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Effect of Administration of Brexanolone Injection for Post-Partum Depression

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Abstract

Background: Postpartum depression (PPD) is a debilitating mental health condition that affects many new mothers, with far-reaching consequences for both individuals and their families.

Methods: Recent research has explore the potential of brexanilone, an allopregnanolone based medication, as a treatment for PPD. This article presents a comprehensive review of existing literature on brexanolone's use in treating PPD, encompassing its mechanism of action, clinical efficacy, safety profile, and potential adverse effects. Multiple clinical trials and studies are discussed to provide a well-rounded perspective on brexanolone's utility in addressing PPD.

Results: Brexanolone has demonstrated rapid and sustained improvement in depressive symptoms, anxiety, and insomnia in women with PPD. Notably, it appears effective within a short timeframe, often within days of administration. Furthermore, brexanolone has shown potential for treating depression in adults with major depressive disorders beyond the postpartum period. It has also exhibited premise in alleviating symptoms of comorbid psychiatric conditions.

Conclusion: While brexanolone's efficacy in addressing PPD is encouraging, several challenges remain, including its high cost, inpatient administration requirement, and limited data on long term use. A multidisciplinary approach involving healthcare professionals, researchers, policymakers, and the pharmaceutical industry is necessary to enhance accessibility and optimize treatment strategies. In conclusion, brexanolone presents a promising avenue for the treatment of PPD and related psychiatric conditions. Future research should focus on improving accessibility, assessing long-term effectiveness, and exploring its potential in treating a broader spectrum of psychiatric illnesses. Effective management of PPD not only benefits mothers but also promotes the overall well-being of families.

INTRODUCTION

A major depressive disorder (MDE) with post-partum onset is what is referred to as post-partum depression (PPD). One must either exhibit a low mood or lose interest in activities for two weeks in order to meet the MDE criterion.[1] The mother's family and social circles undergo significant adjustment. After giving birth, a mother may feel a range of emotions, from happiness and delight to grief and tears. The so-called "baby blues," which primarily subside within the first two weeks of delivery, are feelings of sadness and tearfulness. Beck stated in 2006 that because of privacy issues and a need to keep it confidential from close family members, up to half of PPD cases among new mothers go untreated.

PPD is more typical in some ethnicities such as African American and Hispanic mothers which stated that the onset of symptoms was within 2 weeks of delivery unlike the white mothers which reported it later. In accordance to the American Psychiatric Association, the standard-of-care therapies for PPD— include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, and atypical antidepressants. These may be effective, but the evidence supporting long-term efficacy and safety is inconclusive and requires more research.[2]

A significant milestone for PPD sufferers and their families is the FDA's recent clearance of the allopregnanolone-based medication brexanolone, which is currently marketed under the name Zulresso.[5] Allopregnanolone, a progesterone metabolite, is a gamma aminobutyric acid-A receptor and one of the neuroactive substances.[3] Allopregnanolone levels significantly increase during pregnancy and rapidly drop upon parturition. Brexanolone mimics allopregnanolone because of which it was thought to be useful in postpartum depression.[4]

The drug is given through continuous IV infusion over the course of 2.5 days, lasting 60 hours in a monitored setting. Brexanolone has a 9-hour half-life and is evenly distributed across tissues. They are mostly processed by the extra hepatic by glucuronidation, sulfation, and keto-reduction. About 47% and 42% of these medicines are excreted in the urine and feces.

Due to the medication's quick start of action and lack of data on its long-term harm, it is extensively utilized. Dizziness, sleepiness or sedation, oral dryness, syncope, and hot flashes are some of the frequent adverse effects experienced while taking this medication.[6] The goal of this study is to provide a comprehensive summary of the existing literature on brexanalone injection. It will focus specifically on its application in the treatment of PPD and will also explore its mechanism of action, clinical efficacy, safety profile and potential adverse effects. This study aims to add on to the present state of knowledge on brexanalone by critically analyzing the results from multiple studies.

