A Review on the Use of Brexanolone in the Treatment of Postpartum Depression

By

Yeamin Dhally
20146079

A thesis submitted to School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

School of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Student Full Name
Student ID

Approval

This project titled "A Review on the use of Brexanolone in the treatment of Postpartum Depression" submitted by Yeamin Dhally (20146079) of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervisor:

Dr. Md. Rabiul Islam

Associate Professor

School of Pharmacy

BRAC University

Dean:

A.F.M. Yusuf Haider, PhD

Acting Dean, School of Pharmacy

Professor, Department of Mathematics and Natural Sciences

BRAC University

Ethics Statement

If review or non-human or animal studies: This project does not involve any kind of animal and human trial.

Abstract

Postpartum depression (PPD) is a major mental health concern impacting approximately 10–20% of women following childbirth. Notwithstanding its commonality, the fundamental causes of PPD remain less comprehended, and therapeutic alternatives are frequently constrained. Brexanolone, an innovative neurosteroid and the inaugural medicine sanctioned by the USFDA for postpartum depression (PPD), has shown significant potential in clinical trials owing to its quick and enduring effects. Brexanolone, as a positive allosteric modulator of GABA-A receptors, targets the specific hormonal variations linked to postpartum depression (PPD), offering a more rapid onset of effect than conventional antidepressants. This review analyzes the clinical trial data about brexanolone, its efficacy in mitigating depressive symptoms, and its safety profile compared to alternative therapy. This study seeks to elucidate brexanolone's therapeutic potential through the analysis of existing evidence and to pinpoint avenues for future research to improve the treatment of postpartum depression.

Keywords: Postpartum depression , brexanolone , clinical trial , depression , DNA methylation , Zulresso

Dedication

To All mothers who have suffered from Postpartum Depression.

Acknowledgement

I would like to thank everyone who has helped me to complete my project. First of all, I would like to thank Almighty Allah for giving me the opportunity to complete my degree from School of Pharmacy, BRAC University. I would like to convey my sincere appreciation to the acting dean of School of Pharmacy, Professor A.F.M. Yusuf Haider. I would like to convey my appreciation to my supervisor Dr. Md. Rabiul Islam, Associate Professor, School of Pharmacy for helping me throughout my project work.

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List of Acronyms

DNA	Deoxyribonucleic acid
PPD	Postpartum depression
IV	Intravenous
RNA	Ribonucleic acid
mRNA	Messenger ribonucleic acid
WHO	World health organization
FDA	Food and drug administration
HPA	Hypothalamic-pituitary-adrena
HPG	Hypothalamic-pituitary-gonadal
SERT	The serotonin transporter gene
CBT	Cognitive behavioral therapy
IPT	Interpersonal therapy
SSRIs	Selective serotonin reuptake inhibitors

Chapter 1

Introduction

1.1 Postpartum depression

Postpartum depression (PPD) is a complicated mood condition that impacts women following childbirth. It is more severe and enduring than the "baby blues," commonly encountered by several new mothers. Here are several essential aspects to comprehend regarding PPD. The birth of an infant can evoke a range of intense feelings, including elation and delight, as well as trepidation and anxiety. However, it may also lead to an unexpected outcome—depression. Numerous new mothers experience postpartum "baby blues" after childbirth, marked by mood swings, crying spells, anxiety, and sleep disruptions. Postpartum blues generally begin within the first 2 to 3 days after labor and can last for up to two weeks. However, some new mothers encounter a more severe and enduring variant of depression referred to as postpartum depression. It is occasionally referred to as peripartum depression, as it may commence during gestation and persist post-delivery. Postpartum psychosis, a severe mood illness, may infrequently arise following childbirth. Postpartum depression is neither a flaw in character nor an indication of frailty. Occasionally, it is simply a complication that occurs post-childbirth. Timely intervention for postpartum depression may aid in symptom management and enhance bonding with your infant (*Postpartum Depression - Symptoms and Causes*, 2020). Postpartum depression (PPD) is a significant psychological disease affecting 10–30% of mothers worldwide. In India, it affects 22% of moms. The etiology and pathophysiology remain incompletely elucidated; however, numerous theories about the interaction of hormones, neurotransmitters, genetics, epigenetics, nutrition, and socio-environmental factors are present. Nutrients are crucial for neurotransmitter synthesis and may also indirectly affect genomic pathways involved in DNA methylation. There is evidence of biological connections between

dietary quality and psychological well-being. Elevated behavioral problems have been linked to shortages in macro- and micronutrients, and dietary supplementation has shown useful in addressing many neuropsychiatric conditions. Nutritional deficits are prevalent among women, particularly during pregnancy and lactation (Rupanagunta et al., 2023). PPD was originally characterized as a major depressive disorder (MDD) that manifests within one month following childbirth. Notwithstanding the extensive body of literature on PPD, its cause remains unclear. Nonetheless, evidence suggests various physiological factors, including changes in peptide and steroid hormones during pregnancy and the postpartum period, modified psycho-neuroimmune systems, increased stress levels, and elevated inflammatory biomarkers, all contributing to the disruption of serotonin synthesis in the brain (Amini et al., 2019). Moreover, modifications in peptide and steroid hormones influence the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes in mothers. The dysregulation of these hormonal axis correlates with mental problems throughout pregnancy and the postpartum phase. Postpartum depression (PPD) affects 10–30% of mothers worldwide and 22% of moms in India (Lanjewar et al., 2021). It is associated with the mother's adverse emotionality and her tendency to develop chronic depression. Research indicates that in underdeveloped nations, maternal melancholy can adversely affect a child's growth and weight, leading to stunting and underweight conditions (Surkan et al., 2011).

