients with severe symptoms of insomnia at baseline, a significantly greater proportion of patients achieved a HAMD-17 insomnia subscale score $<$ 4 with BRX90 than with placebo ($p < 0.05$) at all timepoints (starting at Hour 24) except at Day 30 (Supplementary Fig. 1B).

4. Discussion

Standard-of-care treatment for PPD relies on monoaminergic antidepressants, which are often associated with slow response and low remission rates (De Crescenzo et al., 2014; Rush et al., 2006; Trivedi et al., 2006). Brexanolone, a neuroactive steroid and the first agent indicated for the treatment of PPD, acts differently from monoaminergic antidepressants, exerting its effect by enhancing $GABA_A$ receptor function and restoring dysregulated GABA signaling (Edinoff et al., 2021; Luscher and Mohler, 2019; Sage Therapeutics Inc., 2022). The approval by the FDA in 2019 of brexanolone for the treatment of PPD (Sage Therapeutics Inc., 2022) has provided the opportunity for adult women experiencing PPD to achieve a rapid and clinically meaningful reduction in depressive symptoms. Clinical studies of brexanolone in patients with PPD have demonstrated rapid responses at the end of the 60-hour infusion period, which were sustained postinfusion through Day 30 (Kanes et al., 2017a; Kanes et al., 2017b; Meltzer-Brody et al., 2018). Furthermore, an improvement in mood beyond 30 days was recently reported in an open-label, single-institution, follow-up study of patients with PPD who received brexanolone (data collected between 3 and 16 months postinfusion); some patients required psychiatric admission as inpatients before receiving infusion with brexanolone because of the severity of their illness (Patterson et al., 2021). The current post hoc analyses of the pivotal brexanolone trials demonstrate that brexanolone treatment not only achieved rapid (by Hour 24) and sustained (through Day 30) reductions in core depressive symptoms, but also rapidly and persistently improved symptoms of anxiety and insomnia in adult women with PPD. The percentage of responders in terms of anxiety, insomnia, depression, and the degree of clinically meaningful improvement (assessed by CGI-I) also increased with brexanolone treatment.

Because the presence of prominent features of anxiety in patients with PPD can prolong the time to response (ie, to pharmacotherapy) (Hendrick et al., 2000), it is important to include parameters for anxiety during PPD screening (Nakic Rados et al., 2018). Patients with PPD who received BRX90 experienced a significantly greater reduction in symptoms of anxiety (as assessed by CFB in HAMD-17 A/S subscale score), and a higher proportion of these patients achieved HAMD-17 A/S response compared with placebo. These data, together with the rapid and sustained reduction in HAMD-17 depressive symptoms seen with brexanolone (Kanes et al., 2017a, 2017b; Meltzer-Brody et al., 2018), are especially impactful given the high incidence of prominent symptoms of anxiety in patients with PPD (Bobo and Yawn, 2014; Hendrick et al., 2000; Nakic Rados et al., 2018; Ross et al., 2003).

Insomnia is prevalent in approximately 10 % of the general population and is often comorbid with several psychiatric conditions (Krystal et al., 2019). Because poor sleep quality during pregnancy and the early postpartum period has been shown to be an independent predictor of later PPD symptoms, early screening, diagnosis, and sleep interventions could help minimize the risk of PPD (Emamian et al., 2019; McEvoy et al., 2019; Park et al., 2013). Indeed, additional treatment of insomnia in patients with depression has been reported to result in better outcomes than treating depression alone (Manber and Chambers, 2009). The HAMD-17 insomnia subscale has been validated as a global measure of insomnia in depression based on the substantial agreement between insomnia item scores and sleep diary data (Manber et al., 2005). The current post hoc analyses showed that symptoms of insomnia as measured by the HAMD-17 insomnia subscale were significantly reduced in patients treated with BRX90 versus placebo, and a higher proportion of patients treated with BRX90 versus placebo achieved HAMD-17 insomnia response. Given that the current standard-of-care antidepressants often do not improve symptoms of insomnia in patients with PPD, especially at earlier stages of treatment (Okun et al., 2011; Stone et al., 2017), brexanolone represents a novel addition to the therapeutic landscape.

