Psychiatry Research 279 (2019) 83–89

Contents lists available at ScienceDirect

Psychiatry Research

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

Review article

Brexanolone for postpartum depression: A meta-analysis of randomized controlled studies

Wei Zheng[a], Dong-Bin Cai[b], Wei Zheng[c], Kang Sim[d], Gabor S. Ungvari[e,f], Xiao-Jiang Peng[g], Yu-Ping Ning[a], Gang Wang[h,i,**], Yu-Tao Xiang[j,k,*]

[a] The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China
[b] Shenzhen Traditional Chinese Medicine Hospital, Shenzhen, China
[c] School of Medicine, Xiamen University, Xiamen, China
[d] Institute of Mental Health, Buangkok Green Medical Park, Singapore
[e] The University of Notre Dame Australia, Fremantle, Australia
[f] Division of Psychiatry, School of Medicine, University of Western Australia, Perth, Australia
[g] Guangzhou Civil Aviation College, Guangzhou, China
[h] The National Clinical Research Center for Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China
[i] Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital & the Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, China
[j] Unit of Psychiatry, Institute of Translational Medicine, Faculty of Health Sciences, University of Macau, Avenida da Universidade, 3/F, Building E12, Taipa, Macao SAR, China
[k] Center for Cognition and Brain Sciences, University of Macau, Macao SAR, China

ARTICLE INFO

Keywords:
Brexanolone
Postpartum depression
Meta-analysis

ABSTRACT

Objectives: To systematically examine the effectiveness, tolerability, and safety of brexanolone infusion in treating postpartum depression (PPD).
Methods: Randomized controlled trials (RCTs) were included.
Results: Two articles reporting 3 RCTs with 4 active arms (n = 267) covering 156 women with PPD receiving brexanolone infusion and 111 women with PPD on placebo were included. Compared with placebo, women suffering from PPD who received brexanolone had significantly greater response that started after 24 h (risk ratio (RR) = 1.34, 95%CI 1.03–1.73), peaked at 36 h (RR = 1.50, 95%CI 1.06–2.13, P = 0.02) and lasted until Day 7 (RR = 1.32, 95%CI 1.01–1.73). Similarly, PPD women treated with brexanolone had significantly greater remission starting at 24 h (RR = 1.86, 95%CI 1.03–3.34), peaking at 60 h (RR = 2.20, 95%CI 1.31–3.70) and lasting until 72 h (RR = 1.96, 95%CI 1.41–2.72). Brexanolone infusion led to significantly higher rate of discontinuation for any reasons (RR = 2.68, 95%CI 1.35–5.32). Discontinuation due to intolerability and adverse drug reactions was similar between the active agent and placebo.
Conclusion: A single brexanolone infusion appears to have ultra-rapid antidepressant effect for PPD, lasting for up to 1 week. The short and long-term therapeutic effect of brexanolone needs to be examined in large-scale RCTs.

1. Introduction

Postpartum depression (PPD) is a common condition that occurs during the postnatal period with significant impact on maternal and infant wellbeing (Ko et al., 2017). PPD approximately affects 12–20% of mothers (Woody et al., 2017; Fisher et al., 2012), particularly in low- and middle-income countries, and those with a history of psychiatric disorders (Fisher et al., 2012). Depressive symptoms in woman with persistent PPD could last up to 11 years after childbirth and negatively affect the whole family (Netsi et al., 2018). Severe PPD increases the risk of suicidal behavior (Johannsen et al., 2016; Comtois et al., 2008).

The rapid perinatal changes in reproductive hormones including allopregnanolone is thought to underlie the pathogenesis of PPD (Schiller et al., 2015; Bloch et al., 2000). Allopregnanolone is a potent positive allosteric modulator of the gamma-aminobutyric acid type A ($GABA_A$) receptors (Majewska et al., 1986). Reduced level of

* Correspondence author.
** Corresponding author at: Beijing Anding Hospital, Beijing, China.
E-mail addresses: gangwangdoc@gmail.com (G. Wang), xyutly@gmail.com (Y.-T. Xiang).

https://doi.org/10.1016/j.psychres.2019.07.006
Received 28 April 2019; Received in revised form 2 July 2019; Accepted 2 July 2019
Available online 04 July 2019

allopregnanolone in the peripheral blood or cerebrospinal fluid is associated with increased risk of anxiety and depression (Schule et al., 2014), and antidepressant treatment increases the level of allopregnanolone (Romeo et al., 1998). As one of the metabolites of progesterone, the level of allopregnanolone is probably altered in women with depressive symptoms (Girdler et al., 2001,2012).

Allopregnanolone and other progesterone metabolites change significantly in the course of pregnancy and after childbirth (Mostallino et al., 2009). The increase of plasma allopregnanolone concentration occurs with the rise of progesterone throughout pregnancy (Luisi et al., 2000). In the third trimester, both allopregnanolone and progesterone reach the highest concentrations in plasma (Luisi et al., 2000), and abruptly decrease after childbirth, particularly for women with maternity "blues" (Nappi et al., 2001). $GABA_A$ receptors fail to adapt to the sudden changes of allopregnanolone levels at parturition, which is thought to play an important role in triggering PPD (Maguire and Mody, 2008). Elevated allopregnanolone serum concentrations may lower the risk of depressed mood during pregnancy (Hellgren et al., 2014). Neuroactive steroids act as allosteric modulators in the GABA system (Deligiannidis et al., 2016), thus they may play a role in the pathophysiology of PPD. Therefore synthetic neuroactive steroids and their analogs (e.g., allopregnanolone) have been suggested as potential treatment choices for PPD (Frieder et al., 2019).