PPD is a prevalent and profound mental health condition that significantly impacts a considerable number of new mothers worldwide. Typically surfacing within the first year after childbirth, PPD is characterized by persistent emotional symptoms, including overwhelming sadness, hopelessness, and the loss of interest or pleasure in previously enjoyed activities. This debilitating condition not only exacts a considerable toll on the mental and emotional well-being of affected mothers but also bears far-reaching implications for their families. It can disrupt the crucial mother-infant bond, hinder the cognitive and emotional development of the child, and strain relationships within the household.([2] , [18])

Conventionally, the primary therapeutic modalities for PPD encompass psychotherapy and antidepressant pharmacotherapy. Nevertheless, the efficacy of these interventions is known to exhibit variability among individuals, and not all sufferers respond favorably. Moreover, the utilization of traditional antidepressants raises concerns regarding their safety during breastfeeding, a pivotal consideration for postpartum women. Given the intricate nature and profound societal impact of PPD, there exists a pressing imperative for the development of more efficacious and accessible therapeutic alternatives. These alternatives should be capable of providing swift relief from the incapacitating symptoms of PPD while promoting enduring recovery.([2] , [5])

One promising stride in the realm of PPD treatment revolves around brexanolone, a medication designed to address the unique hormonal dynamics experienced during pregnancy and the postpartum period. Brexanolone constitutes a synthetic analog of allopregnanolone, a neuroactive steroid whose levels surge during pregnancy only to precipitously decline following childbirth. This neurosteroid plays a pivotal role in the regulation of mood and responses to stress. Administered via intravenous infusion, brexanolone has exhibited notable efficacy in swiftly alleviating the symptoms of PPD, often within a matter of days. Clinical trials have substantiated not only its capacity to ameliorate depressive symptoms but also its influence on associated afflictions such as anxiety and insomnia.([7 , 13 , 15])

Nonetheless, the integration of brexanolone into PPD management is beset with certain challenges. Among these are the exorbitant costs associated with the medication and the mandate for inpatient administration.

Further research is imperative to elucidate the long term ramifications and safety profile of brexanolone employment in a broader demographic. This entails investigating its potential as a treatment modality for individuals grappling with diverse severities of PPD and exploring its application in scenarios where conventional therapies have yielded unsatisfactory outcomes. Additionally, the complementary roles of adjunctive therapies, encompassing psychotherapy and social support, continue to constitute integral facets of comprehensive PPD care. The interplay between these holistic approaches and pharmacological interventions such as brexanolone warrants in-depth scrutiny for the purpose of formulating holistic strategies aimed at addressing the multifaceted nature of PPD.([11], [21])

In a pooled analysis of 3-double blind, randomized- placebo-controlled clinical trials in the HUMMINGBIRD clinical program conducted in 2023 in 209 women with postpartum depression who have passed the Hamilton Rating Scale for Depression (HAMD-17)score of ≥26 for the first two studies and ≥20 or 25 for the third study. Both the control group and experimental group received a 60h infusion of brexanolone or placebo under monitoring. The outcomes of the study showed that the time-to-onset of HAMD-17 response was greater in the BRX90 group than in the placebo group at hour 60 (81.4 % vs 67.3 %). Time-to-onset clinical global impression (CGI) response was also higher in the BRX90 group at hour 60 (81.4 % vs 67.3 %). Anxiety and insomnia symptoms were also reduced in theBRX90 group. In the subgroup of patients with baseline insomnia symptoms (HAMD-17 insomnia subscale score 1), a significantly larger proportion of BRX90 patients reported a total absence of insomnia symptoms when compared to placebo patients .[7] The latter finding shows us the possibility of using brexanolone for treating depressive symptoms in adults with major depressive disorders as well.

An Open-label, study conducted by Stephen J. Kanes in 2017 and colleagues as a proof-of-concept study studied four women with severe Postpartum depression who were given brexanolone as a continuous infusion for 30 hours and tapered over 12 hours. Safety and effectiveness were the primary and secondary outcomes respectively. Few adverse effects were found but none of them were severe. Most common of them being dizziness or lightheadedness and headache. All the four candidates tolerated brexanolone very well and the drug proved to be effective in them as the mean HAMD scores decreased significantly with remission of symptoms.[8]

According to Hutcherson's 2020 study brexanolone showed improvement in Hamilton Rating Scale for Depression (HAM D) scores compared to a placebo in trials. Three randomized controlled trials (RCTs) and one quasi-experimental research were examined. In all the studies there were steady improvements in HAMD scores. The few adverse effects noticed were dizziness, sedation, headache and somnolence. None of them were severe. However, in 4% of participants, loss of consciousness or syncope was reported. Concerns regarding long term use and use outside a health care facility remain.[9]

