International Journal of Basic & Clinical Pharmacology
Kumar SA et al. Int J Basic Clin Pharmacol. 2022 May;11(3):275-278
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20221045

Review Article

Investigational synthetic neuroactive steroid zuranolone in treatment of major depressive disorder with peripartum onset

Shivakumar A. Kumar*, Ravi Chandra C. V.

Department of Pharmacology, ESIC Medical College PGIMSR and Model Hospital, Rajajinagar, Bangalore, Karnataka, India

Received: 31 January 2022
Accepted: 28 February 2022

***Correspondence:**
Dr. Shivakumar A. Kumar,
Email: shivk1370@gmail.com

ABSTRACT

Major depressive disorder with peripartum onset or peripartum depression is a common condition experienced by a large proportion of women and to some extent even in men. The current treatment strategies involve the use of conventional pharmacotherapeutic classes of drugs like selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and psychotherapy methods in the management of this condition. In this article, we try to review and evaluate the pathophysiology of the condition along with the safety and efficacy of the novel investigational therapeutic drug zuranolone, which is a synthetic neuroactive steroid (NAS) that has shown promise in clinical trials for the management of conditions like major depressive disorder, peripartum depression and bipolar disorder. The synthetic NAS zuranolone is an orally bioavailable positive allosteric modulator of the gamma amino butyric acid ($GABA_A$) receptor, which can regulate the action of the GABAergic pathway implicated in many depressive episodes and also affect the normal functioning of the hypothalmo pituitary-adrenal (HPA) axis which is the core pathophysiological cause behind major depressive disorder with peripartum onset.

Keywords: Zuranolone, Peripartum depression, Neuroactive steroids, $GABA_A$ receptor

INTRODUCTION

According to the diagnostics and statistical manual of mental disorders-V, a patient is diagnosed to have depression if there is a change from his/her previous functioning and need to have a minimum of 5 symptoms out of the following 9, during the same 2-week period: depressed mood, diminished interest in all activities, significant weight loss (when not dieting) or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, ratigue or loss of energy, feeling of worthlessness or guilt, diminished ability of concentration, and recurrent suicidal ideation, suicidal attempt, recurrent thought of death.

Major depressive disorder causes impairment and distress in occupational, and social settings and the episode is not attributable to a specific medical condition or substance.[1]

A diagnosis of major depressive disorder with peripartum onset is made if the patient has the above-mentioned symptoms either during pregnancy or the 4-weeks following delivery. One out of two peripartum depressive disorders begins before delivery.[1] Women may experience the onset of symptoms either during pregnancy or after delivery. Over half the women diagnosed with "postpartum depression" show onset during pregnancy and not post-delivery. Hence the condition is collectively referred to as "peripartum major depression" or major depressive disorder with peripartum onset.[1]

The postpartum period continues to be a stage where the neuroendocrine changes in the body alter the psychological and physical well being of the mother and possibly have implications on further family planning and quality of life. Symptoms like irritability and restlessness, anxiety, crying for no reason which develops within a few days of delivery, should not be confused for peripartum depression, as they constitute a transient and self-limiting condition called "baby blues" which resolves on its own within 2 weeks.[2]

1 out of 7 women continue to experience peripartum depressive disorder and the numbers are possibly higher due to the underreporting of cases due to the lack of primary healthcare facilities in underdeveloped areas and the taboos associated with mental health illnesses.[21] There is a significant increase in risk observed in patients who experience anxiety and mood symptoms during gestation. Peripartum depression is also observed in 4% of fathers until 1 year after a child's birth.[22]

Currently, the condition can be treated by using multiple classes of drugs like selective serotonin reuptake inhibitors (SSRIs), selective nor-epinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAO), estradiol and progestin preparations.[7] Women with peripartum depression tend to prefer psychotherapy more than pharmacological therapy.[7,17] Electroconvulsive therapy (ECT) is also an option in the management of severe or refractory cases, but further data is necessary to analyze the safety of ECT over pharmacological therapy.[7,18]

The complex and multifactorial etiological factors of peripartum disorders and the need to improve the available treatment modalities warrant the need for the development of novel strategies which tackle the underlying pathophysiology of the disease.

DISCUSSION

Pathophysiology of major depressive disorder with peripartum onset

Dysregulation of the hypothalamic-pituitary axis remains to be one of the main etiological factors in peripartum depression. During the 3rd trimester of pregnancy, there is a surge in the levels of hormones like cortisol, estrogen, progesterone with an elevated functioning of the hypothalmo pituitary-adrenal (HPA) axis.[3,4] After delivery, there is a decrease in levels of hormones which were previously higher and a blunted activity of the HPA axis is noticed.[5] Hyperreactivity of the HPA axis coupled with elevated cortisol levels is seen in patients with major depressive disorders.[6] A hyporeactive HPA axis is observed in patients only 6-12 weeks after delivery.[5] A normally functioning HPA axis regulates itself via the negative feedback control mechanisms, and appears to be dysregulated in depressive disorders. Since the majority of the women face similar hormonal changes during pregnancy and after delivery, the following factors also play an important role in the pathophysiology of the disease.

