

Review Article Brexanolone: A Pharmacotherapy Approach in Post Partum Depression

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ABSTRACT

Postpartum depression is characterized by feelings of sadness, worthlessness or guilt, cognitive impairment, and/or possibly suicidal ideation, it is considered as a life-threatening condition in postpartum women's. Brexanolone is an efficient drug approved for the first time by the USFDA on March 19, 2019 for immediate release through Intravenous route used for the treatment of postpartum depression (PPD). This review article is about the detailed information of Brexanolone includes its drug information, mechanism of action, pharmacokinetic and pharmacodynamics studies, side effects, drug prescribing detail. This article also includes the information about the postpartum depression- its epidemiology, etio-pathology, signs and symptoms, diagnostic pattern.

Keywords: Postpartum depression, Brexanolone, Pathology, Drug dosing, Treatment

INTRODUCTION

Post partum depression

Women after puberty (pregnancy, parturition, lactation) undergoes numerous changes mentally, physically, and behavior which affect on offspring hence it is necessary to adjust for the new demands. If not various neuropsychiatric disorders such as postpartum depression, anxiety and psychosis disorders occur during postpartum period⁴⁰. As per the Andersson et al- 5%-12% of mothers display postpartum anxiety⁴¹, Beck et al- 5%-25% postpartum depression⁴² and Jones et al- 0.1% postpartum psychosis⁴³. It is a major depressive episode with onset during pregnancy or within 4 weeks of delivery. As with other forms of depression, it is characterized by sadness and/or anhedonia and may present with symptoms such as cognitive impairment, feelings of worthlessness or guilt, or suicidal ideation. Indeed, the most common cause of maternal death after childbirth in the developed world is suicide¹. A depressive episode at this time in a woman's life can not only deprive her of the enjoyment of a new infant, but can have serious effects on the maternal-infant bond and later infant development. Estimates place the prevalence of PPD in the United States at approximately 12% of births [1].

Epidemiology

As the survey made by National Institutes of Health, turning discovery into health reveals that approximately 1 in 9 women in the United States experiences symptoms of postpartum depression, according to the Centers for disease control and prevention. According to National National Institute for Health and Care Excellence 10-15% of women's are more prone to PPD after delivery hence they required intervention [2].

According to standardized diagnostic and statistical manual, postpartum depression is a type of depressive episode, which occur within 1 year of childbirth. It is a significant public health problem which affects about 17% and 19% mothers globally and in low and middle income countries respectively. As a study conducted by Upadhyay RP et al.,⁵ Postpartum psychiatric disorders can be divided into three categories: postpartum blues; postpartum psychosis and postpartum depression. Postpartum blues, with an incidence of 300–750 per 1000 mothers globally, may resolve in a few days to a week. Postpartum psychosis, which has a global prevalence ranging from 0.89 to 2.6 per 1000 births, is a severe disorder that begins within four weeks postpartum and requires hospitalization. Postpartum depression can start soon after childbirth or as a continuation of antenatal depression and needs to be treated. The global prevalence of postpartum depression has been estimated as 100–150 per 1000 birth [3].

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In the 1980s, NIMH IRP researchers discovered that metabolites (products formed when the body breaks down or “metabolizes” other substances) of the steroid hormones progesterone and deoxycorticosterone bound to gamma - aminobutyric acid (GABA) a major inhibitory neurotransmitter in the brain. These steroids were found to amplify GABA-activated chloride ion currents, thereby impacting the excitability of neurons. These findings explain that how the metabolites fluctuate during stress and during the estrous cycle in rats and the menstrual cycle in humans. Research indicated that the concentration of one of these metabolites (allopregnanolone) increases during pregnancy, but then drops after birth. In some women, this drop triggers the development of depression and anxiety [4].