Similarly, in C.M. Rodriguez mercado's systematic review about efficacy of brexanolone in Postpartum depression, he found that treatment with brexanolone led to response and remission in women while comparing it to placebo. Brexanolone appears to be generally safe when administered under monitoring. He emphasized the ultra-rapid antidepressant effect of brexanolone.large-scale studies are essential in determining the long-term effectiveness of brexanolone.[10]

However, the limitations and challenges in relation to the availability and cost of brexanolone are clearly pointed out in the 2020 article by Angela F. Jarman. It is still unsure whether this medication will be available to all patients who need it because of its outrageously high price. The cost of the medicine itself is $34,000. Another limitation is the method of administration which is a continuous infusion over 60 hours in a monitored inpatient setting. Studies on lactation while on medication is also very scant. Therefore, a comprehensive and strategical approach for Postpartum depression which is accessible to all patients in need is recommended.[11]

A double-blind, randomized, placebo-controlled, phase 3 trials were conducted between Aug 2016 and Oct 2017 and between July 2016 and Oct 2017. Women aged between 18 and 45 years,6 month after delivery or less at screening, with post-partum depression and qualifying 17-item Hamilton Rating Scale for Depression were selected. Patients were randomly divided and assigned to receive BRX90(n=45) and BRX60 (n=47) or placebo (n=46) in study 1 and in study 2, patients were assigned to receive BRX90 (n-54) or placebo(n=54). In study 1, at 60 h, Mean scores in HAM-D were reduced by 19.5 points in the BRX60 group, the BRX90 group had a mean reduction in HAM-D of 17.7 points, and the placebo group had a mean reduction in HAM-D score of 14.0 points. In study 2, at 60 h, the mean reduction in HAM-D total was reduced by 14·6 points in the BRX90 group compared with 12·1. (difference -2·5 (95% CI -4·5 to -0·5), p=0·0160). In study 1, 19 patients in BRX60 and 22 patients in BRX90 had adverse effects compared to 22 patients in placebo group.

The most commonly stated adverse effects were headache (for study1,7 patients in BRX60 and 6 patients in BRX60 group vs 7 patients in placebo; for study 2, 9 patients in BRX90 vs 6 patients in placebo), dizziness (for study 6 patients in both BRX60 and BRX90 group n=6 vs 1 patient in placebo; for study 2, 5 patients in BRX90 vs 4 patients in placebo), and somnolence (for study 1, 7 patients in BRX60 group and 2 patients in BRX90 group vs 3 patients in placebo; for study 2, 4 patients in BRX90 vs 2 patients in placebo). One patient from study 1 receiving BRX60 had 2 serious adverse effects, including suicidal thoughts and an intentional attempts of overdose during follow-up, and one patient from study 2 receiving BRX90 also had 2 serious adverse effects, including altered state of consciousness and syncope.[12]

A double-blind, randomized, placebo-controlled trial was done for severe postpartum depression (HAM-D total score >26) from December 2015 to May 2016. There were no withdrawals, and 21 women finished the trial. At 60 hours, the mean HAM-D score decreased by 21.0 points in the brexanolone group while it decreased by 8.8 points in the placebo group (difference -12•2, 95% CI -20•77 to -3•67; p=0•0075; effect size 1•2). Compared to eight of eleven patients in the placebo group, four to ten patients in the brexanolone group experienced negative side effects.

Two patients in the group who were in the brexanolone group experienced dizziness, when compared to three patients in the placebo group, while two patients in the brexanolone group complained of somnolence. Sinus tachycardia and somnolence, both of which were mildly treated-emergent (n=1).[13]

In a different 2017 trial, BRX was administered to 4 postpartum women who had severe depression and had HAM-D scores under 20. The dose was increased until it reflected allopregnanolone levels in the third trimester. By gradually reducing over 12 hours, the infusion was kept going for 36 hours. There were 14 adverse effects documented, however none were particularly serious. Mean HAMD total scores decreased to levels compatible with symptom remission starting at the first measurement following infusion beginning and continued until Hour 84.[14]

METHODOLOGY

This article presents a thorough and insightful review of the existing literature concerning the utilization of brexanolone in the treatment of postpartum depression (PPD). The review encompasses a detailed exploration of various facets, including the mechanism of action, clinical efficacy, safety profile, and potential adverse effects associated with brexanolone.