Due to the low aqueous solubility and rapid metabolization of oral allopregnanolone, brexanolone (USAN; formerly SAGE-547 injection), a soluble, proprietary, β-cyclodextrin-based parenterally administered formulation of allopregnanolone, was developed (Meltzer-Brody et al., 2018; Kanes et al., 2017a,b). An open-label study found that a single infusion of brexanolone had rapid antidepressant effects for severe PPD with good safety (Kanes et al., 2017b), which was confirmed in two double-blind, randomized clinical trials (RCTs) (Meltzer-Brody et al., 2018; Kanes et al., 2017a).

To date no meta-analysis or systematic review on brexanolone for PPD has been published. Thus, a systematic review and meta-analysis was conducted to evaluate the efficacy and safety of a single infusion of brexanolone for PPD.

2. Methods

2.1. Data sources and search strategy

This meta-analysis was conducted following the recommendations of preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist. Both Chinese (WanFang and Chinese Journal Net) and English (PubMed, Cochrane Library, PsycINFO, EMBASE) databases were independently and systematically searched from their commencement until March 20th, 2019 by two co-authors [DBC and WZ (Xiamen University)] to identify studies on the efficacy and safety of brexanolone treatment for PPD using the following search terms "("Brexanolone"[Mesh] OR SAGE-547 OR Zulresso) AND ("depression"[Mesh] OR depression OR depressive OR depressed OR melancholia)". They also inspected the reference list of all included studies and relevant reviews for additional studies.

2.2. Eligibility criteria and data extraction

According to the PICOS acronym, the inclusion criteria of this meta-analysis were: **P**articipants: patients with PPD diagnosed according to any international diagnostic criteria. **I**ntervention versus **C**omparison: brexanolone injection/infusion versus placebo. **O**utcomes: the primary outcomes were response according to study-defined criteria (e.g., ≥50% reduction of the Hamilton Depression Rating Scale (HAMD-17, HAMD-21 or HAMD-24) total score (Hamilton, 1960) and remission based on study-defined criteria (e.g., HAMD total score ≤7) at study-defined time points. Key secondary outcomes were the change of depressive symptoms measured by standardized rating scales, discontinuation due to any reason, and adverse drug reaction (ADRs). ***S***tudy design: RCTs on brexanolone injection/infusion versus placebo for PPD. Data were extracted independently by two co-authors [DBC and WZ (Xiamen University)]. Inconsistencies were resolved by a discussion with a senior investigator [WZ (Guangzhou Huiai Hospital)]. Whenever meta-analyzable data were not reported in the included RCTs, the first/corresponding authors were contacted by email for more information. Data were extracted from the graphs or figures of the included RCTs by using the WebPlotDigitizer, Version 4.1 (https://automeris.io/WebPlotDigitizer/). Two doses of brexanolone injections/infusion were examined in one study (Meltzer-Brody et al., 2018). The data of the two brexanolone groups were extracted and analyzed with the placebo group separately in two subgroups. In order not to inflate the number of patients in the placebo group, following another meta-analysis (Gu et al., 2018) half of the patients in the placebo group were assigned into each subgroup (i.e., sample size of patients in the placebo group/2) for continuous outcomes.

2.3. Risk assessment and publication bias

The same two co-authors independently assessed the methodological quality of RCTs using the Cochrane Collaboration's risk-of-bias tool (Higgins and Higgins, 2008) and the Jadad scale (Jadad et al., 1996). Studies were considered "high quality" when a Jadad total score was more than 3. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Balshem et al., 2011; Atkins et al., 2004) was employed to examine the quality of evidence of all meta-analytical outcomes. Publication bias for primary outcomes was examined using the funnel plots and the Egger's test (Egger et al., 1997) if there were more than 10 studies in the meta-analysis (Sterne et al., 2011).

2.4. Statistical analysis

For continuous and dichotomous outcomes, standardized mean difference (SMD) and risk ratio (RR) with 95% confidence intervals (CIs) were calculated, respectively with the Review Manager, Version 5.3 software. All meta-analytic primary and secondary outcomes were analyzed using the random effects model (DerSimonian and Laird, 1986). If the RR value was significant, number-needed-to-treat/harm (NNT/NNH) was also calculated. Heterogeneity was expressed by τ^2, I^2, Q and p values (Higgins and Thompson, 2002). In case of $I^2 \geq 50\%$ for the primary outcome, a sensitivity analysis or subgroup analyses were conducted to determine the sources of heterogeneity. All analyses were considered significant with alpha set at 0.05 (two-sided).

3. Results

3.1. Literature search

The search yielded 471 hits and having eliminated irrelevant publications eventually 2 articles (Meltzer-Brody et al., 2018; Kanes et al., 2017a) reporting 3 RCTs with 4 active arms were included in the meta-analysis (Fig. 1).

3.2. Patient and study characteristics

Table 1 shows the 3 RCTs that compared brexanolone injection/infusion (n = 156) with placebo (n = 111) for 267 women with moderate and severe PPD. Their weighted age was 27.7 (range = 27.4 to 28.1) years. The treatment and study duration in the 3 RCTs conducted in USA were 60 h and 30 days, respectively. Brexanolone injection/infusion is a sterile solution of 5 mg/ml allopregnanolone in 250 mg/ml sulfobutylether-β-cyclodextrin.