1.2 Etiologies of postpartum depression

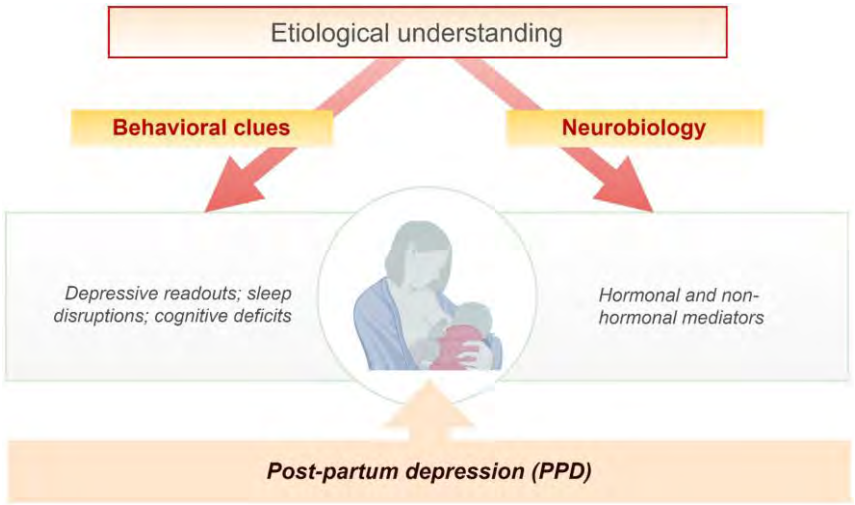

Figure 1: Etiologices of PPD *(Moreira et al., 2023)*

Although the precise cause of PPD is unknown, hormone abnormalities, genetic predispositions, and psychosocial stressors are all possible contributing factors. Significant alterations in steroid and peptide hormones that impact the mother's hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes have been associated with pregnancy and the postpartum phase. Given the correlation between mood disorders and dysregulations in these endocrine axes, it is not surprising that pregnancy and the postpartum period could have a substantial impact on a mother's mood. Women who are pregnant or who have recently given birth are more likely to experience depressive symptoms. Ten to fifteen percent of women experience postpartum depression, which interferes with mother-infant relationships, which are vital to a child's growth. For an infant's social, cognitive, and behavioural skills to develop in a healthy way, the mother's attachment, sensitivity, and parenting style are essential. Depressed mothers frequently exhibit diminished attachment, reduced sensitivity, and harsher or disrupted parenting behaviors, which may contribute to negative outcomes in their children (Brummelte & Galea, 2015). Postpartum depression (PPD)

is a debilitating disorder that has recently exhibited a rise in occurrence, rendering it a significant public health issue. The predominant risk variables were identified in the domains of economic and social influences, obstetric history, lifestyle choices, and mental health history. Recent research has focused on the genetic underpinnings of PPD to identify the genes involved for developing targeted therapy approaches and elucidating its pathophysiology. The serotonin transporter gene (SERT) was the most extensively researched potential gene linked to PPD. In biological research, antidepressants and psychological therapies demonstrated the strongest evidence of effective intervention. The obstetrician plays a crucial role in the detection and treatment of postpartum depression (PPD). Postpartum ladies with risk indicators ought to be assessed utilizing the Edinburgh Postnatal Depression Scale (EPDS); nonetheless, currently, there are no preventative programs available in Europe (Dimcea et al., 2024).

1.3 Signs and symptoms

Postpartum depression may initially be confused with baby blues; however, its symptoms are more severe and persist for a longer duration. These may ultimately impede your capacity to care for your infant and manage other everyday responsibilities. Symptoms typically manifest within the initial weeks following childbirth. However, they may commence earlier—during gestation—or later—up to one year postpartum. The common signs and symptoms are given below:

- Depressed mood / severe mood swings
- Crying too much than before
- Difficult to create bonding with baby
- Withdrawing from family and friends
- Loss of appetite or eating much more than usual
- Inability to sleep / called insomnia/sleeping too much than usual

- Overwhelming tiredness or loss of energy
- Less interest and pleasure in activities you used to enjoy
- Intense irritability and anger
- Fear that patient is not a good mother
- Hopelessness
- Feelings of worthlessness, shame, guilt or inadequacy
- Reduced ability to think clearly, concentrate or make decisions
- Restlessness
- Severe anxiety and panic attacks
- Thoughts of harming by own or own baby
- Recurring thoughts of death or suicide

Untreated postpartum depression may last for many months or longer.

Figure 2: Sign and symptoms of Postpartum Depression *(Humanistic Burden of Postpartum Depression in the United States, 2023)*

1.4 Pathophysiology

The specific mechanism behind the development of PPD remains contentious, constituting a significant area of current research. It is clear that the pathophysiology of the disorder results from both psychosocial and biological components. The discussion begins with the GABAergic theory of depression, followed by neurobiological differences observed in postpartum depression (PPD), and concludes with the neurosteroids involved in the pathophysiology of PPD (Edinoff et al., 2021). The pathophysiology of postpartum depression (PPD) may result from disruptions in various biological and endocrine systems, including the immune system, the hypothalamic-pituitary-adrenal (HPA) axis, and lactogenic hormones. Postpartum depression is a significant psychiatric disease that remains under researched and frequently misdiagnosed. Postpartum depression, the most prevalent consequence of childbirth, adversely affects the mother, with suicide representing around 20% of postpartum fatalities (Lindahl et al., 2005). Postpartum depression (PPD) is a complex mental illness that certain women encounter following childbirth. The underlying causes are many, encompassing hormone changes, genetic influences, psychological issues, and environmental settings. Post-delivery, there is a substantial decline in hormones such as estrogen and progesterone, which may induce neurochemical alterations in the brain, affecting mood control. The dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in modified cortisol levels, is also implicated. Furthermore, dysregulations in neurotransmitters including serotonin, dopamine, and norepinephrine may exacerbate the emotional and cognitive manifestations. A genetic predisposition, a history of depression, and external stresses such as insufficient support and sleep deprivation can exacerbate these physiological alterations, leading to postpartum depression (PPD) (Payne & Maguire, 2018).