The mechanism of action section delves into the pharmacological processes by which brexanolone exerts its therapeutic effects in the context of postpartum depression. Clinical efficacy is extensively discussed, drawing insights from multiple clinical trials and studies that have investigated brexanolone's effectiveness in alleviating symptoms of PPD. The safety profile of brexanolone is thoroughly examined, shedding light on its tolerability and potential benefits in comparison to other treatment options. Furthermore, potential adverse effects are carefully considered to provide a balanced perspective on the medication's risk-benefit profile.

By integrating findings from various clinical trials and studies, this comprehensive review aims to offer a well-rounded and evidence-based perspective on brexanolone's utility in addressing postpartum depression. The synthesis of information from diverse sources contributes to a nuanced understanding of the medication's role in the management of PPD, providing valuable insights for clinicians, researchers, and healthcare professionals.

RESULTS

Several clinical trials with Brexanolone in postpartum depressive patients showed rapid response and it persisted for 30 days post infusion, also they showed a significant long-lasting improvement in insomnia and anxiety of the patient as well. If BRX can help non-PPD patients with their depression symptoms, further research must be done on this topic. Treatment with BRX require inpatient facilities so, most of the patients during the trial were admitted to the hospitals or research centres for the infusion treatment. Most candidates who took the treatment had moderate to severe PPD symptoms.[15]

BRX is available in 100 mg/20ml and given through 60 hours IV. Most of the patients felt improvement in the first 24 hours or in 2 or 3 days. Patients must be checked before the treatment for they are taking any other sedative medicines because, along with BRX treatment, it can be excessive sedation.[16]

In a open-label, single-institution, follow-up study of patients with PPD found out that there has been improvement in mood beyond 30 days. This data was collected from 3 to 16 months of post infusion.[15]

Phase 3 trial of BRX injection confirmed that it rapidly reduced significant depressive symptoms and sustained for 30 days and beyond, and 94% of patients did not relapse, which is a huge milestone that is achieved through these studies for the struggling mothers in the society.[17] Additionally, children may suffer negative consequences if their moms have prolonged PPD. Low mathematical aptitude in children is a possibility, and depression in adolescence is probably a possibility as well. After giving delivery, PPD can linger for at least 11 years.[18]

An essential component of Brexanolone's effectiveness, particularly for those with severe PPD who may be significantly distressed and impaired in their everyday life, is that some studies demonstrate a fast decrease in depression symptoms within 3 days can be attained. The acute and debilitating nature of PPD symptoms may be addressed with this quick improvement, relieving those struggling mothers and empowering them to take an active role in their own rehabilitations. For close monitoring of any potentially major side effects, BRX 60-hour IV infusion is administered in an inpatient setting.

However, further research must be conducted to find a more practical way to speed up recovery. Headache, dizziness, and somnolence were the most common adverse effects that were noted in most of the investigations, although they weren't severe enough to result in any conditions that may be life-threatening. All side effects were manageable and minor.[17]

The industry-recognized scoring method for assessing depressed symptoms is the HAMD. So, in a study of PPD women with a history of PPD; just a handful reported suicidal thoughts and one tried. Immediately following their BRX therapy, they displayed a striking improvement in their HAMD score. Four out of six patients had total HAMD ratings of less than seven, suggesting symptom remission, at all evaluations starting at hour 24.[19]

As of right now, the disadvantages of BRX injections include their necessity for hospital settings for therapy, high cost, IV administration, and extreme sedation. The $38,000 cost of the procedure makes it unaffordable for many in the middle or lower socioeconomic groups. More research must be done to make the medicine more accessible so that women of all socioeconomic backgrounds can use it for recovery.[20]

Patients who were suffering with anxiety, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and borderline personality disorder, in addition to PPD, demonstrated astounding improvements in these symptoms. Therefore, research is required to determine whether BRX can be administered to people with various psychiatric diseases. Following BRX infusion treatment, several patients reported feeling noticeably better after receiving prescription antidepressants and outpatient counselling. Also, according to certain observations, collaboration among multidisciplinary has led to an almost total improvement in their condition.[21]

DISCUSSION

Postpartum depression (PPD) is a significant mental health issue affecting many new mothers, with profound implications for both the affected individuals and their families. This discussion will examine the key findings and implications of the research papers cited, focusing on the potential use of brexanolone as a treatment for PPD.

