Review Article

Brexanolone: Targeted Pharmacotherapeutic Agent for Postpartum Depression

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ABSTRACT

Postpartum depression is a major depressive disorder episode which can occur anytime from the third trimester of pregnancy to 4 weeks postpartum. The primary treatments options for postpartum depression are psychotherapy and pharmacotherapy which include antidepressants. Severe drug resistant depression is usually treated with electro convulsive therapy, but its patient acceptability is poor. The approval of brexanolone for management of severe post-partum depression is a highly appreciated as none of the existing agents are specifically approved for this purpose. Brexanolone is a novel, allopregnanolone analogue acting as GABA A receptor modulator specifically approved for use in severed postpartum depression. This article reviews about pharmacology of this new agent.

Keywords: Postpartum depression, Brexanolone, Severe postpartum depression, GABA A receptor modulator, Allopregnanolone analogue.

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INTRODUCTION

Postpartum depression (PPD) is defined as a major depressive disorder (MDD) episode which can occur anytime from the third trimester of pregnancy to 4 weeks postpartum.[1] As per WHO, worldwide prevalence of PPD is approximately 100–150 per 1000 births whereas in India PPD is prevalent in 22% cases.[2] PPD has severe adverse implications for mother, offspring and family and therefore is a major public health concern.[3] PPD can lead to impaired ability of mother for self-care and therefore affect the child care as well, which in turn can lead to impaired cognitive, emotional and behavioural development of the child. Severe PPD can also result in suicidal thoughts and pose a risk for child health. Since none of the pharmacological agents are approved for use in PPD, therefore most of the treatment options are adapted from the treatment for major depressive disorders (MDD). The primary treatments options for PPD are psychotherapy and pharmacotherapy. Lack of clinical trials in pregnant participants due to ethical constraints makes it difficult to establish the efficacy of pharmacotherapy in PPD.[4] The recommended antidepressants include selective serotonin/ norepinephrine reuptake inhibitors, as well as tricyclic and second-generation antidepressants.[3] Severe postpartum unipolar major depression refractory to multiple (e.g., four) sequential medication trials is usually treated with electro convulsive therapy (ECT) due to its rapid action.[3] Even though ECT has proven clinical effectiveness and is also cost-effective, but it is associated with social stigma and negative attitude leading to poor patient acceptability.[5] The introduction of brexanolone provides the psychiatrist with an additional hope for the treatment of PPD patients who may decline or not respond to ECT. This article reviews pharmacological aspects of brexanolone which is a revolutionary targeted drug therapy for the management of moderate to severe postpartum depression.

Mechanism of action

Figure 1 demonstrates the postulated mechanism of action of brexanolone. Regulation of stress response by hypothalamic-pituitary-

adrenal (HPA) axis, by increasing cortisol levels is found to be over-reactive in depression.[6] Allopregnanolone is an endogenous progesterone metabolite produced in the body which acts as a positive allosteric modulator at the γ-aminobutyric acid type A (GABA-A) receptor.[7] Plasma concentrations of allopregnanolone increase during pregnancy, reach a peak at the end of pregnancy, and drop quickly after parturition. This leads to reduction of GABA-A activity in postpartum period leading to dysregulated neural network resulting into postpartum episodes.[8] Allopregnanolone binds to GABA-A receptors located on hypothalamus and facilitates the binding of GABA to GABA-A receptors and thereby dampens the overactivation of the HPA axis. Brexanolone is a synthetic analogue of allopregnanolone agonist having a chemical formula $C_{12}H_{34}O_2$, and acts as positive allosteric modulator at GABA-A receptors.