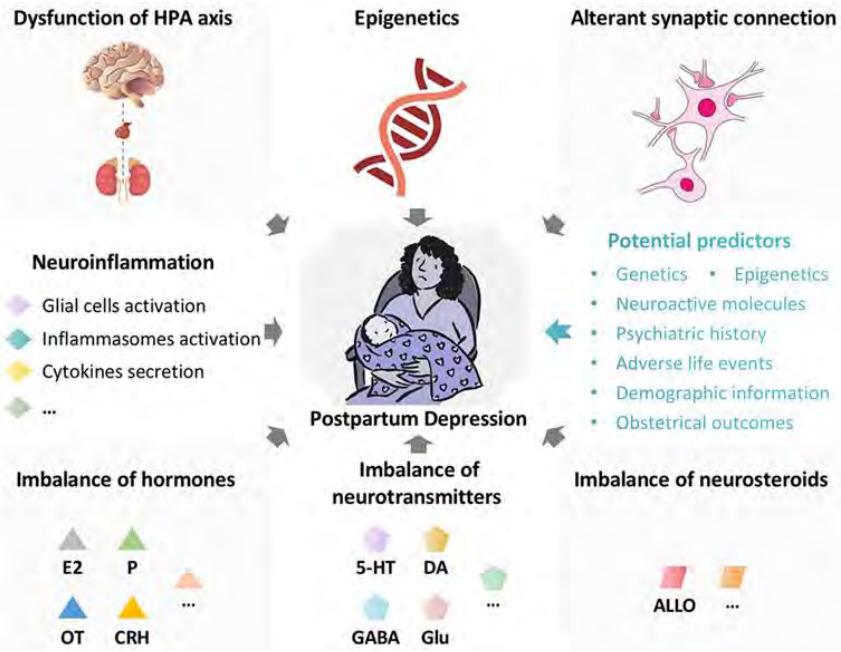

Figure 3: The potential pathogenesises and predictors in postpartum depression *(Zhu et al., 2022)*

1.5 Other treatments

Post-partum depression (PPD) arises following childbirth and adversely impacts the health of both the mother and the infant by obstructing good bonding. Women with postpartum depression (PPD) endure severe anxiety, depressive symptoms, insomnia, difficulties in child care, and an elevated risk of suicide. Brexanolone, an intravenous infusion derived from progesterone, received approval from the U.S. Food and Drug Administration for the treatment of postpartum depression in 2019. The rapid-acting medicine substantially alleviates depressive symptoms and maintains efficacy for up to 90 days. Nonetheless, the precise mechanism by which the medication elicits these therapeutic effects has remained enigmatic until now (Daniels, 2023). Besides brexanolone, other alternative therapies exist for postpartum depression (PPD).

Psychotherapy: Cognitive Behavioral Therapy (CBT) assists clients in recognizing and altering detrimental thought patterns and behaviors. Interpersonal Therapy (IPT) Concentrates on enhancing interpersonal relationships and social functioning. (*Postpartum Depression - Diagnosis and Treatment - Mayo Clinic*, 2018)

Medicines: Antidepressants, Selective serotonin reuptake inhibitors (SSRIs), such as sertraline and fluoxetine, are frequently recommended. These pharmaceuticals can assist in equilibrating neurotransmitters in the brain. Hormone Therapy such as Estrogen therapy may be deemed appropriate in certain instances to stabilize hormone levels (Pietrangelo, 2022).

Complementary Treatments: Mindfulness and Meditation, Mindfulness meditation practices can alleviate stress and enhance happiness. Acupuncture, Certain research indicate that acupuncture may aid in mitigating symptoms of depression (Pietrangelo, 2022).

Modifications to Lifestyle: A nutritious diet abundant in omega-3 fatty acids, proteins, and vitamins can enhance general mental well-being. Engagement in regular physical activity can alleviate symptoms of depression through the release of endorphins. Sleep Hygiene: Maintaining sufficient and high-quality sleep is essential for mental well-being (Howard et al., 2022).

1.6 Aims and objective

This thesis aims to evaluate the efficacy, safety, and clinical use of brexanolone in the treatment of postpartum depression (PPD). The objectives encompass a comprehensive analysis of brexanolone's pharmacological properties, an examination of its mechanism of action and its function in mitigating the pathophysiology of postpartum depression (PPD), as well as an assessment of clinical trial data and real-world outcomes related to its efficacy and safety. The thesis will compare brexanolone with alternative PPD treatments, examine patient selection

criteria, evaluate brexanolone's effect on the quality of life of postpartum women, and identify potential barriers to its wider clinical implementation.