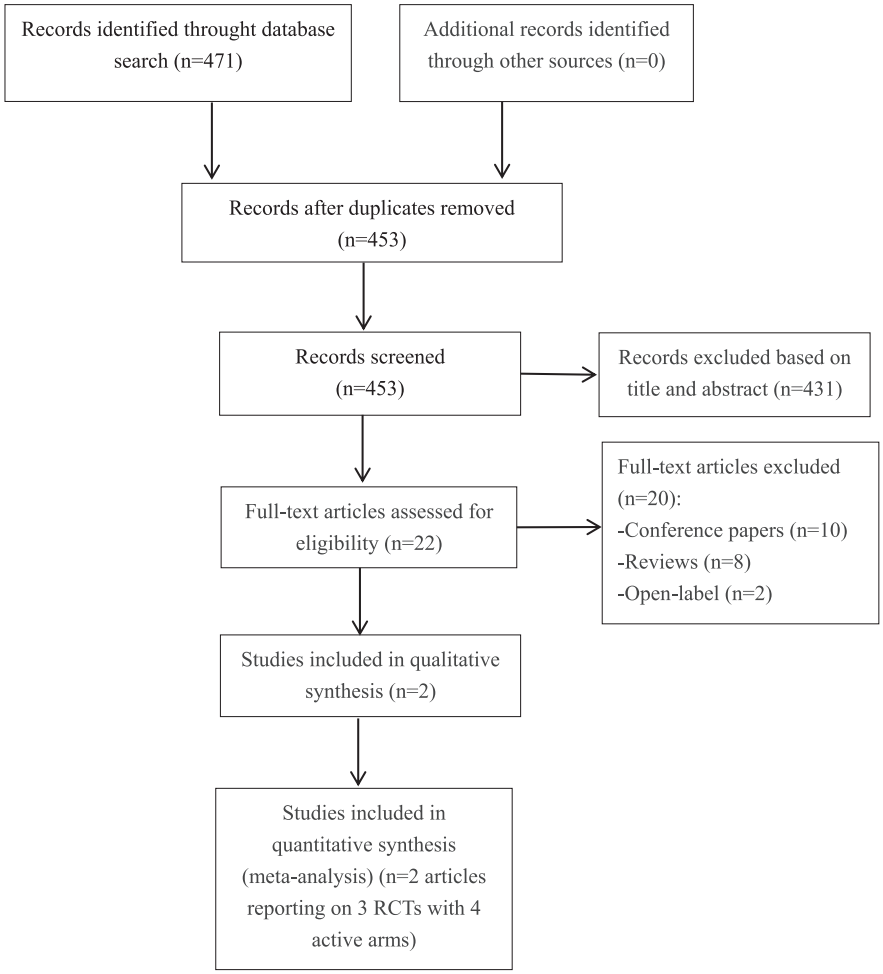

Fig. 1. PRISMA flow diagram.

3.3. Treatment response and remission

Compared with placebo, brexanolone infusion produced significantly better response that started at 24 h (brexanolone infusion = 52.9% vs. placebo = 39.3%; RR = 1.34, 95%CI 1.03–1.73, $P = 0.03$; NNT = 7; heterogeneity: $\tau^2 = 0.00$, $I^2 = 3\%$, $Q = 3.11$, $P = 0.38$), peaked at 36 h (brexanolone infusion = 65% vs. placebo = 44.7%; RR = 1.50, 95% CI 1.06–2.13, $P = 0.02$; NNT = 4; heterogeneity: $\tau^2 = 0.07$, $I^2 = 57\%$, $Q = 6.92$, $P = 0.07$) and lasted until day 7 (brexanolone infusion = 63.5% vs. placebo = 47.3%; RR = 1.32, 95%CI 1.01–1.73, $P = 0.04$; NNT = 5; heterogeneity: $\tau^2 = 0.02$, $I^2 = 30\%$, $Q = 4.29$, $P = 0.23$) (Table 2).

Similarly, brexanolone infusion achieved significantly greater short-term remission that started at 24 h (brexanolone infusion = 24.3% vs. placebo = 12.7%; RR = 1.86, 95%CI 1.03–3.34, $P = 0.04$; NNT = 8; heterogeneity: $\tau^2 = 0.05$, $I^2 = 13\%$, $Q = 3.43$, $P = 0.33$), peaked at 60 h (brexanolone infusion = 50.7% vs. placebo = 24.0%; RR = 2.20, 95%CI 1.31–3.70, $P = 0.003$; NNT = 3; heterogeneity: $\tau^2 = 0.12$, $I^2 = 45\%$, $Q = 5.50$, $P = 0.14$) and lasted until 72 h (3 brexanolone infusion = 48.6% vs. placebo = 24.0%; RR = 1.96, 95%CI 1.41%–2.72, $P < 0.0001$; NNT = 4; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0\%$, $Q = 1.83$, $P = 0.61$) (Table 2).

3.4. Changes of depressive symptoms

In all three RCTs brexanolone infusion for PPD caused clinically meaningful, significant reduction of the HAMD total score at 60 h when compared to placebo. Brexanolone had rapid onset of action and durable treatment response. However, only baseline [mean +/− standard deviation (SD)] and change [least squares mean +/− standard error (SE)] data were used to assess depressive symptoms, which were not meta-analyzable.