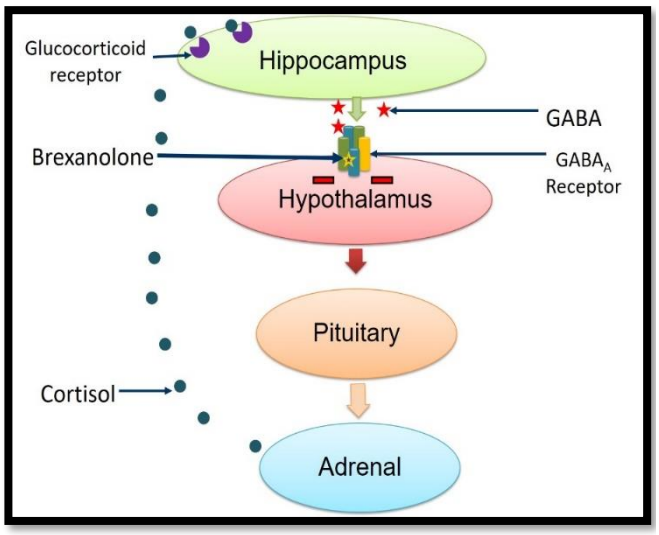

Figure 1: Postulated mechanism of action of brexanolone

Pharmacokinetics

Brexanolone is available as buffered, isotonic solution of allopregnanolone in sulfobutylether-β-cyclodextrin to be administered intravenously. It is widely distributed in tissues and the protein binding is greater than 99%. The volume of distribution of brexanolone is (3L/Kg). It is extensively metabolized by three non-cytochrome (CYP) pathways (sulfation, ketoreduction & glucuronidation), into 3 inactive metabolites and thus minimal drug interaction is suspected. It is almost equally excreted in urine and faeces. The half-life of the drug is 9 hr and total plasma clearance is 1L/h/kg.[9]

Clinical indication

Brexanolone is the foremost clinically approved agent for the management of postpartum depression by the Food and Drug Administration.

The safety and efficacy of brexanolone was evaluated in series of four trials.[10-12] The primary scale used to assess the efficacy in postpartum depression was change in Hamilton Rating Scale for Depression (HAM-D), which is validated questionnaire with scores ranging from 0 to 52. Decrease in the scores correlates with decrease in severity of depressive episodes. The summary of the clinical trials is represented in Table 1.

Administration and dosing schedule

Brexanolone is available as a 100mg/20mL vials and has to be administered as a single intravenous infusion over 60 hours under continuous medical supervision.[13] The dosing schedule during 60 hours is given in Figure 2.

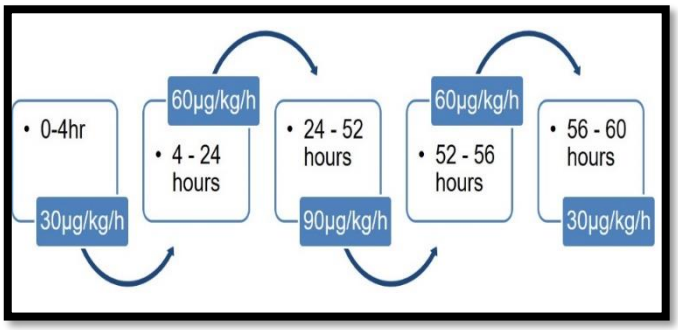

Figure 2: Dosing schedule of brexanolone during 60 hours infusion

Safety profile

Most frequent adverse reactions (incidence ≥ 5%) were sedation/ somnolence, dry mouth, loss of consciousness and flushing. Other reported adverse effects (≤10% incidence) are nausea, rash, postural dizziness, pyrexia, vertigo, sinus tachycardia, fatigue and infusion site pain. Unlike other GABA$_A$ receptor modulators, brexanolone did not exhibit features of drug dependence, withdrawal or abuse hence is categorized as a Schedule IV drug. It has FDA

black box warnings for loss of consciousness, CNS depression and specialized medical setting requirement during drug infusion. During the drug infusion women should be continuously monitored for hypoxemia and excessive sedation during planned non-sleep periods. Infusion should be terminated in case of hypoxemia and stopped until symptoms resolve in case of excessive sedation. In addition, patient already suffering from depression should be strictly monitored for any provoked suicidal ideation during brexanolone treatment. [13]