Etiopathology

The etiological factors for PPD includes hormonal impairment, genetic factor, sleep disturbance, psychological factors, neuro-immune factors described briefly in below figure. The pathophysiology of postpartum depression is complex, and not yet completely known. Based on above mentioned etiological factors influences. Environmental factors includes marital problems, low socio-economic status, lack of social support, obstetric pregnancy-related complications (e.g *Caesarean* section or instrumental delivery), and alcohol or other drug abuse, psychosocial stress. A systemic review conducted by Couto et al [48] reveals that the gene cause for major depression is responsible for PPD, several genes implicated in major depression, PPD such as serotonin transporter (5-HTT), Tryptophan Hydroxylase 2 (TPH2), monoamine oxidase (MAO), Catechol-O-Methyl Transferase (COMT). A 5-HTT gene polymorphisms- 5HTTLPR long allele might be a risk factor for postpartum depression, especially with other risk factors, such as unfavorable environments, previous psychiatric history, and maternity stressors and for COMT-Val158Met allele, autumn or winter delivery, and stressful life events, etc. Lin et al [49] explained TPH2 (rate-limiting enzyme of serotonin biosynthesis) was found only in women with peripartum major depression and anxiety disorder where TPH2 2755A allele act as a dominant gene with higher risk [5].

Signs and symptoms

Many studies report that symptoms of PPD are variable. Rapid changes in several hormonal levels following delivery affect prominently neurotic symptoms such as: Anxiety including somatic and social anxiety are fairly common, affecting up to 10-50%, Suicidal tendency affecting upto 3-20% other symptoms include: phobias, irritability, 7, 8, 9 somatic symptoms and fatigue, insomnia. **DIAGNOSTIC CRITERIA FOR PPD:** Major Depressive Episode (MDE) are diagnosed by Diagnostic and Statistical Manual (DSM-IV) criteria, similarly to diagnose PPD following Criteria are used: Diagnostic and Statistical Manual (DSM-IV) do not differ in the postpartum period as compared to other times, and include at least 2 weeks of persistent low mood or anhedonia, as well as at least four of the following: increased or decreased appetite, sleep disturbance, psychomotor agitation or retardation, low energy, feelings of worthlessness, low concentration, and suicidal ideation [6].

Physical and psychological changes are seen during Pregnancy upto first week of delivery due to hormonal imbalance hence there is complicate to diagnose the condition. Edinburgh Postnatal Depression Scale (EPDS), Postpartum Depression Screening Scale (PDSS) and Physician's Health Questionnaire (PHQ-9) are used to screen usually 4-6 weeks after delivery [7].

Treatment for pppd

Treatment for patient who had a history of severe depression during pregnancy and mild PPD follows: tricyclic antidepressants (TCAs), Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin and Norepinephrine Reuptake Inhibitors (SNRI). For a woman with moderate or severe depression in pregnancy or the postnatal period, follows: A high-intensity psychological intervention (for example, cognitive behavioral therapy), TCA, SSRI /SNRI or a high-intensity psychological intervention in combination with medication [8].

New drug therapy for pppd-brexanolone drug details

Brexanolone is an analog of the endogenous human hormone allopregnanolone. It is a synthetic neuroactive steroid gamma-aminobutyric acid A [GABA(a)] receptor positive modulator. It is available in the market with brand name “Zulresso” by the Sage Therapeutics Inc. A commonly used anti-depressive medications elicit actions that may modulate the presence and activity of substances like serotonin, norepinephrine, and monoamine oxidase but do not mediate activities directly associated with PPD like natural fluctuations in the levels of endogenous neuroactive steroids like allopregnanolone [9].