4.1. Limitations

One limitation of these analyses is that the HAMD-17 A/S subscale used to assess symptoms of anxiety was not developed or validated to diagnose symptoms of anxiety, and these data should therefore be interpreted with caution. In addition, the study was not powered to assess secondary and exploratory outcomes. Patients in this study population showed relatively high rates of response to placebo, similar to previous studies of antidepressants (Furukawa et al., 2016; Khan et al., 2017). Placebo responses were observed across the three placebo-controlled trials of brexanolone injection in postpartum depression (Kanes et al., 2017a, 2017b; Meltzer-Brody et al., 2018). While these three trials demonstrated clinically meaningful and statistically significant reductions in symptoms of PPD, as assessed by CFB in HAMD-17 total score (brexanolone injection versus placebo), the large placebo effects observed in some studies of antidepressant agents may contribute to nonsignificant treatment differences in those studies (Walsh et al., 2002; Undurraga and Baldessarini, 2012). It is hypothesized that frequent supervision and assessment of patients in clinical trials of depression contributes to the placebo effect (Khan et al., 2017; Walsh et al., 2002). In this study population, patients receiving placebo were also hospitalized with the attention and care associated with hospitalization and participation in an RCT. Lastly, patients were followed up for only 30 days posttreatment, and additional studies on the longer-term impact of treatment are needed.

5. Conclusions

These post hoc analyses demonstrate that adult women with PPD have a rapid response to treatment with brexanolone, showing a sustained reduction in depressive symptoms and symptoms of anxiety and insomnia. The data reported here support brexanolone as a rapid-acting antidepressant for adult women with PPD that may potentially eliminate the need for additional pharmacotherapies to treat anxiety or insomnia. Because patients with PPD and anxiety or insomnia symptoms have more complex and often harder to treat symptoms/disease that can require multiple different medications, treatment with brexanolone may offer the advantage of adequately treating symptoms not only of depression but also of anxiety and insomnia. Overall, this study provides meaningful insights that can aid shared decision-making in clinical practice for the treatment of PPD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.09.143.

Role of the funding source

This study was funded by Sage Therapeutics, Inc., United States of America. The study funder was involved in the study design, data analysis, interpretation, and writing of the report. All authors had full access to all data, and the corresponding author had final responsibility for the decision to submit for publication. Medical writing and editorial support were provided by Symbiotix, LLC, and funded by Sage Therapeutics, Inc.

CRediT authorship contribution statement

C. Neill Epperson: Conceptualization, Validation, Investigation, Writing – review & editing, Visualization, Supervision, Project administration. **David R. Rubinow:** Conceptualization, Methodology, Writing – review & editing. **Samantha Meltzer-Brody:** Conceptualization, Investigation, Writing – review & editing, Supervision, Project administration. **Kristina M. Deligiannidis:** Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization. **Robert Riesenberg:** Investigation, Writing – review & editing, Supervision, Project administration. **Andrew D. Krystal:** Conceptualization, Writing – review & editing. **Kemi Bankole:** Writing – review & editing. **Ming-Yi Huang:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Haihong Li:** Methodology, Software, Validation, Formal analysis, Data curation, Writing – review & editing. **Colville Brown:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Stephen J. Kanes:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Robert Lasser:** Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Funding acquisition.