3.5. Discontinuation and ADRs rate

Brexanolone injection/infusion led to significantly higher rate of discontinuation due to any reason (3 RCTs, brexanolone infusion = 17.3% vs. placebo = 6.4%; RR = 2.68, 95%CI: 1.35–5.32, $P = 0.005$; NNH = 11; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0\%$, $Q = 0.12$, $P = 0.94$) (Fig. 2). Discontinuation due to intolerability (brexanolone infusion = 2.1% vs. placebo = 1.3%; RR = 1.31, 95%CI 0.24–7.24, $P = 0.75$; NNH = non-significant; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0\%$, $Q = 1.49$, $P = 0.47$) was similar between brexanolone and placebo groups. Discontinuation due to inefficacy was not reported.

Meta-analysis of ADRs (Table 2) were not significantly different between brexanolone and placebo ($P = 0.12$ to 0.98). No death or other unexpected ADRs were reported.

3.6. Assessment of study quality and publication bias

The risk of bias assessment is presented in Supplemental Fig. 1. Jadad score was 5 in all 3 RCTs indicating high quality (Table 1). The overall evidence level of all 50 outcomes ranged from low (4%, 2/50), to moderate (66%, 33/50) to high (30%, 15/50) with the GRADE approach (Supplemental Table 1). Publication bias was not performed due to the small number of trials.

Table 1
Patient and treatment characteristics of the included studies.

Study (Country)	Number of patients	Blinding	Analyses	Trial Duration (days)	BRX infusion duration (hour)	Setting (%)	Diagnosis (%)	Diagnostic criteria	Illness duration	Age[a]: yrs (range)	Control-Group: Dose (mg/d): mean (range)	Intervention-Group: Dose (μg/kg/hour): mean (range)		**Jadad score**
Kanes et al., 2017a (USA)	T: 21, C: 10, I: 11	DB	ITT	30	60	NR[b]	PPD (100)	DSM-IV	NR	28.1 (18–45)	ADs[c]: Ø = NR (NR)	ADs[C]: Ø = NR (NR)	BRX[d]: Ø = NR (30–90)	5
Meltzer-Brody et al., 2018 –Study −1 (USA)	T: 138, C: 46, I: 92	DB	mITT	30	60	Clinical research centres and specialised psychiatric units	PPD (100)	DSM-IV	NR	27.4 (18–45)	ADs[e]: Ø = NR (NR)	ADs[e]: Ø = NR (NR) ADs[g]: Ø = NR (NR)	BRX[f]: Ø = NR (30–60) BRX[d]: Ø = NR (30–90)	5
Meltzer-Brody et al., 2018-study-2 (USA)	T: 108, C: 54, I: 54	DB	mITT	30	60	Clinical research centres and specialised psychiatric units	PPD (100)	DSM-IV	NR	27.9 (18–45)	ADs[g]: Ø = NR (NR)	ADs[h]: Ø = NR (NR)	BRX[d]: Ø = NR (30–90)	5

Abbreviations: ADs = antidepressants; BRX = brexanolone; C = control; DB = double blind; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th edition; I = intervention; ITT = intent-to-treat; mITT = modified intent-to-treat; NR = not report; PPD = post-partum depression; T = total; yrs = years.

[a] Available data were extracted based on mean baseline value of each included trials.

[b] Subjects remained as in-patients during the study treatment period, which is approximately 60 h/2.5 days in duration. The screening period assessments may have been conducted on an in-patient or an out-patient basis. The follow-up period assessments were conducted on an out-patient basis.

[c] Only 3 patients in each group were treated with antidepressants.

[d] Infusion was administered under the following schedule: 30 μg/kg/h (0–4 h); 60 μg/kg/h (4–24 h); 90 μg/kg/h (24–52 h); 60 μg/kg/h (52–56 h); 30 μg/kg/h (56–60 h).

[e] Only 12 patients with baseline antidepressant use.

[f] Infusion was administered under the following schedule: 30 μg/kg/h (0–4 h); 60 μg/kg/h (4–56 h); 30 μg/kg/h (56–60 h).

[g] Only 10 patients with baseline antidepressant use.

[h] Only 9 patients with baseline antidepressant use.

Table 2
Brexanolone infusion for postpartum depression: primary and secondary outcomes.