Structure: 3 α -OH DHP/ allopregnan-3 α -ol-20-one/ Allopregnanolone/ Brexanolone

Chemical formula: C₂₁H₃₄O₂ Molecular weight: 322.53

IUPAC name

1-[(1S,3aS,3bR,5aS,7R,9aS,9bS,11aS)-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-1-yl]ethan-1-one
Categories: Anesthetics, Anticonvulsants, Central Nervous System Agents, Central Nervous System Depressants, Corpus Luteum Hormones, GABA Modulators, Gonadal Hormones, Gonadal Steroid Hormones, Hormones, Hormone Substitutes, and Hormone Antagonists, Pregnanes, Pregnenediones, Pregnenes, Progesterone Congeners, Steroids.
Pharmacodynamics: Mechanism of action: (ZULRESSO™) is a potent, positive allosteric modulator because it modulates neuronal excitability through positive allosteric modulation on the synaptic and extrasynaptic γ -aminobutyric acid (GABA) type A receptors. It is a combination of allopregnanolone, an endogenous inhibitory pregnaneneurosteroid, and sulfobutylether-beta-cyclodextrin (a solubilizing agent). Allopregnanolone being a major metabolite of progesterone, its levels continue to rise with progesterone during pregnancy (third trimester). The stimulation of extrasynaptic GABA type A receptors mediate tonic inhibition which makes allopregnanolone's mechanism unique when compared to benzodiazepines hence comparing with other class of drug, brexanolone advanced to treat pppd [10].

Pharmacokinetics: Absorption- low oral bioavailability of approximately < 5% in adults

Distribution -approximately 3 L/kg, (extensive distribution into tissues)

Protein binding -greater than 99%

Half-life -approximately 9 hours

Metabolism -metabolized by non-cytochrome (CYP) based pathways by way of three main routes - keto-reduction (via aldo-ketoreductases), glucuronidation (via UDP - glucuronosyl transferases), and sulfation (via sulfotransferases) Elimination -47% in the feces and 42% in urine, where less than 1% as recovered as unchanged brexanolone [11].

Side effects

Cardiac disorder(tachycardia), GI disorder (Diarrhea 2%, Dry mouth 1-3%, Dyspepsia 2%, Oropharyngeal pain 2%), Nervous System Disorders(Dizziness, presyncope, vertigo 13-12%, Loss of consciousness 5-3%, sedation, somnolence 13-21%), Vascular Disorders(Flush, hot flush), sudden loss of consciousness, excessive sedation 14, respiratory thoracic and mediastinal disorder, nasal congestion [12].

Drug interactions

Brexanolone majorly interacts with CNS Depressants (opioids, benzodiazepines) close monitoring is required with 168 drugs.

Warnings

Patients consuming this drug are at risk of sudden loss of consciousness, excessive sedation hence monitoring on these conditions with continuous pulse oximetry monitoring required. ZULRESSO REMS- It is a program through ZULRESSO is available. Prescribing information and medication guide: Dosage and Administration -to reduce the possible risk by the drug [13].

- A healthcare professional must be on site for the duration of the 60-hour (2.5 days) infusion.
- Instructions are included to start infusion in the morning, so that the increases in dose from 30 µg/kg/h to 60 µg/kg/h and from 60 µg/kg/h to 90 µg/kg/h always take place during waking hours, in order to periodically monitor for excessive sedation.
- Instructions are included for admixture preparation such that the total amount of brexanolone in the IV bag is reduced relative to the amount employed in the clinical trials.
- Instructions are included to use a peristaltic infusion pump to ensure accurate administration of the infusion rates of Brexanolone IV and to avoid the possibility of a wide-open infusion line.

Special population

Hepatic impairment- Dosage adjustment in patients with hepatic impairment is not necessary. Modest increases in exposure to unbound brexanolone and modest decreases in exposure to total brexanolone were observed in patients with moderate to severe hepatic impairment with no associated change in tolerability. Renal impairment- No dosage adjustment is recommended in

patients with mild (eGFR 60 to 89 mL/minute/1.73m²), moderate (eGFR 30 to 59 mL/minute/1.73 m²) or severe (eGFR 15 to 29 mL/minute/1.73 m²) renal impairment. Avoid use of ZULRESSO in patients with end stage renal disease (ESRD) with eGFR of < 15 mL/minute/1.73 m² because of the potential accumulation of the solubilizing agent, betadexsulfobutyl ether sodium [14].