Chapter 2

Novel drug for postpartum depression

2.1 Rational for the development of new drug

Creating novel pharmacological interventions for postpartum depression (PPD) is crucial given the inadequacies of existing therapies and the significant effects PPD exerts on maternal and newborn health. Conventional antidepressants, including selective serotonin reuptake inhibitors (SSRIs), typically necessitate weeks to manifest effects, hindering the initial bonding between mother and child and extending the distress experienced by affected women. Furthermore, several women may exhibit partial responses or resistance to current medications, and apprehensions regarding side effects, especially those impacting nursing, might result in suboptimal adherence. PPD possesses a unique hormonal and neurochemical foundation that conventional antidepressants inadequately address, underscoring the necessity for treatments aimed at its special pathogenesis. Pharmaceuticals such as brexanolone, which regulate the GABAergic system and are intended to mitigate the acute hormonal fluctuations post-childbirth, present a promising strategy for more efficient, swift, and precise interventions. Moreover, the development of novel pharmaceuticals can enhance therapeutic alternatives, guaranteeing individualized and accessible care, alleviating the enduring mental health burden on moms, and boosting familial outcomes.

Unsolved Healthcare Requirements: The available therapeutic choices for postpartum depression (PPD) are restricted, and not all patients exhibit favorable responses to current medications. Numerous current therapies require weeks to demonstrate efficacy, whereas novel medications such as brexanolone can offer swift relief (Frieder et al., 2019).

Enhanced Safety Profiles: Certain contemporary drugs exhibit considerable side effects that may provide challenges for new mothers. New pharmaceuticals can be developed to ensure safety for lactating moms and their infants (Yoon et al., 2022).

Targeted Mechanisms of Action: Novel pharmaceuticals may focus on particular biological pathways implicated in PPD, potentially resulting in more efficacious therapies. Progress in pharmacogenomics can facilitate the creation of medications customized to individual genetic profiles (Yoon et al., 2022).

Managing Comorbid Conditions: Women with postpartum depression frequently experience anxiety and sleep difficulties. Novel pharmaceuticals can more effectively manage these comorbid diseases.

Improving Quality of Life: Effective treatment of PPD can markedly enhance the quality of life for both the mother and the child, fostering bonding and general family well-being.Novel therapies can facilitate moms' expedited reintegration into their everyday activities and obligations.

Economic Advantages: Efficient interventions can diminish the prolonged healthcare expenditures linked to unmanaged PPD. Facilitating expedited recovery for moms can enhance workforce engagement and productivity (*Creative Person-Centered Psychopharmacotherapy in the Context of Prenatal Psychiatry Dilemmas and Challenges*, 2021)

2.2 Mechanism of Action of Brexanolone

The schematic representation of potential brain activity processes for brexanolone is explained in the accompanying image. Like other neurosteroids, BX interacts with GABA-A receptors that are extra synaptic (containing the δ subunit) and synaptic (containing the γ2 subunit). These receptors can have α4 and α6 subunits, which indicate benzodiazepine sensitivity, or they can lack the γ2 subunit that is necessary for benzodiazepine sensitivity. BX allosterically enhances

GABA-A receptor activity, resulting in neuronal hyperpolarization via chloride ion inflow, a reduction in resting membrane potential, and hyperpolarization of the postsynaptic neuron and its network. BX boosts phasic currents by binding to and activating synaptic receptors, resulting in increased amplitude and decreased decay of micro inhibitory postsynaptic currents (mIPSC; left panel). BX interacts with extrasynaptic receptors, augmenting tonic current by a sustained increase in channel conductance without desensitization (right panel). This results in optimal network inhibition, a distinctive characteristic of the neurosteroid, unlike benzodiazepines or other GABAergic agents. Postpartum women exhibit significantly reduced endogenous neurosteroids, termed neurosteroid withdrawal, compared to the heightened levels observed during pregnancy. Nonetheless, the quantity of extrasynaptic GABA-A receptors may be increased despite diminished AP levels. The administration of BX (an injectable formulation of AP) swiftly restores allopregnanolone levels, and the expression of extrasynaptic GABA-A receptors is believed to facilitate the rapid and effective alleviation of PPD symptoms, owing to the neurosteroid's intrinsic anxiolytic and anti-dysphoric properties. Consequently, BX therapy seeks to elevate brain AP levels similar to those observed during the third trimester of pregnancy to alleviate PPD symptoms. GZ: gabazine; DGGC: granule cells of the dentate gyrus (Reddy et al., 2023)