Declaration of competing interest

C. Neill Epperson serves on an advisory board for Asarina Pharma and Babyscripts; reports grants awarded to the University of Colorado from Sage Therapeutics, Inc. and HealthRhythms; and receives consulting fees/honoraria from Sage Therapeutics, Inc. **David R. Rubinow** serves as a consultant and a clinical advisory board co-chair for Sage Therapeutics, Inc.; receives consulting fees and travel/meeting support from Sage Therapeutics, Inc.; and reports grants awarded to University of North Carolina from Sage Therapeutics, Inc. Dr. Rubinow also holds stock options from Sage Therapeutics, Inc. **Samantha Meltzer-Brody** reports grants awarded to University of North Carolina from Sage Therapeutics, Inc. Dr. Meltzer-Brody also received honoraria from Sage Therapeutics, Inc. **Kristina M. Deligiannidis** serves as a consultant to Sage Therapeutics, Inc., Brii Biosciences, Inc., and GH Research Ireland Limited, and as a council/board member for Society of Biological Psychiatry and American Society of Clinical Psychopharmacology. Dr. Deligiannidis reports grants awarded to Zucker Hillside Hospital/Feinstein Institutes for Medical Research from Sage Therapeutics, Inc. during the conduct of the brexanolone injection and zuranolone clinical trials. Dr. Deligiannidis also received grants from NIH and Vorso Corporation, royalties from an NIH employee invention outside of the submitted work, payments/honoraria from Platform Q Health Education CME and Peer View Institute for Medical Education, and travel/meeting support from Sage Therapeutics, Inc. and Vorso Corporation. **Robert Riesenberg** has no conflict of interest to declare. **Andrew D. Krystal** participates on a data safety monitoring board/advisory board for Idorsia and Neurocrine Biosciences; receives payments/honoraria from Eisai and Idorsia and consulting fees from Adare, Axsome Therapeutics, Big Health, Eisai, Evecxia, Ferring Pharmaceuticals, Galderma, Harmony Biosciences, Idorsia, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Millenium Pharmaceuticals, Merck, Neurocrine Biosciences, Neurawell, Pernix, Otsuka Pharmaceuticals, Sage Therapeutics, Inc., Takeda, and Angelini; and reports grants from Janssen Pharmaceuticals, Axsome Pharmaceutics, Reveal Biosensors, The Ray and Dagmar Dolby Family Fund, and NIH. Dr. Krystal also holds stock options from Big Health. **Kemi Bankole, Ming-Yi Huang**, **Colville Brown**, and **Robert Lasser** are employees of Sage Therapeutics, Inc. and hold stock and/or stock options. **Haihong Li** and **Stephen J. Kanes** are former employees of Sage Therapeutics, Inc. and may hold stock and/or stock options. Dr. Kanes is also an inventor of the patent entitled "Neuroactive steroids, compositions, and uses thereof" (US10940156B2), which relates to methods of using brexanolone to treat certain diseases.

Acknowledgments

Medical writing and editorial assistance were provided by Symbiotix, LLC (Linda M. Ritter, PhD; Hui Zhang, PhD) and funded by Sage Therapeutics, Inc., United States of America.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-5), 5th ed. Arlington, VA.

Bauman, B.L., Ko, J.Y., Cox, S., D'Angelo Mph, D.V., Warner, L., Folger, S., Tevendale, H. D., Coy, K.C., Harrison, L., Barfield, W.D., 2020. Vital signs: postpartum depressive symptoms and provider discussions about perinatal depression - United States, 2018. MMWR Morb. Mortal. Wkly Rep. 69, 575–581. https://doi.org/10.15585/mmwr.mm6919a2.

Martin, J.A., Hamilton, B.E., Osterman, M.J.K., Driscoll, A.K., Drake, P., 2018. Births: final data for 2017. Natl. Vital Stat. Rep. 67, 1–50.

DeSisto, C.L., Kim, S.Y., Sharma, A.J., 2014. Prevalence estimates of gestational diabetes mellitus in the United States, pregnancy risk assessment monitoring system (PRAMS), 2007–2010. Prev. Chronic Dis. 11, E104. https://doi.org/10.5888/pcd11.130415.

Centers for Disease Control and Prevention, 2019. Data on selected pregnancy complications in the United States. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-complications-data.htm. (Accessed 8 April 2022).

Biaggi, A., Conroy, S., Pawlby, S., Pariante, C.M., 2016. Identifying the women at risk of antenatal anxiety and depression: a systematic review. J. Affect. Disord. 191, 62–77. https://doi.org/10.1016/j.jad.2015.11.014.

Moses-Kolko, E.L., Roth, E.K., 2004. Antepartum and postpartum depression: healthy mom, healthy baby. J. Am. Med. Womens Assoc. (1972) 59, 181–191.

Robertson, E., Grace, S., Wallington, T., Stewart, D.E., 2004. Antenatal risk factors for postpartum depression: a synthesis of recent literature. Gen. Hosp. Psychiatry 26, 289–295. https://doi.org/10.1016/j.genhosppsych.2004.02.006.