Preclinical and clinical studies on brexanolone

In spite the lack of preclinical animal models to study on PPD, Melón et al. has developed unique preclinical mouse models that exhibit abnormal postpartum behaviors. Mice with a loss or reduction in the expression of the GABA α receptor (GABA α R) α subunit (Gabra α -/- or Gabra α +/-, respectively) and mice that lack the K⁺/Cl⁻-co-transporter, KCC 2, specifically. Corticotropin-releasing hormone (CRH) neurons (KCC 2 / Crh mice) exhibit depression-like behaviors restricted to the postpartum period and deficits in maternal care, he studied using this model on brexanolone against benzodiazepines and clobazam as standard drug. He observed that the brexanolone treated group shows increased latency to immobile time, reduced time of immobile and also its maternity state i.e. Increased time spent with its pups [15].

Phase II clinical studies on brexanolone vs placebo, as carried out on 32 female with age group of 18-45 years with severe postpartum depression, Patients received a single continuous intravenous infusion of brexanolone for 60h during inpatient care under the following schedule: 30 µg/kg per h (0-4 h); 60 µg/kg per h (4-24 h); 90 µg/kg per h (24-52 h); 60 µg/kg per h (52-56 h); 30 µg/kg per h (56-60 h) followed for 30 days. Primary outcome of this study shows that increase in Hamilton Rating Scale for Depression (HAM - D) when compared to placebo injection and secondary outcomes shows HAM-D; proportion of patients achieving remission (HAM-D total score \leq 7), the proportion of patients achieving response (\geq 50% reduction in HAM-D total score), change from baseline in the Bech-6 subscore [16].

Phase 3: Studies and Trials Included in the Population PK Analyses A multicenter, randomized, double blind, parallel group, placebo controlled study was conducted on 108 patients to evaluating the efficacy, safety in the form of injection in treatment of adult female with moderate PPD. Subjects were randomized in 1:1 ratio. Continuous IV infusion of blinded study drug administered as 30 microg/kg/h for 4 h, 60mcg/kg/h for 20h and 4h, 90mcg/kg/h for 28h etc. data described as rich PK- pre infusion just prior infusion 30,36,48,60h after infusion onset and 72 hr after infusion onset (12 h post infusion) Primary outcome after 3 days reports that baseline change in Hamilton Rating Scale for Depression (HAM-D) when compared effect of brexanolone on depressive symptoms in subjects with moderate postpartum depression with placebo injection [17-19].

Secondary efficacy outcome measures were mean HAM-D total score and least-squares (LS) mean change from baseline during the inpatient stay at 0, 2, 4, 8, 12, 24, 36, 48, 60, and 72 h after infusion and follow-up days 7 and 30; HAM-D total scores were further examined for remission (HAM-D total score \leq 7) and

response (reduction in HAM-D total score $\geq 50\%$); Clinical Global Impression-Improvement (CGI-I) response, defined as a rating score of 1 (very much improved) or 2 (much improved); change from baseline in score on the Montgomery-Asberg Depression Rating Scale; change from baseline in HAM-D subscale (including Bech 6, Core, Anxiety, and Maier) score and individual item scores; and change from baseline in scores on the Edinburgh Postnatal Depression Scale, Patient Health Questionnaire 9, and the Generalized Anxiety Disorder 7-item questionnaire. Safety and tolerability of brexanolone compared with placebo as measured by the change from baseline in the incidence of adverse events, vital signs, clinical laboratory evaluations, and ECG parameters [Time frame: 30 days]. Safety of brexanolone compared to placebo as measured by the change from baseline in suicidal ideation and behaviour assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) score [Time frame: 30 days].

CONCLUSION

In conclusion during writing process of a review article on Brexanolone and PPD. We concluded that based on various surveys, PPD is one of the serious psychological disorder. Improper diagnosis and treatment can worsen the patient condition. Available non pharmacological (CBT, ECT) and pharmacological treatment (TCA, SSRI /SNRI) which are non-specific for depression where brexanolone is a FDA approved drug to treat specifically PPD.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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