Postpartum Depression and Brexanolone

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Brexanolone is being hailed as a ‘breakthrough’ medication for the treatment of PPD. As highlighted in this review, the positive outcomes with regard to the clinical use of the drug obtained from the three RCTs gave extensive evidence in favor of the safety, tolerability, and efficacy of brexanolone. Consequently, it prompted the FDA to give brexanolone a ‘priority review’ and ‘breakthrough therapy’ classification, which ultimately led to its approval.

Keywords: postpartum depression ; brexanolone ; pregnancy ; safety ; effectiveness

1. Introduction

The Diagnostic and Statistical Manual (DSM-V) defines postpartum depression (PPD) as a recurrent or new onset of major depressive disorder (MDD) in mothers, with the episodes transpiring during pregnancy or within 4 weeks post-delivery [1]. However, in the realm of clinical practice and research, PPD is described as occurring from 4 weeks to 12 months following childbirth [2].

Many comorbidities, such as gestational diabetes and preeclampsia, have been classified as predictors of PPD. In fact, Moreira et al. attempted to review state-of-the-art artificial intelligence (AI) and machine learning mechanisms to classify and predict the risk of psychological disorders in pregnant women based on their biomedical and sociodemographic characteristics [3]. It also highlighted emotion-aware computing that could enable the detection of behavioral changes, especially applicable to women with a high risk of developing PPD [3].

According to the American College of Obstetricians and Gynecologists’ 2018 recommendations, the primary application of first-line treatment of PPD has relied on screening and pharmacologic intervention for the symptomatic management of depression and anxiety in addition to referral to mental healthcare providers [4][5]. The predominance of data in favor of selective serotonin reuptake inhibitors (SSRIs) and insufficient experimental data on adjunctive cognitive therapy or hormonal supplementation has often led to them being used as the default first-line drug therapy for PPD [6].

On 19 March 2019, however, the Food and Drug Administration (FDA) approved brexanolone, an aqueous formulation of allopregnanolone, as the first ever drug to be used specifically for the treatment of PPD [7]. The purpose of this article is to briefly review the pharmacology of brexanolone, evaluate the latest available clinical data and outcomes concerning its use, and review its position as a ‘break through’ in managing PPD worldwide.

2. Pharmacology

Brexanolone, an exogenous analog of allopregnanolone and a neuroactive steroid, binds to five-unit transmembrane GABA type A receptors. Although the exact mechanism of action is still unknown, it is believed that, by binding to these receptors, the drug enhances the activity of GABA (inhibitory neurotransmitter). Subsequently, this results in reduced anxiety and depression-like symptoms. As a consequence of the inhibitory effects, the drug has side effects of sedation, manifesting as drowsiness and dizziness [8].

Brexanolone is usually administered at inpatient facilities via a continuous intravenous infusion over a period of 60 h. The dosage per hour is gradually increased from 30 µg/kg/h to a maintenance dose of 90 µg/kg/h till 52 h, before being tapered off back to 30 µg/kg/h by 60 h. The specific dosage divided into hourly time periods is provided in **Table 1** [9].

Table 1. Dosage of Brexanolone.

Time Frame	Dosage (In µg/kg/h)
0 to 4	30
4 to 24	60

Time Frame	Dosage (In µg/kg/h)
24 to 52	90
52 to 56	60
56 to 60	30

Table 1: Dosage of brexanolone during the 60-h infusion as described by Kanes et al. [9].

Brexanolone, having a half-life of nearly 9 h, has three major inactive metabolites with a total plasma clearance of 1 L/h/kg and equal amounts of excretion in the urine and feces. The drug undergoes considerable non-cytochrome P450 enzyme-mediated hepatic metabolism via keto reduction, glucuronidation, and sulfation, rendering the use of oral analog of allopregnanolone in clinical settings inefficacious and a resultant low oral bioavailability [10]. Furthermore, to date, no drug interaction has been reported apart from drug–drug interactions with CNS depressants and antidepressants, owing to the sedating adverse effects of brexanolone [8][11].

3. Review of Clinical Trials

The study found that apart from sedation, no serious adverse effects were reported by the participants. Assessing the secondary outcome, from a baseline of 26.5 recorded in participants, the mean HAM-D score reduced to 4.8 at 12 h post-commencement and 1.8 at the end of infusion (60 h).

On the other hand, the secondary outcomes were to ascertain how many participants achieved ‘remission’ (a drop in HAM-D score to 7 or below), how many participants achieved ‘response’ (a drop in HAM-D score to ≥50% of baseline), the Montgomery–Asberg Rating Scale (MADRS) total score [12], major depression, and changes in CGI-I score.

Furthermore, developing suicidal ideation assessment was carried out with the Columbia-Suicide Severity Rating Scale [13], and reports of sedation were evaluated with the Stanford Sleepiness Scale [14]. Improvements were noted in suicide severity, and a further worsening of suicide ideation was not recorded in either group. The mean Stanford Sleepiness Scale scores were alike (2.7 in the brexanolone group compared to 2.6 in the placebo group).

In study 1, LS mean reduction in HAM-D score at the end of the 60 h infusion was 19.5 in the BRX60 group and 17.7 in the BRX90 group, which were both significantly greater than the placebo group, recording more improvement in brexanolone-receiving groups. Continuing this trend, a significantly higher reduction in HAM-D total scores from baseline at day 30 was observed in the BRX60 and BRX90 groups in contrast to the placebo group (**Table 2**).

4. SSRIs and Brexanolone

Typically, moderate-to-severe PPD is managed using selective serotonin reuptake inhibitors (SSRIs). A total of four open-label [15][16][17][18] and eight RCTs [19][20][21][22][23][24][25][26] have evaluated SSRIs with assessment indicating mixed results in terms of efficacy and tolerability in using them as antidepressants to treat PPD. Furthermore, a Cochrane review on three studies comparing SSRIs with placebos for PPD was conducted by Molyneaux et al. [27], which reported that patients did exhibit response and remission to the treatment [28].

In 2019, Cooper et al. conducted a meta-analysis to compare the efficacy of brexanolone infusion with SSRIs for treating PPD. Due to the lack of RCTs comparing both drug therapies, an indirect treatment comparison (ITC) [29] approach was adopted. Using the data from available studies, the HAM-D score was selected, as it is regarded as the ‘gold standard’ for measuring outcomes relating to depression. Since EPDS is regularly used to screen for PPD in clinical practice, it was also chosen as an outcome.

Randomized and controlled studies with at least one pharmacological arm and outcome in the form of two parameters, HAM-D and/or EPDS, were selected for this comparison. Matching-adjusted indirect comparison (MAIC) results indicated greater effectiveness of BRX90 compared to SSRIs. Furthermore, using the MAIC-adjusted Bucher ITC and standard network meta-analysis (NMA), it was deduced that not only was brexanolone’s efficacy rapid, but it also had sustained efficacy compared to the other group.

The authors of this study, however, did point out the lack of evidence in determining the impact of the variable severity of depression of the study participants on the ITC results. Additionally, the placebo groups to which brexanolone was matched/adjusted was ‘subjective’; therefore, a difference may lead to a change in results [30].

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