Variables Clinical efficacy Response:	Active arms (subjects)	RRs (95%CI)	I^2 (%)	*P*	NNT/NNH	95%CI
Response at 2 h	4 (290)	1.06 (0.40, 2.80)	0	0.91	NA	NA
Response at 4 h	4 (290)	1.25 (0.71, 2.18)	0	0.44	NA	NA
Response at 8 h	4 (290)	1.20 (0.80, 1.80)	0	0.38	NA	NA
Response at 12 h	4 (290)	0.96 (0.68, 1.36)	0	0.81	NA	NA
Response at 24 h	4 (290)	1.34 (1.03, 1.73)	3	**0.03**	7	4–100
Response at 36 h	4 (290)	1.50 (1.06, 2.13)	57	**0.02**	4	2–50
Response at 48 h	4 (290)	1.40 (1.16, 1.70)	0	**0.0005**	5	3–10
Response at 60 h	4 (290)	1.40 (1.19, 1.66)	0	**<0.0001**	4	3–8
Response at 72 h	4 (290)	1.37 (1.15, 1.64)	8	**0.0005**	4	3–9
Response at day 7	4 (290)	1.32 (1.01, 1.73)	30	**0.04**	5	3–50
Response at day 30	4 (290)	1.37 (0.93, 2.03)	77	0.12	NA	NA
Remmison:						
Remmison at 2 h	2 (125)	1.04 (0.07, 16.18)	NA	0.98	NA	NA
Remmison at 4 h	2 (125)	0.81 (0.17, 3.75)	6	0.78	NA	NA
Remmison at 8 h	4 (290)	1.14 (0.28, 4.60)	28	0.86	NA	NA
Remmison at 12 h	4 (290)	1.15 (0.28, 4.75)	34	0.84	NA	NA
Remmison at 24 h	4 (290)	1.86 (1.03, 3.34)	13	**0.04**	8	4-+ ∞
Remmison at 36 h	4 (290)	1.59 (1.02, 2.48)	1	**0.04**	8	4–100
Remmison at 48 h	4 (290)	2.18 (1.49, 3.18)	0	**<0.0001**	4	3–8
Remmison at 60 h	4 (290)	2.20 (1.31, 3.70)	45	**0.003**	3	2–7
Remmison at 72 h	4 (290)	1.96 (1.41, 2.72)	0	**<0.0001**	4	3–7
Remmison at day 7	4 (290)	1.33 (0.72, 2.46)	61	0.36	NA	NA
Remmison at day 30	4 (290)	1.32 (0.76, 2.32)	71	0.32	NA	NA
ADRs						
Rash	4 (290)	0.60 (0.14, 2.52)	0	0.49	NA	NA
Fatigue	3 (269)	2.06 (0.52, 8.18)	0	0.30	NA	NA
Dizziness	4 (290)	2.05 (0.71, 5.92)	37	0.19	NA	NA
Dry mouth	3 (206)	3.75 (0.77, 18.14)	0	0.10	NA	NA
Abonormal dreams	4 (290)	0.43 (0.10, 1.93)	0	0.27	NA	NA
Headache/tension headache	4 (290)	1.09 (0.63, 1.89)	0	0.76	NA	NA
Infusion site pain	4 (290)	1.84 (0.63, 5.41)	0	0.27	NA	NA
Somenolence	4 (290)	1.93 (0.84, 4.47)	0	0.12	NA	NA
Abodominal pain	4 (290)	0.74 (0.20, 2.65)	0	0.64	NA	NA
Anxiety	3 (186)	0.36 (0.06, 2.23)	0	0.27	NA	NA
Dizziness postural	3 (186)	0.77 (0.13, 4.75)	0	0.78	NA	NA
Hot flush	2 (125)	1.72 (0.22, 13.43)	0	0.60	NA	NA
Infusion site extrasation	4 (290)	0.50 (0.11, 2.27)	0	0.37	NA	NA
Localised oedema/infusion site oedema	2 (125)	1.03 (0.11, 9.49)	0	0.98	NA	NA
Pain in extremity	2 (125)	1.03 (0.11, 9.49)	0	0.98	NA	NA
Pyrexia	2 (125)	3.20 (0.35, 29.33)	0	0.30	NA	NA
Sedation	4 (290)	2.37 (0.60, 9.39)	0	0.22	NA	NA
Sinus tachycardia/tachycardia	3 (186)	1.52 (0.30, 7.63)	0	0.61	NA	NA
Vertigo	2 (125)	3.20 (0.35, 29.33)	0	0.30	NA	NA
Nausea/vomiting	4 (290)	0.55 (0.14, 2.19)	42	0.39	NA	NA
Back pain	3 (269)	0.79 (0.18, 3.48)	0	0.76	NA	NA
Alanine aminotransferase increased	3 (269)	0.55 (0.10, 3.14)	0	0.50	NA	NA
Asparatate aminotransferase increased	3 (269)	0.55 (0.10, 3.14)	0	0.50	NA	NA
Loss of consciousness	2 (165)	4.28 (0.48, 37.91)	0	0.19	NA	NA
Device infusion issue	2 (165)	3.26 (0.35, 30.73)	0	0.30	NA	NA
Oropharyngeal pain	3 (269)	2.64 (0.52, 13.44)	0	0.24	NA	NA
Infusion site erythema	2 (188)	3.13 (0.33, 29.55)	0	0.32	NA	NA
Syncope	2 (188)	3.13 (0.33, 29.55)	0	0.32	NA	NA
Infusion site pruritus	3 (269)	0.74 (0.12, 4.63)	0	0.75	NA	NA

Bolded *p*-values: $P < 0.05$.
Abbreviations: ADRs = adverse drug reactions; CI = confidence interval; NA = not applicable; NNT = number-needed-to-treat; NNH = number-needed-to-harm; RRs = risk ratio.

4. Discussion

In this meta-analysis of 3 RCTs ($n = 267$), brexanolone infusion for women with moderate to severe PPD was significantly superior to placebo regarding antidepressant response and short-term (up to 72 h) remission. The statistically significant superiority of brexanolone started as early as within 24 h, peaked on 36 h, and lasted at least 7 days. Similarly, short-term remission started at 24 h, peaked at 60 h and lasted until 72 h. Effect sizes were large for response (NNT = 4–7) and remission (NNT = 3–8). At the end of the 60 h post-treatment, 77.9% of patients responded and 50.7% remitted on brexanolone infusion compared with the corresponding figures of 55.3% and 24.0% on placebo. Importantly, findings in most meta-analyzable outcomes were homogeneous. Although administration of brexanolone led to significantly higher rate of discontinuation for any reason (NNH = 11), the rates of ADRs and discontinuation due to intolerability were similar between the brexanolone and placebo groups.