Diagnostic Tools:

The discussion also touches upon diagnostic tools for PPD, particularly the Edinburgh Postnatal Depression Scale (EPDS).[5] The EPDS is considered the gold standard for PPD screening due to its sensitivity and specificity. However, the limitation of the original 10-item questionnaire in busy primary care settings led to the development of shorter versions like the Quick DIS. The emphasis on enhancing specificity by including questions about willingness to accept assistance is noteworthy, as it can aid in early diagnosis and intervention.

Brexanolone as a Treatment for PPD:

The core of the discussion revolves around the potential use of brexanolone in treating PPD. Several studies and clinical trials have explored its efficacy and safety (8-15). These studies collectively suggest that brexanolone may be a promising treatment option for PPD, with rapid onset of action and significant reductions in depression symptoms.

Safety and Administration:

Safety considerations are crucial when evaluating any medication. The discussed trials report mostly manageable adverse effects such as headache, dizziness, and somnolence, with no severe cases reported. However, one patient in the BRX60 group experienced serious adverse effects, emphasizing the importance of close monitoring during treatment.[13] The necessity for inpatient administration due to potential sedation and the high cost of brexanolone are significant limitations.([17], [21]) Efforts should be made to make this treatment more accessible to a wider range of patients.

Long-Term Effectiveness and Impact on Families:

Administering Brexanolone appears to rapidly alleviate Postpartum Depression. However, rigorous large-scale randomized controlled studies are essential to assess both short-term and long-term therapeutic effects.[11] Brexanolone could be a suitable treatment for women with severe Postpartum Depression, particularly those with limited response to standard therapies. However, current efficacy studies lack data beyond 30 days, necessitating further trials to evaluate its long-term effectiveness, safety, and role in treatment approaches.([17], [21])

Untreated PPD can result in the mother's distress, increased family stress, and potential developmental challenges for the infant.([1], [19]) Effective treatment of PPD not only benefits the mother but also contributes to the well-being of the entire family.

Future Directions:

In conclusion, the discussed research collectively suggests that brexanolone holds promise as a treatment for PPD. However, there are still limitations, including cost and the need for inpatient administration. Future research should focus on making this treatment more accessible and exploring its long-term effectiveness. Additionally, brexanolone's potential in treating other psychiatric conditions should be further investigated.

PPD is a complex and multifaceted condition, and addressing it comprehensively will require a multi-disciplinary approach involving healthcare professionals, researchers, policymakers, and the pharmaceutical industry. Ultimately, the goal should be to provide effective, accessible, and safe treatments for all individuals affected by PPD, improving the well-being of mothers and their families.

CONCLUSION

In conclusion, postpartum depression (PPD) stands as a significant mental health challenge that necessitates effective and accessible interventions for the well-being of new mothers and their families. While traditional therapies like psychotherapy and antidepressant medications have been central to PPD management, the variable response rates and safety concerns have prompted exploration into innovative treatments.

Brexanolone, an intravenously administered synthetic analog of allopregnanolone, has emerged as a promising option in the treatment of PPD. Clinical trials have demonstrated its ability to swiftly alleviate depressive symptoms, often within a matter of days, along with improvements in associated conditions like anxiety and insomnia. However, the integration of brexanolone into standard PPD care presents challenges related to cost and the need for inpatient administration. Further research is imperative to assess its long-term effectiveness, safety profile, and applicability to a broader demographic.

Moreover, it's essential to recognize that PPD is a complex and multifaceted condition, requiring a holistic approach to treatment. This approach should not only encompass pharmacological interventions like brexanolone but also incorporate psychotherapy, social support, and a comprehensive strategy tailored to the individual's needs. The well-being of both the mother and the child hinges on addressing PPD effectively, emphasizing the urgency of ongoing research and the development of more accessible treatment modalities. Collaborative efforts between healthcare professionals, researchers, policymakers, and the pharmaceutical industry are essential to provide a robust and integrated approach to combatting PPD, ultimately ensuring the brighter futures of new mothers and their families.

DECLARATION

Ethical Statement

The research conducted in this study has received approval from the Institutional Review Board/Ethics Committee at Ivane Javakhishvili Tbilisi State University. All procedures performed in this study involving human participants were in accordance with the ethical standards of Ivane Javakhishvili Tbilisi State University and with the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards.

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Conflicts of Interest

The authors maintain that there are no conflicts of interest related to this research. Neither financial nor non-financial competing interests are present.

Data Availability

The data supporting the findings of this study are comprehensively presented within the article and its supplementary materials. For any additional data, interested parties may request access, and such requests will be considered.

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