2.3 Preferred Medications

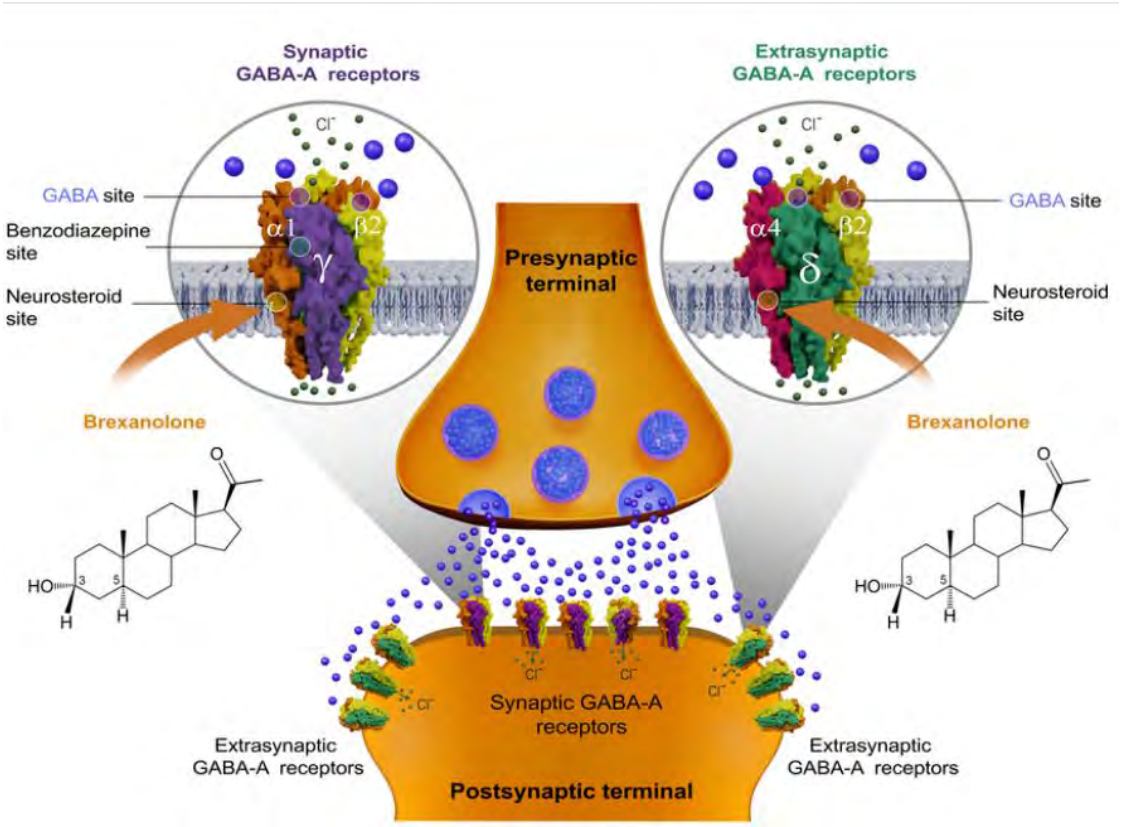

Figure 4: Mechanism of action of Brexanolone *(Reddy et al., 2023)*

2.3 Preferred Medications

Postpartum depression (PPD) is characterized as a serious depressive episode that transpires during pregnancy or within four weeks following delivery, potentially resulting in substantial repercussions for both mother and newborn. Antidepressants are utilized to address PPD, although their efficacy may be constrained by a prolonged onset of peak effect. Brexanolone is approved by the Food and Drug Administration for the treatment of postpartum depression; its administration necessitates patient involvement in a risk evaluation and mitigation strategies (REMS) program. (Hutcherson et al., 2020). Now let's discuss about the

Pharmacokinetics and pharmacodynamics of brexanolone:

Pharmacokinetics: Brexanolone, an allosteric modulator of the GABA-A receptor, is delivered intravenously for the treatment of postpartum depression (PPD). It demonstrates linear pharmacokinetics, with plasma concentrations rising proportionately to the dosage. The medication possesses a brief half-life of approximately 9 hours, rendering it appropriate for urgent intervention. Brexanolone is rapidly disseminated into tissues, attaining peak plasma concentrations within 12 hours after continuous intravenous infusion. It is predominantly metabolized through non-CYP enzymatic routes, including keto-reduction and glucuronidation, and is primarily eliminated by the kidneys as inactive metabolites, presenting minimal risk of accumulating (Reddy et al., 2023)

Pharmacodynamic: Brexanolone increases GABAergic inhibition, which is important for mood regulation and neuroprotection. It does this by acting as a positive allosteric modulator of GABA-A receptors. It is similar to the neuroactive steroid allopregnanolone, which lowers postpartum substantially and is linked to PPD. Brexanolone increases the inhibitory effects of GABA via binding to GABA-A receptors, which lowers neuronal excitability and swiftly stabilizes mood. Contrary to conventional antidepressants, which can take weeks to become effective, clinical investigations show that brexanolone can provide fast antidepressant effects within 60 hours of continuous infusion. Because of its pharmacodynamic effects, postpartum women's acute neurochemical imbalances can be effectively addressed (Edinoff et al., 2021).

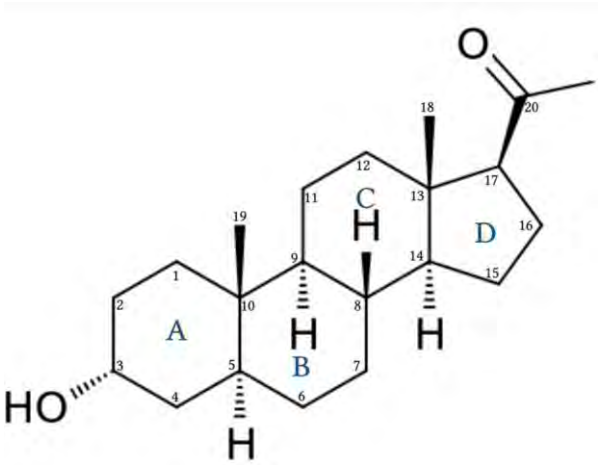

Figure 5: Chemical structure of Brexanolone *(Reddy et al., 2023b).*

Chapter 3

Methodology

3.1 Study Selection

Some website data was used to collect all the information for the review paper. These websites are PubMed, ScienceDirect, ctg.govt, and SpringerLink. And for collecting all the primary information, these databases were used. The search for information took place in the month of April 2024. Primary care physicians are frequently in charge of providing perinatal care, which includes treating mental health concerns. Up to 15% of women have postpartum depression (PPD), which is a prevalent issue. Based on their mental history, symptoms during pregnancy, and recent psychosocial stresses, the majority of women who are at risk can be diagnosed before they give birth. Thankfully, a number of beneficial therapy trials have demonstrated the effectiveness of antidepressants, nonpharmacologic interactions, and most recently, allopregnanolone (Brexanolone) infusion. The 10-item self-rated Edinburgh Postnatal Depression Scale, which is the most widely used screening tool, has been translated into many different languages (Kroska & Stowe, 2020). A new FDA-approved medication for moderate-to-severe postpartum depression is brexanolone. Women who exhibit depressed symptoms, such as emotional, behavioral, or cognitive abnormalities, as early as the third trimester or up to four weeks after birth, may be diagnosed with postpartum depression. Given brexanolone's effectiveness, neurosteroids like allopregnanolone may be crucial for the treatment of post-partum depression. It is not yet known, nevertheless, if brexanolone relieves depression symptoms permanently at or after 30 days of treatment. To make this decision, more research is required (*Brexanolone to Treat Postpartum Depression in Adult Women*, 2021). In this study, the most recent and accurate and complete clinical trial data were use for the intended target.