Yim, I.S., Tanner Stapleton, L.R., Guardino, C.M., Hahn-Holbrook, J., Dunkel Schetter, C., 2015. Biological and psychosocial predictors of postpartum depression: systematic review and call for integration. Annu. Rev. Clin. Psychol. 11, 99–137. https://doi.org/10.1146/annurev-clinpsy-101414-020426.

Barkin, J.L., Wisner, K.L., Bromberger, J.T., Beach, S.R., Wisniewski, S.R., 2016. Factors associated with postpartum maternal functioning in women with positive screens for depression. J. Women's Health (Larchmt) 25, 707–713. https://doi.org/10.1089/jwh.2015.5296.

Bobo, W.V., Yawn, B.P., 2014. Concise review for physicians and other clinicians: postpartum depression. Mayo Clin. Proc. 89, 835–844. https://doi.org/10.1016/j.mayocp.2014.01.027.

Gagliardi, L., Petrozzi, A., Rusconi, F., 2012. Symptoms of maternal depression immediately after delivery predict unsuccessful breast feeding. Arch. Dis. Child. 97, 355–357. https://doi.org/10.1136/adc.2009.179697.

Wouk, K., Stuebe, A.M., Meltzer-Brody, S., 2017. Postpartum mental health and breastfeeding practices: an analysis using the 2010–2011 pregnancy risk assessment monitoring system. Matern. Child Health J. 21, 636–647. https://doi.org/10.1007/s10995-016-2150-6.

Balbierz, A., Bodnar-Deren, S., Wang, J.J., Howell, E.A., 2015. Maternal depressive symptoms and parenting practices 3-months postpartum. Matern. Child Health J. 19, 1212–1219. https://doi.org/10.1007/s10995-014-1625-6.

McLearn, K.T., Minkovitz, C.S., Strobino, D.M., Marks, E., Hou, W., 2006. Maternal depressive symptoms at 2 to 4 months post partum and early parenting practices. Arch. Pediatr. Adolesc. Med. 160, 279–284. https://doi.org/10.1001/archpedi.160.3.279.

Da Costa, D., Dritsa, M., Rippen, N., Lowensteyn, I., Khalife, S., 2006. Health-related quality of life in postpartum depressed women. Arch. Womens Ment. Health 9, 95–102. https://doi.org/10.1007/s00737-005-0108-6.

Nierenberg, A.A., Husain, M.M., Trivedi, M.H., Fava, M., Warden, D., Wisniewski, S.R., Miyahara, S., Rush, A.J., 2010. Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. Psychol. Med. 40, 41–50. https://doi.org/10.1017/S0033291709006011.

Sakurai, H., Suzuki, T., Yoshimura, K., Mimura, M., Uchida, H., 2017. Predicting relapse with individual residual symptoms in major depressive disorder: a reanalysis of the STAR*D data. Psychopharmacology 234, 2453–2461. https://doi.org/10.1007/s00213-017-4634-5.

Hendrick, V., Altshuler, L., Strouse, T., Grosser, S., 2000. Postpartum and nonpostpartum depression: differences in presentation and response to pharmacologic treatment. Depress. Anxiety. 11, 66–72. https://doi.org/10.1002/(sici)1520-6394(2000)11:2<66::aid-da3>3.0.co;2-d.

Nakic Rados, S., Tadinac, M., Herman, R., 2018. Anxiety during pregnancy and postpartum: course, predictors and comorbidity with postpartum depression. Acta Clin. Croat. 57, 39–51. https://doi.org/10.20471/acc.2017.56.04.05.

Ross, L.E., Gilbert Evans, S.E., Sellers, E.M., Romach, M.K., 2003. Measurement issues in postpartum depression part 1: anxiety as a feature of postpartum depression. Arch. Womens Ment. Health 6, 51–57. https://doi.org/10.1007/s00737-002-0155-1.

Postpartum Depression: Action Towards Causes and Treatment Consortium, 2015. Heterogeneity of postpartum depression: a latent class analysis. Lancet Psychiatry 2, 59–67. https://doi.org/10.1016/S2215-0366(14)00055-8.