Compared to other types of depression, PPD is less likely to respond to antidepressants and frequently requires polypharmacy (Hendrick et al., 2000). This meta-analysis confirmed the rapid antidepressant response of brexanolone infusion first reported in an open label trial of severe PPD (Kanes et al., 2017b). A rapid onset of antidepressant action is crucial because it give quick relief for the patients and their families (Kanes et al., 2017a) and early improvement is a

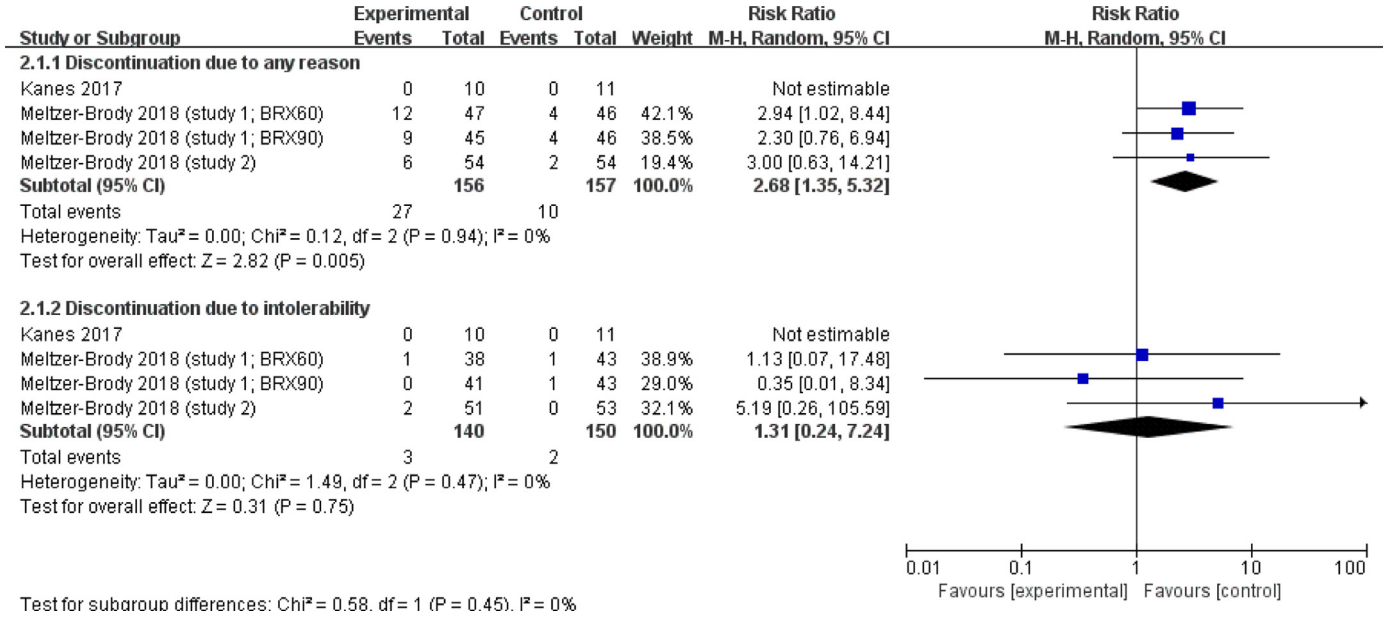

Fig. 2. Brexanolone infusion for postpartum depression: Forest plot for discontinuation.

strong determinant for continuing response or remission (van Calker et al., 2009).

Low allopregnanolone level during pregnancy could predict the increased risk of PPD (Osborne et al., 2017), and following successful antidepressant therapy, blood allopregnanolone level increases (Schule et al., 2007; Eser et al., 2006). The mechanism of antidepressive action of brexanolone for PPD is still unknown. A possible explanation is that PPD is mainly stress-related causing dysfunction in the neurosteroid and GABAergic systems (Maguire, 2019). Stress adversely affects the hypothalamic-pituitary-adrenal (HPA) axis and alter neurosteroid signaling, which further affects GABAergic inhibition in neurocircuits relevant to the pathomechanism of depression (Maguire, 2019). Allopregnanolone could reduce stress level and regulate neuronal functions, which, in turn, could improve mood that co-occurs with changes in reproductive endocrine functions (Schiller et al., 2014).

Apart from the rapid antidepressant response, this meta-analysis found that the response to brexanolone infusion could last at least for a week, similar to the antidepressant response of a single ketamine infusion in major depressive disorder (MDD) (Kishimoto et al., 2016). A meta-analysis concluded that ketamine caused significant response within 40–60 min (NNT = 3) that peaked at 230–240 min (NNT = 2) and lasted until Day 7 (NNT = 5) (Kishimoto et al., 2016). Brexanolone infusion was considered safe with comparable rates of ADRs compared to placebo. Although the rate of discontinuation for any reason was higher in the brexanolone group, the rate of discontinuation due to intolerability and inefficacy was similar between the two groups.