3.2 Study Selection for clinical trial

The selection of clinical trial data on brexanolone for postpartum depression will focus on randomized controlled trials (RCTs), open-label studies, and observational studies involving postpartum women diagnosed with major depressive disorder. Qualification studies must assess the effectiveness, safety, and pharmacokinetics/pharmacodynamics of brexanolone delivered intravenously. Trials must employ explicit diagnostic criteria for postpartum depression (e.g., DSM-5 or ICD-10) and validated depression assessment measures to evaluate results. Only papers published in peer-reviewed publications in the English language will be considered. The exclusion criteria encompass trials that do not identify postpartum depression as the principal condition, those with insufficient data regarding brexanolone dosing and outcomes, and studies that use supplementary treatments or interventions not associated with brexanolone. The study will use data from both finished and continuing studies with available findings.

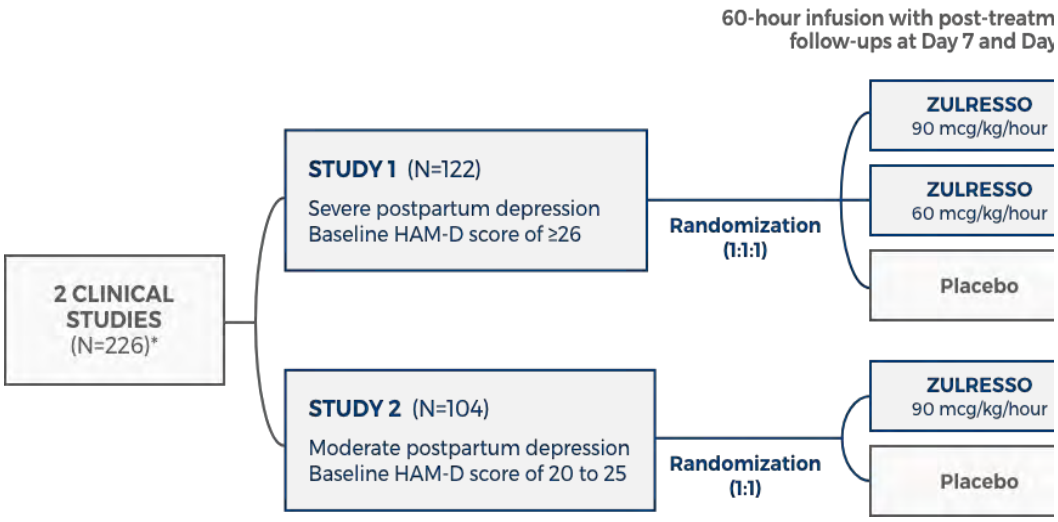

Figure 6: Search criteria for Brexanolone clinical trial data *(Treat Postpartum Depression | ZULRESSO® (Brexanolone) CIV, 2022)*

3.3 Inclusion and Exclusion criteria

3.3.1 Inclusion criteria

For this study, inclusion criteria are given below:

1) Only phase 3 clinical trial data were selected

2) Complete clinical trial with complete result data were used

3) Monotherapy of brexanolone

4) Therapy that is only used for Postpartum Depression

5) Primary and secondary outcomes were measured in median parentage

3.3.2 Exclusion criteria

For this study, the exclusion criteria are given below:

1) Clinical trial data without result

2) Phase 2 and 3 clinical trial data

3) If patient number are less than 10

4) Any other physical condition without Postpartum depression

5) There is no requirement for clinical trial data for specific dose of Brexanolone

Chapter 4

Result and Discussion

4.1 Result

Table 1 : Clinical Trial Data of Brexanolone

Patient No.	Disease	Intervention	Dose	Primary/ Secondary outcomes	Side Effects	Reference
1)12 Patients	Postpartum Depression	Brexanolone	Participants received a 60-hour single continuous IV infusion of brexanolone, at 30 mcg/kg/hour (0 to 4 hours), at 60 mcg/kg/hour (4 to 24 hours), at 90 mcg/kg/hour (24 to 52 hours), followed by a taper to 60 mcg/kg/hour (52 to 56 hours), and 30 mcg/kg/hour (56 to 60 hours)	Primary outcomes: Median % improvement in depression: 41.7 Secondary outcomes: Median% improvement in depression at the highest infused dose 79.4	Dizziness, Loss of consciousness, infusion site pain, localized infection, Weight decreased, dizziness, sedation, headache	(*ClinicalTrials.gov*, 2022)
2) 39 patients	Post Partum Depression	Brexanolone	Participants received a 4-hour dose titration period	Primary outcomes: Median % improvement	Intensional overdose, suicidal ideation,	(*ClinicalTrials.gov*, 2017)