Dorheim, S.K., Bjorvatn, B., Eberhard-Gran, M., 2014. Can insomnia in pregnancy predict postpartum depression? A longitudinal, population-based study. PLoS One 9, e94674. https://doi.org/10.1371/journal.pone.0094674.

Marques, M., Bos, S., Soares, M.J., Maia, B., Pereira, A.T., Valente, J., Gomes, A.A., Macedo, A., Azevedo, M.H., 2011. Is insomnia in late pregnancy a risk factor for postpartum depression/depressive symptomatology? Psychiatry Res. 186, 272–280. https://doi.org/10.1016/j.psychres.2010.06.029.

Okun, M.L., 2015. Sleep and postpartum depression. Curr. Opin. Psychiatry 28, 490–496. https://doi.org/10.1097/YCO.0000000000000206.

Wolfson, A.R., Crowley, S.J., Anwer, U., Bassett, J.L., 2003. Changes in sleep patterns and depressive symptoms in first-time mothers: last trimester to 1-year postpartum. Behav. Sleep Med. 1, 54–67. https://doi.org/10.1207/S15402010BSM0101_6.

Emamian, F., Khazaie, H., Okun, M.L., Tahmasian, M., Sepehry, A.A., 2019. Link between insomnia and perinatal depressive symptoms: a meta-analysis. J. Sleep Res. 28, e12858 https://doi.org/10.1111/jsr.12858.

Park, E.M., Meltzer-Brody, S., Stickgold, R., 2013. Poor sleep maintenance and subjective sleep quality are associated with postpartum maternal depression symptom severity. Arch. Womens Ment. Health. 16, 539–547. https://doi.org/10.1007/s00737-013-0356-9.

Felder, J.N., Epel, E.S., Neuhaus, J., Krystal, A.D., Prather, A.A., 2022. Randomized controlled trial of digital cognitive behavior therapy for prenatal insomnia symptoms: effects on postpartum insomnia and mental health. Sleep 45. https://doi.org/10.1093/sleep/zsab280.

Kanes, S., Colquhoun, H., Gunduz-Bruce, H., Raines, S., Arnold, R., Schacterle, A., Doherty, J., Epperson, C.N., Deligiannidis, K.M., Riesenberg, R., Hoffmann, E., Rubinow, D., Jonas, J., Paul, S., Meltzer-Brody, S., 2017a. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet 390, 480–489. https://doi.org/10.1016/S0140-6736(17)31264-3.

Sage Therapeutics Inc., 2022. ZULRESSO (brexanolone) Injection for Intravenous Use [Prescribing Information]. Sage Therapeutics, Inc, Cambridge, MA.

Reddy, D.S., Estes, W.A., 2016. Clinical potential of neurosteroids for CNS disorders. Trends Pharmacol. Sci. 37, 543–561. https://doi.org/10.1016/j.tips.2016.04.003.

Edinoff, A.N., Odisho, A.S., Lewis, K., Kaskas, A., Hunt, G., Cornett, E.M., Kaye, A.D., Kaye, A., Morgan, J., Barrilleaux, P.S., Lewis, D., Viswanath, O., Urits, I., 2021. Brexanolone, a GABAA modulator, in the treatment of postpartum depression in adults: a comprehensive review. Front. Psychiatry. 12, 699740 https://doi.org/10.3389/fpsyt.2021.699740.

Fogaca, M.V., Duman, R.S., 2019. Cortical GABAergic dysfunction in stress and depression: new insights for therapeutic interventions. Front. Cell. Neurosci. 13, 87. https://doi.org/10.3389/fncel.2019.00087.

Northoff, G., Sibille, E., 2014. Why are cortical GABA neurons relevant to internal focus in depression? A cross-level model linking cellular, biochemical and neural network findings. Mol. Psychiatry 19, 966–977. https://doi.org/10.1038/mp.2014.68.

Roux, L., Buzsaki, G., 2015. Tasks for inhibitory interneurons in intact brain circuits. Neuropharmacology 88, 10–23. https://doi.org/10.1016/j.neuropharm.2014.09.011.

Duman, R.S., Sanacora, G., Krystal, J.H., 2019. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. Neuron 102, 75–90. https://doi.org/10.1016/j.neuron.2019.03.013.