Table 1: Summary of the clinical trials conducted with brexanolone[10 -12]

Study	Study design/ duration	Number of patients	Dose & duration	Change from Baseline in HAM-D Score at 60 Hour	Change from Baseline in HAM-D Score at 30 days
Phase 2	Open-label	4	86mcg/kg/hr; 60 hours	-24.7 (P=0.001)	Not assessed
Phase 2	Randomized, double-blind, placebo-controlled	21	60mcg/kg/hr; 60 hours	-12.2 (P=0.0075)	–11·9 (P=0·0095)
Phase 3	Randomized, double-blind, placebo-controlled	138	60mcg/kg/hr; 60 hours	-5.5 (P=0.0013)	-5.7 (P=0·0044)
			90mcg/kg/ hr; 60 hours	-3.7 (P=0.0252)	–3·8 (P=0·0481)
Phase 3	Randomized, double-blind, placebo-controlled	108	90mcg/kg/hr; 60 hours	–2.5 (P=0.0160)	-5.7 (P=0·0044)

Table 2: Comparative features of available treatment option for PPD.

	Selective serotonin reuptake inhibitors (SSRI)	Serotonin norepinephrine reuptake inhibitors (SNRIs) and Tricyclic antidepressants (TCA)	Electro-convulsive therapy (ECT)	Brexanolone
Mechanism of action	Serotonin reuptake inhibition	Serotonin norepinephrine reuptake inhibition	Not well defined	$GABA_A$ Modulator
Efficacy	Mixed data	Limited data	Effective	More effective
Response	3-6 weeks, sustained effect	4-6 weeks, sustained effect	1-2 week, rapid effect	2-3 days, rapid & sustained effect
Relapse rate	20-80%	28-87%	27%	6%
Inpatient Hospitalization	No	No	Yes	Yes
Side effects	Less	More	Less, Temporary memory loss	Less, Excessive sedation Stop infusion or taper dose.
Cost	Cheap	Cheap	Cost effective	Expensive
Indication	Major Depressive Disorder	Depression	Therapy resistant depression	Postpartum depression

Drug interactions and precautions

Currently, only pharmacodynamics drug interactions with CNS depressants and antidepressants are reported. Concomitant use of these agents pose increased risk for sedation-related adverse effects and therefore it should be used cautiously with opioids or other CNS depressants. Patients should also be warned against performing activities needing mental alertness, such as driving after infusion.

Brexanolone is contraindicated in end stage-kidney disease because of possible accumulation of solubilizing agent (betadex sulfobutyl ether sodium) which might damage the epithelial cells. Dose adjustment is not required in hepatic impairment or renal impairment. However, brexanolone should not be used in pregnant

women because of risk of developmental defects to fetus. Developmental defects have occurred in animal fetuses when brexanolone was given at higher dose.[13] Brexanolone is not expected to pose a significant risk to breastfed infants as it has low oral bioavailability. The safety and effectiveness of brexanolone has not been established in pediatric patient.

Merits and Demerits

The comparative assessment of the available treatment options for PPD is given in table 2.[14-17] The major advantage of brexanolone as compared to existing treatment option is rapid resolution of symptoms of PPD within 72 hours as compared 4 to 6 weeks with other conventional oral treatments. The demerits of brexanolone therapy include intravenous infusion, prolonged hospitalization (> 60 hours) and high cost of therapy. Although, brexanolone has quicker response and remission but the maintenance of this effect at after 30 days is yet to be explored.

CONCLUSION

Brexanolone is the foremost agent approved for the management of postpartum depression. It appears a promising targeted pharmacotherapeutic intervention for PPD, with few adverse effects and interactions. Availability of brexanolone provides an alternative to the patients suffering from severe PPD who may decline or not respond to ECT.

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