Neuroactive steroids (NAS) like allopregnenalone are important factors in decreasing the activity of the HPA axis in response to stressors during pregnancy.[7,10] NAS is also a positive allosteric modulator of the gamma amino butyric acid ($GABA_A$) receptor. The levels of NAS fluctuate in the body during pregnancy. During the antepartum period, studies have shown an increase in allopregnanolone, while during the postpartum period there is a decrease observed.[8,9] Elevated allopregnanolone levels result in downregulation of $GABA_A$ δ and γ2 receptors, which physiologically get reversed after delivery.[8,9] Failure of this reversal may result in insufficient upregulation of $GABA_A$ receptors, resulting in dysregulation of the GABAergic pathway and symptoms of peripartum depression. GABA being the main inhibitory neurotransmitter in the body plays a crucial role in the neural circuitry which manifests in multiple mood disorders is dysregulated. NASs modulates the neuronal activity in the body by action on $GABA_A$ receptors and has shown anxiolytic effects and improvement in mood in preclinical settings.[13,19,20]

Several studies have shown that inability to adapt to stressors (from life events), the physical toll of pregnancy and genetics also play a major role in the pathogenesis of peripartum depression.[3,11,12]

Efficacy and safety of zuranolone in treatment of peripartum depression

Synthetic NASs work at multiple $GABA_A$ receptor subtypes to enhance the GABAergic transmission in the central nervous system (CNS). Synaptic and extrasynaptic potentiation afforded by the drug zuranolone, which is an investigational orally bioavailable, synthetic NAS positive allosteric receptor modulator at $GABA_A$ receptor shows promise in the management of depressive disorders. The success of allopregnanolone formulations like brexanole, which is an intravenous drug used in the management of peripartum depression, warrants the push towards evaluating the safety and efficacy of zuranolone.

A double-blind, placebo-controlled, dose-finding Phase-I study was conducted in 108 healthy volunteers. Multiple ascending dose (MAD) and single ascending dose (SAD) studies were conducted to evaluate the tolerability, maximum dose and safety of the drug zuranolone.[13] Doses ranging from 0.25 to 66 mg were used across 9 cohorts, where 36 volunteers were part of the MAD study and 72 volunteers were part of the SAD study.[13] In the MAD study, subjects were randomized 9:3 and received a once-daily dose (15 mg, 30 mg or 35 mg) of the drug or placebo for 7 days.[13] In the SAD study, subjects were randomized 6:2 and were administered a single dose of the drug or placebo. The study revealed that the half-life of zuranolone was around 16-23 hours and a Tmax of 1 hour.[13] The

maximum tolerated dose in MAD and SAD studies were found to be 30 mg and 55 mg respectively. The Phase- I study revealed that the drug was well tolerated.[13]

A randomized, double-blind placebo-controlled Phase-III trial was conducted for the first time. The study included women of the age groups 18-45 years old who were less than 6 months postpartum and have had a major depressive episode (without psychosis) during the period ranging anytime from the 3rd trimester of pregnancy up to 4 weeks after delivery.[14] An interesting consideration of HAMD17 scores was made. Hamilton rating scale for depression is the most commonly used clinical assessment tool to check for the severity of depression in patients.[15,16] Originally designed to measure depression severity using 17 items, it has evolved over the last few decades where multiple versions are being used in clinical medicine and psychiatry. Patients with HAMD17 scores of 26 or higher were considered for this study. 153 patients were randomized at 1:1 and 76 subjects received the placebo whereas 77 subjects received 30 mg of zuranolone.[14] HAMD17 score improvement was observed in the group being administered the drug over the placebo. Efficacy outcomes showed a bigger decrease in HAMD17 scores of patients receiving zuranolone versus placebo with a difference of -4.2 points between them (least-squares mean, -17.8 points with zuranolone versus -13.6 points with placebo; and p=0.003) at the end of 15 days.[14] The difference was sustained past day 15 after stopping the drug up to day 45 when the difference between HAMD17 scores was -4.1 between zuranolone and placebo groups.[14]

The most common adverse effects observed were Somnolence in 15% and headache in 9% of the volunteers who received zuranolone.[14] The study showed an overall well-tolerated response in volunteers along with an improvement in the severity of depression, measured by HAMD17 scores and provides hope for further development to improve the management strategies in depressive disorders.[14]

Another open-label placebo-controlled Phase 2 trial was conducted for evaluation of the safety and efficacy of zuranolone in the treatment of patients with bipolar disorders. The study revealed an improvement in the depressive symptoms of patients and an overall improvement in the patient's condition.[17]

CONCLUSION

Major depressive disorder with peripartum onset is a common mood disorder experienced by 1 in 7 women. It usually goes undiagnosed in many women due to the stigma related to mental health illnesses and privacy concerns amongst mothers.[21] The disease is known to have long term implications on the quality of life, and bonding between the child and mother. The role of NAS in the complex pathophysiology of this disease shows the potential benefits of the development of investigational synthetic NAS positive allosteric modulators like zuranolone which enhances the $GABA_A$ receptor action. It provides an advantage of being a once-daily dose, orally bioavailable drug over brexanolone, which is an intravenous synthetic NAS requiring long duration and hospital admission for administration. Trials conducted confirms the clinical improvement in patients, measured using the decreasing baseline HAMD17 scores. The safety and efficacy shown by the drug in multiple trials for treating conditions like major depressive disorder, peripartum depression, and bipolar disorder make it an exciting prospect for exploring its potential therapeutic benefits in other psychiatric illnesses.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Kumar SA, Ravi CCV. Investigational synthetic neuroactive steroid zuranolone in treatment of major depressive disorder with peripartum onset. Int J Basic Clin Pharmacol 2022;11:275-8.