Lener, M.S., Niciu, M.J., Ballard, E.D., Park, M., Park, L.T., Nugent, A.C., Zarate Jr., C.A., 2017. Glutamate and gamma-aminobutyric acid systems in the pathophysiology of major depression and antidepressant response to ketamine. Biol. Psychiatry 81, 886–897. https://doi.org/10.1016/j.biopsych.2016.05.005.

Luscher, B., Mohler, H., 2019. Brexanolone, a neurosteroid antidepressant, vindicates the GABAergic deficit hypothesis of depression and may foster resilience. F1000Res. 8. https://doi.org/10.12688/f1000research.18758.1.

Gunduz-Bruce, H., Takahashi, K., Huang, M.Y., 2021. Development of neuroactive steroids for the treatment of postpartum depression. J. Neuroendocrinol., e13019 https://doi.org/10.1111/jne.13019.

Maguire, J., Mody, I., 2008. GABA(A)R plasticity during pregnancy: relevance to postpartum depression. Neuron 59, 207–213. https://doi.org/10.1016/j.neuron.2008.06.019.

Rudolph, U., Knoflach, F., 2011. Beyond classical benzodiazepines: novel therapeutic potential of GABAA receptor subtypes. Nat. Rev. Drug Discov. 10, 685–697. https://doi.org/10.1038/nrd3502.

Department of Health and Human Services, 2020. Integrated drug utilization, epidemiology and pharmacovigilance review: benzodiazepine use, misuse, abuse, dependence, withdrawal, morbidity, and mortality. https://www.benzoinfo.com/wp-content/uploads/2020/11/Benzodiazepine-Information-Coalition-FOIA-FDA-.pdf.

Meltzer-Brody, S., Colquhoun, H., Riesenberg, R., Epperson, C.N., Deligiannidis, K.M., Rubinow, D.R., Li, H., Sankoh, A.J., Clemson, C., Schacterle, A., Jonas, J., Kanes, S., 2018. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet 392, 1058–1070. https://doi.org/10.1016/S0140-6736(18)31551-4.

Kanes, S.J., Colquhoun, H., Doherty, J., Raines, S., Hoffmann, E., Rubinow, D.R., Meltzer-Brody, S., 2017b. Open-label, proof-of-concept study of brexanolone in the treatment of severe postpartum depression. Hum. Psychopharmacol. 32 https://doi.org/10.1002/hup.2576.

Kroska, E.B., Stowe, Z.N., 2020. Postpartum depression: identification and treatment in the clinic setting. Obstet. Gynecol. Clin. N. Am. 47, 409–419. https://doi.org/10.1016/j.ogc.2020.05.001.

De Crescenzo, F., Perelli, F., Armando, M., Vicari, S., 2014. Selective serotonin reuptake inhibitors (SSRIs) for post-partum depression (PPD): a systematic review of randomized clinical trials. J. Affect. Disord. 152–154, 39–44. https://doi.org/10.1016/j.jad.2013.09.019.

Gerbasi, M.E., Meltzer-Brody, S., Acaster, S., Fridman, M., Bonthapally, V., Hodgkins, P., Kanes, S.J., Eldar-Lissai, A., 2021. Brexanolone in postpartum depression: post hoc analyses to help inform clinical decision-making. J. Women's Health (Larchmt) 30, 385–392. https://doi.org/10.1089/jwh.2020.8483.

Holbrook, A.M., Crowther, R., Lotter, A., Cheng, C., King, D., 2000. Meta-analysis of benzodiazepine use in the treatment of insomnia. CMAJ 162, 225–233.

Mitte, K., Noack, P., Steil, R., Hautzinger, M., 2005. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. J. Clin. Psychopharmacol. 25, 141–150. https://doi.org/10.1097/01.jcp.0000155821.74832.f9.

Bobo, W.V., Anglero, G.C., Jenkins, G., Hall-Flavin, D.K., Weinshilboum, R., Biernacka, J. M., 2016. Validation of the 17-item Hamilton depression rating scale definition of response for adults with major depressive disorder using equipercentile linking to clinical global impression scale ratings: analysis of pharmacogenomic research network antidepressant medication pharmacogenomic study (PGRN-AMPS) data. Hum. Psychopharmacol. 31, 185–192. https://doi.org/10.1002/hup.2526.