			of 30 µg/kg/h (0 to 4 hours), then 60 µg/kg/h (4 to 24 hours), then 90 µg/kg/h (24 to 52 hours), followed by a taper to 60 µg/kg/h (52 to 56 hours), and 30 µg/kg/h (56 to 60 hours).	in depression -17.72 Secondary outcomesMedian % improvement in depression at the highest infused dose 17.62	Dry mouth, nausea, infusion site pain, dizziness, headache, lose of consciousness, somnolence, Flushing	
3)42 patients	Post Partum Depression	Brexanolone	Participants received a 60-hour single continuous IV infusion, At 30 mcg/kg/hour (0 to 4 hours), at 60 mcg/kg/hour (4 to 24 hours), at 90 mcg/kg/hour (24 to 52 hours), followed by a taper to 60 mcg/kg/hour (52 to 56 hours), and 30 mcg/kg/hour (56 to 60 hours) during the study.	Primary outcomes: Median % improvement in depression 7.1 Secondary outcomes: Median % improvement in depression at the highest infused dose 76.19	Fatigue, infusion site pain, headache, somnolence,	(*ClinicalTrials.gov*, 2021)
4)49 Patients	Post Partum Depression	Brexanolone	Participants received a 4-hour dose titration period of 30 µg/kg/h (0 to 4 hours), then 60 µg/kg/h (4 to 24 hours), then 90 µg/kg/h (24 to 52 hours),	Primary outcomes: Median % improvement in depression-14.62 Secondary outcomes:	Altered state of consciousness, syncope, nausea, fatigue, infusion site pain, Dizziness,	(*ClinicalTrials.gov*, 2022)

			followed by a taper to 60 µg/kg/h (52 to 56 hours), and 30 µg/kg/h (56 to 60 hours).	Median % improvement in depression at the highest infused dose - 14.69	headache, somnolence, infusion site pain	
5)10 Patients	Post Partum Depression	Brexanolone	Participants received a 4-hour dose titration period of 30 micrograms/kg/hr (0 to 4 hours), then 60 micrograms/kg/hr (4 to 24 hours), then 90 micrograms/kg/hr (24 to 52 hours), followed by a taper to 60 micrograms/kg/hr (52 to 56 hours), and 30 micrograms/kg/hr (56 to 60 hours).	Primary outcomes: Median % improvement in depression -20.97 Secondary outcomesMedian % improvement in depression at the highest infused dose - 26.26	Sinus tachycardia, vertigo, abdominal pain, dry mouth, nausea, infusion site extravasation, infusion site pain, localised edema, pyrexia, skin abrasion, pain in extremity, dizziness, somnolence, dizziness postural, sedation, tensions headache, abnormal dreams, insomnia, anxiety, rash.	(*ClinicalTrials.gov*, 2022)

4.2 Discussion

The objective is to address postpartum depression with the utilization of neurosteroids. The provided clinical trial data for treating postpartum depression (PDD) reveals that brexanolone demonstrates significant efficacy in both primary and secondary outcomes. Brexanolone is provided via intravenous infusion at varying durations and dosages according on the patient's condition. Postpartum depression (PPD) is characterized as a serious depressive episode that arises during pregnancy or within four weeks following birth, potentially resulting in substantial repercussions for both the mother and the newborn. Antidepressants are employed to address PPD, although their efficacy may be constrained by a prolonged onset of peak impact. Brexanolone is licensed by the Food and Drug Administration for the treatment of postpartum depression (PPD); its administration necessitates patient involvement in a risk evaluation and mitigation strategies (REMS) program. This review assesses the effectiveness and safety of brexanolone in postpartum depression. (Hutcherson et al., 2020). Brexanolone has a quick onset of action, which makes it a potentially better option for PPD patients than standard medications when a quick response is necessary because of the severity of their condition. Regarding long-term impact and usage in patients outside of clinical trial settings, there are still serious concerns (Hutcherson et al., 2020). Allopregnanolone is a neuroactive steroid that affects neuronal excitability. Brexanolone is a soluble, patented, injectable version of this steroid. Levels of allopregnanolone rise throughout pregnancy and sharply fall following delivery. The impacts of these oscillations on sadness and anxiety are significant. Brexanolone has been shown to be safe and effective in treating postpartum depression in three clinical trials. Brexanolone was well accepted and had an acceptable safety profile throughout all three trials. Loss of consciousness, drowsiness, dry mouth, headache, dizziness, and flushing were the most frequent side effects. Continuous pulse oximetry is advised due to abrupt unconsciousness and severe sedation. For the treatment of moderate to severe postpartum depression, brexanolone

looks to be safe and effective due to its unique mechanism of action. Currently, its usage in clinical practice may be limited because to its expensive cost, substantial adverse effects, and restricted accessibility (Patatanian & Nguyen, 2020). The following study reported a median percentage of numbers which indicate the improvement of patients in depression. A phase 3 clinical trial was conducted (ClinicalTrials.gov registration no. NCT03665038) and 12 patients were taking part in this trial, and it was an open label trial. In this trial the primary and secondary outcome was 41.7 % and 79.4% which indicates the improvement in depression by intravenous administration of brexanolone and intravenous administration of highest dose of brexanolone. In result 2, A phase 3 clinical trial was conducted (ClinicalTrials.gov registration no. NCT02942004) and 39 patients were taking part in this trial, and it was an open label trial. In this trial the primary and secondary outcome was -17.72 % and 17.62% which indicates the improvement in depression by intravenous administration of brexanolone and intravenous administration of highest dose of brexanolone. In result 3, A phase 3 clinical trial was conducted (ClinicalTrials.gov registration no. NCT05059600) and 42 patients were taking part in this trial and it was an open label trial. In this trial the primary and secondary outcome was 7.1 % and 76.19% which indicates the improvement in depression by intravenous administration of brexanolone and intravenous administration of highest dose of brexanolone. In result4,A phase 3 clinical trial was conducted (ClinicalTrials.gov registration no.NCT02942017) and 49 patients were took part in this trial and it was an open label trial . In this trial the primary and secondary outcome was -14.97 % and -14.69% which indicates the improvement in depression by intravenous administration of brexanolone and intravenous administration of highest dose of brexanolone. In result 5, A phase 3 clinical trial was conducted (ClinicalTrials.gov registration no. NCT02614547) and 10 patients were taking part in this trial, and it was an open label trial. In this trial the primary and secondary outcome

was -20.97 and -26.97% which indicates the improvement in depression by intravenous administration of brexanolone and intravenous administration of highest dose of brexanolone.