Several methodological limitations of this study need to be acknowledged. First, only 2 articles with three RCTs were included which did not allow to subgroup, sensitivity and meta-regression analyses. Similarly, publication bias for the primary outcomes could not be examined. Second, data on the change of depressive symptoms, were not available even after the authors were contacted, thus pooling the changes of depressive symptoms was not possible. Third, to date, no head-to-head trial comparing brexanolone with other antidepressants has been published. Finally, the 3 RCTs administered brexanolone infusion for moderate to severe PPD, thus limiting the generalizability of the findings to mild PDD.

In conclusion, brexanolone injection/infusion appears to be efficacious and safe for women with moderate to severe PPD based on limited RCT data. Larger sample sizes, multi-centre design, longer follow-up period and double-blind assessment should be adopted in future RCTs of brexanolone to examine its effectiveness, tolerability, and safety.

Acknowledgements

The study was supported by the University of Macau (SRG2014-00019-FHS; MYRG2015-00230-FHS; MYRG2016-00005-FHS), the Affiliated Brain Hospital of Guangzhou Medical University (2016YFC0906302; 2014Y2-00105; 2015BAI13B02), and Science and Technology Department of Guangdong Province major science and technology (2016B010108003). The University of Macau and the Affiliated Brain Hospital of Guangzhou Medical University had no role in the study design, generating or interpreting the results and publication of the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.07.006.

References

Atkins, D., Best, D., Briss, P.A., Eccles, M., Falck-Ytter, Y., Flottorp, S., Guyatt, G.H., Harbour, R.T., Haugh, M.C., Henry, D., Hill, S., Jaeschke, R., Leng, G., Liberati, A., Magrini, N., Mason, J., Middleton, P., Mrukowicz, J., O'Connell, D., Oxman, A.D., Phillips, B., Schunemann, H.J., Edejer, T., Varonen, H., Vist, G.E., Williams Jr., J.W., Zaza, S., 2004. Grading quality of evidence and strength of recommendations. BMJ 328 (7454), 1490.

Balshem, H., Helfand, M., Schunemann, H.J., Oxman, A.D., Kunz, R., Brozek, J., Vist, G.E., Falck-Ytter, Y., Meerpohl, J., Norris, S., Guyatt, G.H., 2011. GRADE guidelines: 3. Rating the quality of evidence. J. Clin. Epidemiol. 64 (4), 401–406.

Bloch, M., Schmidt, P.J., Danaceau, M., Murphy, J., Nieman, L., Rubinow, D.R., 2000. Effects of gonadal steroids in women with a history of postpartum depression. Am. J. Psychiatry 157 (6), 924–930.

Comtois, K.A., Schiff, M.A., Grossman, D.C., 2008. Psychiatric risk factors associated with postpartum suicide attempt in Washington State, 1992–2001. Am. J. Obstet. Gynecol. 199 (2), 120 e121-125.

Deligiannidis, K.M., Kroll-Desrosiers, A.R., Mo, S., Nguyen, H.P., Svenson, A., Jaitly, N., Hall, J.E., Barton, B.A., Rothschild, A.J., Shaffer, S.A., 2016. Peripartum neuroactive steroid and gamma-aminobutyric acid profiles in women at-risk for postpartum depression. Psychoneuroendocrinology 70, 98–107.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control Clin. Trials 7 (3), 177–188.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315 (7109), 629–634.

Eser, D., Schule, C., Baghai, T.C., Romeo, E., Rupprecht, R., 2006. Neuroactive steroids in depression and anxiety disorders: clinical studies. Neuroendocrinology 84 (4), 244–254.