Montgomery, S.A., Herman, B.K., Schweizer, E., Mandel, F.S., 2009. The efficacy of pregabalin and benzodiazepines in generalized anxiety disorder presenting with high levels of insomnia. Int. Clin. Psychopharmacol. 24, 214–222. https://doi.org/10.1097/YIC.0b013e32832dceb9.

Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., McGrath, P.J., Rosenbaum, J.F., Sackeim, H.A., Kupfer, D.J., Luther, J., Fava, M., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am. J. Psychiatry 163, 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905.

Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M., Team, S.D.S., 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am. J. Psychiatry 163, 28–40. https://doi.org/10.1176/appi.ajp.163.1.28.

Patterson, R., Krohn, H., Richardson, E., Kimmel, M., Meltzer-Brody, S., 2021. A brexanolone treatment program at an academic medical center: patient selection, 90-day posttreatment outcomes, and lessons learned. J. Acad. Consult. Liaison Psychiatry 63, 14–22. https://doi.org/10.1016/j.jaclp.2021.08.001.

Krystal, A.D., Prather, A.A., Ashbrook, L.H., 2019. The assessment and management of insomnia: an update. World Psychiatry 18, 337–352. https://doi.org/10.1002/wps.20674.

McEvoy, K.M., Rayapati, D., Washington Cole, K.O., Erdly, C., Payne, J.L., Osborne, L.M., 2019. Poor postpartum sleep quality predicts subsequent postpartum depressive symptoms in a high-risk sample. J. Clin. Sleep Med. 15, 1303–1310. https://doi.org/10.5664/jcsm.7924.

Manber, R., Chambers, A.S., 2009. Insomnia and depression: a multifaceted interplay. Curr. Psychiatry Rep. 11, 437–442. https://doi.org/10.1007/s11920-009-0066-1.

Manber, R., Blasey, C., Arnow, B., Markowitz, J.C., Thase, M.E., Rush, A.J., Dowling, F., Koscis, J., Trivedi, M., Keller, M.B., 2005. Assessing insomnia severity in depression: comparison of depression rating scales and sleep diaries. J. Psychiatr. Res. 39, 481–488. https://doi.org/10.1016/j.jpsychires.2004.12.003.

Okun, M.L., Kiewra, K., Luther, J.F., Wisniewski, S.R., Wisner, K.L., 2011. Sleep disturbances in depressed and nondepressed pregnant women. Depress. Anxiety 28, 676–685. https://doi.org/10.1002/da.20828.

Stone, K.C., Salisbury, A.L., Miller-Loncar, C.L., Mattera, J.A., Battle, C.L., Johnsen, D.M., O'Grady, K.E., 2017. Pregnancy and postpartum antidepressant use moderates the effects of sleep on depression. Arch Womens Ment Health. 20, 621–632. https://doi.org/10.1007/s00737-017-0726-9.

Furukawa, T.A., Cipriani, A., Atkinson, L.Z., Leucht, S., Ogawa, Y., Takeshima, N., Hayasaka, Y., Chaimani, A., Salanti, G., 2016. Placebo response rates in antidepressant trials: a systematic review of published and unpublished double-blind randomised controlled studies. Lancet Psychiatry 3, 1059–1066. https://doi.org/10.1016/s2215-0366(16)30307-8.

Khan, A., Fahl Mar, K., Faucett, J., Khan Schilling, S., Brown, W.A., 2017. Has the rising placebo response impacted antidepressant clinical trial outcome? Data from the US Food and Drug Administration 1987–2013. World Psychiatry 16, 181–192. https://doi.org/10.1002/wps.20421.

Walsh, B.T., Seidman, S.N., Sysko, R., Gould, M., 2002. Placebo response in studies of major depression: variable, substantial, and growing. JAMA 287, 1840–1847. https://doi.org/10.1001/jama.287.14.1840.

Undurraga, J., Baldessarini, R.J., 2012. Randomized, placebo-controlled trials of antidepressants for acute major depression: thirty-year meta-analytic review. Neuropsychopharmacology 37, 851–864. https://doi.org/10.1038/npp.2011.306.