Brexanolone was associated with a multitude of side effects, including discomfort at the infusion site, disorientation, and loss of awareness, despite its effectiveness. Notable other severe side effects included headaches, nausea, and drowsiness. In several instances, more severe side effects, such as fainting and altered awareness, were observed (Results _ (1)). Even though these side effects were unpleasant, medical assistance was typically provided to control them. People with severe symptoms may benefit more from treatment because PPD is a serious illness overall.

4.3 Evaluation of effectiveness of Brexanolone

Brexanolone is a breakthrough in the treatment of PPD because of its quick beginning impact, which is a significant advantage over other antidepressants that often take weeks to show results. The trials show that brexanolone can significantly reduce depressive symptoms in a matter of days, giving women who are suffering from severe postpartum depression a critical window of time for therapy. However, because of the need for ongoing IV infusion and the need for medical supervision due to the potential for serious adverse effects, this treatment is less accessible in typical outpatient settings. As a result, only hospitalized or closely monitored individuals may use it. Despite these challenges, brexanolone has the potential to rapidly and dramatically reduce severe PPD symptoms, particularly for women who need immediate relief from debilitating symptoms. Future studies could focus on enhancing the safety profile and possibly investigating alternative delivery methods in order to increase its utilization. Brexanolone offers a novel and incredibly effective option for treating severe postpartum depression, addressing a critical need for faster-acting medicines in this population

Chapter 5

Conclusion

5.1 Limitations

There are some limitations of this study, and they are given below:

1) There are different kinds of clinical trial data available for Brexanolone but many of them are not totally completed. There are only a few of them which are fully completed data. And among of them only Phase 3 clinical data were selected.

2)postpartum and depression is a disease and so many patients are not ready to treat this disease after pregnancy that is why they are less amount of patience to complete the clinical trial result.

3) All Clinical trial data have so many end points and these kind of data with diverse types of end point are difficult to analyses the efficacy.

5.2 Future Studies

Research on brexanolone's potential applications and delivery methods is ongoing as it attempts to address postpartum depression (PPD). Future research should concentrate on the following areas:

Oral Formulations: In contrast to the present injectable form of brexanolone, researchers are exploring oral forms of the drug, such as LPCN 1154, which may make the treatment more convenient and accessible (Lipocine, 2024).

Broader Applications: Because of its distinct mode of action, brexanolone may be utilized to treat several types of anxiety or depression (Edinoff et al., 2021).

Other Delivery Methods: Brexanolone is now given intravenously over the course of 60 hours. Subsequent research endeavors could investigate more expedient modes of administration, like oral or subcutaneous formulations (Kose & Cetin, 2017).

Long-term Safety and Efficacy: Although early research has demonstrated that brexanolone is both safe and effective, more long-term information is still required to fully comprehend its long-term benefits and any potential negative effects (Garafola et al., 2023).

Mechanisms of Action: More investigation into the molecular mechanisms of brexanolone's action is desired, with a focus on how it affects inflammatory pathways and GABA-A receptors (Daniels, 2023).

Comparative Studies: To ascertain brexanolone's relative efficacy and ideal use scenarios, a comparison with alternative PPD treatments, such as non-pharmacological therapies and newer drugs, is necessary (Edinoff et al., 2021b).

5.3 Conclusion

Postpartum, the emphasis transitions from maternal health to neonatal well-being. The perceived disregard for the mother's health following childbirth may result in adverse long-term health consequences for both the mother and child, including postpartum depression (PPD). Postpartum depression (PPD) is a significant concern impacting one in six new moms. The symptoms of this illness encompass irritation, anhedonia, worry, chronic discouragement, guilt, and further manifestations. These symptoms often manifest approximately four to six weeks postpartum. Postpartum depression (PPD) can hinder mother-infant bonding and may also result in moms being less inclined to participate in newborn safety measures and attend healthcare appointments. Depressive symptoms may endure for months or even years following childbirth, heightening the risk of maternal suicide (De Sá Vieira et al., 2018). In conclusion, brexanolone signifies a significant progression in the treatment of postpartum

depression (PPD), providing an innovative therapeutic option with swift and enduring benefits. This review has analyzed the pharmacological mechanism of brexanolone, its clinical studies, and practical uses. In contrast to conventional antidepressants, brexanolone's capacity to modify GABA-A receptors targets the distinct neurobiological alterations linked to postpartum depression (PPD), offering treatment within hours to days rather than weeks. Nonetheless, despite its potential, brexanolone has constraints, including the requirement for continuous intravenous infusion in a controlled environment and its substantial cost, which may restrict accessibility for several patients. Furthermore, the long-term impacts and possible adverse reactions necessitate additional research to thoroughly comprehend its significance in comprehensive postpartum care. Subsequent study should focus on enhancing delivery mechanisms, investigating oral formulations, and identifying biomarkers for customized therapy. Although brexanolone is not a panacea, it provides a vital new alternative for meeting the pressing requirements of women experiencing postpartum depression, thereby improving maternal mental health and overall family welfare.

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