Fisher, J., Cabral de Mello, M., Patel, V., Rahman, A., Tran, T., Holton, S., Holmes, W., 2012. Prevalence and determinants of common perinatal mental disorders in women in low- and lower-middle-income countries: a systematic review. Bull. World Health Organ. 90 (2), 139g–149g.
Frieder, A., Fersh, M., Hainline, R., Deligiannidis, K.M., 2019. Pharmacotherapy of postpartum depression: current approaches and novel drug development. CNS Drugs 33 (3), 265–282.
Girdler, S.S., Lindgren, M., Porcu, P., Rubinow, D.R., Johnson, J.L., Morrow, A.L., 2012. A history of depression in women is associated with an altered GABAergic neuroactive steroid profile. Psychoneuroendocrinology 37 (4), 543–553.
Girdler, S.S., Straneva, P.A., Light, K.C., Pedersen, C.A., Morrow, A.L., 2001. Allopregnanolone levels and reactivity to mental stress in premenstrual dysphoric disorder. Biol. Psychiatry 49 (9), 788–797.
Gu, X.J., Chen, R., Sun, C.H., Zheng, W., Yang, X.H., Wang, S.B., Ungvari, G.S., Ng, C.H., Golenkov, A., Lok, G.K.I., Li, L., Chow, I.H.I., Wang, F., Xiang, Y.T., 2018. Effect of adjunctive ranitidine for antipsychotic-induced weight gain: a systematic review of randomized placebo-controlled trials. J. Int. Med. Res. 46 (1), 22–32.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23 (?), 56–62.
Hellgren, C., Akerud, H., Skalkidou, A., Backstrom, T., Sundstrom-Poromaa, I., 2014. Low serum allopregnanolone is associated with symptoms of depression in late pregnancy. Neuropsychobiology 69 (3), 147–153.
Hendrick, V., Altshuler, L., Strouse, T., Grosser, S., 2000. Postpartum and nonpostpartum depression: differences in presentation and response to pharmacologic treatment. Depress. Anxiety 11 (2), 66–72.
Higgins, J., Higgins, J., 2008. Cochrane Handbook for Systematic Reviews of Interventions. Chichester, UK. John Wiley & Sons.
Higgins, J.P., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558.
Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., McQuay, H.J., 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Contr. Clin. Trials 17 (1), 1–12.
Johannsen, B.M., Larsen, J.T., Laursen, T.M., Bergink, V., Meltzer-Brody, S., Munk-Olsen, T., 2016. All-cause mortality in women with severe postpartum psychiatric disorders. Am. J. Psychiatry 173 (6), 635–642.
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 (10093), 480–489.
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 (2), 1–6.
Kishimoto, T., Chawla, J.M., Hagi, K., Zarate, C.A., Kane, J.M., Bauer, M., Correll, C.U., 2016. Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. Psychol Med 46 (7), 1459–1472.
Ko, J.Y., Rockhill, K.M., Tong, V.T., Morrow, B., Farr, S.L., 2017. Trends in postpartum depressive symptoms - 27 States, 2004, 2008, and 2012. MMWR Morb. Mortal. Wkly. Rep. 66 (6), 153–158.
Luisi, S., Petraglia, F., Benedetto, C., Nappi, R.E., Bernardi, F., Fadalti, M., Reis, F.M., Luisi, M., Genazzani, A.R., 2000. Serum allopregnanolone levels in pregnant women: changes during pregnancy, at delivery, and in hypertensive patients. J. Clin. Endocrinol. Metab. 85 (7), 2429–2433.
Maguire, J., 2019. Neuroactive steroids and GABAergic involvement in the neuroendocrine dysfunction associated with major depressive disorder and postpartum depression. Front. Cell. Neurosci. 13, 83.
Maguire, J., Mody, I., 2008. GABA(A)R plasticity during pregnancy: relevance to postpartum depression. Neuron 59 (2), 207–213.
Majewska, M.D., Harrison, N.L., Schwartz, R.D., Barker, J.L., Paul, S.M., 1986. Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Science 232 (4753), 1004–1007.
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 (10152), 1058–1070.
Mostallino, M.C., Sanna, E., Concas, A., Biggio, G., Follesa, P., 2009. Plasticity and function of extrasynaptic GABA(A) receptors during pregnancy and after delivery. Psychoneuroendocrinology 34 (Suppl 1), S74–S83.
Nappi, R.E., Petraglia, F., Luisi, S., Polatti, F., Farina, C., Genazzani, A.R., 2001. Serum allopregnanolone in women with postpartum "blues" Obstet. Gynecol. 97 (1), 77–80.
Netsi, E., Pearson, R.M., Murray, L., Cooper, P., Craske, M.G., Stein, A., 2018. Association of persistent and severe postnatal depression with child outcomes. JAMA Psychiatry 75 (3), 247–253.
Osborne, L.M., Gispen, F., Sanyal, A., Yenokyan, G., Meilman, S., Payne, J.L., 2017. Lower allopregnanolone during pregnancy predicts postpartum depression: an exploratory study. Psychoneuroendocrinology 79, 116–121.
Romeo, E., Strohle, A., Spalletta, G., di Michele, F., Hermann, B., Holsboer, F., Pasini, A., Rupprecht, R., 1998. Effects of antidepressant treatment on neuroactive steroids in major depression. Am. J. Psychiatry 155 (7), 910–913.
Schiller, C.E., Meltzer-Brody, S., Rubinow, D.R., 2015. The role of reproductive hormones in postpartum depression. CNS Spectr. 20 (1), 48–59.
Schiller, C.E., Schmidt, P.J., Rubinow, D.R., 2014. Allopregnanolone as a mediator of affective switching in reproductive mood disorders. Psychopharmacology (Berl) 231 (17), 3557–3567.
Schule, C., Baghai, T.C., di Michele, F., Eser, D., Pasini, A., Schwarz, M., Rupprecht, R., Romeo, E., 2007. Effects of combination treatment with mood stabilizers and mirtazapine on plasma concentrations of neuroactive steroids in depressed patients. Psychoneuroendocrinology 32 (6), 669–680.
Schule, C., Nothdurfter, C., Rupprecht, R., 2014. The role of allopregnanolone in depression and anxiety. Prog. Neurobiol. 113 (?), 79–87.
Sterne, J.A., Sutton, A.J., Ioannidis, J.P., Terrin, N., Jones, D.R., Lau, J., Carpenter, J., Rucker, G., Harbord, R.M., Schmid, C.H., Tetzlaff, J., Deeks, J.J., Peters, J., Macaskill, P., Schwarzer, G., Duval, S., Altman, D.G., Moher, D., Higgins, J.P., 2011. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 343, d4002.
van Calker, D., Zobel, I., Dykierek, P., Deimel, C.M., Kech, S., Lieb, K., Berger, M., Schramm, E., 2009. Time course of response to antidepressants: predictive value of early improvement and effect of additional psychotherapy. J. Affect. Disord. 114 (1–3), 243–253.
Woody, C.A., Ferrari, A.J., Siskind, D.J., Whiteford, H.A., Harris, M.G., 2017. A systematic review and meta-regression of the prevalence and incidence of perinatal depression. J. Affect. Disord. 219, 86–92.