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Brexanolone: an allosteric modulator of GABA-A receptors in the rapid treatment of postpartum depression

Postpartum depression (PPD) is a distinct and readily identified major depressive disorder that is one of the most common neurobiological complications of childbirth, which occurs in 13% of women after delivery (one in every eight) and affecting a subset of women typically commencing in the third trimester of pregnancy or within four weeks after giving birth [1]. It is a serious mood disorder associated with a range of debilitating symptoms that impact a women's ability to function, and is a leading cause of maternal suicide. It is estimated that PPD affects 500,000–750,000 mothers in the US each year [2]. PPD may have devastating consequences for a woman and for her family, which may include significant functional/occupational/interpersonal impairment, depressed mood and/or loss of interest in her newborn, and accompanying depression symptoms such as loss of appetite, difficulty sleeping, psychomotor retardation/agitation, lack of concentration, loss of energy, and poor self-esteem. PPD also poses serious risks to the emotional, cognitive, behavioural, and physical development of the infant and siblings. Suicide is the leading cause of maternal death following childbirth. There are no approved therapies for PPD and there is a high unmet need for improved pharmacological therapy in the management of PPD.

Findings from several studies implicate peripartum fluctuations in reproductive hormones (particularly, the major progesterone metabolite allopregnanolone) having pivotal pathophysiological roles in PPD [3]. The rapid decline in the levels of reproductive hormones that occurs after delivery is believed to contribute to the development of depression in susceptible women. Although it is tempting to attribute PPD to hormonal decline, several other factors may predispose women to this condition. Stressful life events, past episodes of depression (not necessarily related to childbearing), and a family history of mood disorders [4], all recognized predictors of major depression in women [5] are also known to be predictors of PPD. The likelihood of PPD does not appear to be related to a woman's educational level, the gender of her newborn infant, whether or not she breast-feeds, the mode of delivery, or whether or not the pregnancy was planned ahead [4]. Preclinical and clinical studies have shown that neuroactive steroids might have an

important role in the pathophysiology of PPD. These findings lend support to the hypothesis that changes in neuroactive steroid concentrations during pregnancy and postpartum are capable of provoking affective dysregulation in mothers.

The phenomenology of major depression (as in PPD) probably mirrors the relative involvement of various functional neuroanatomical systems. Focal limbic (anterior cingulate), paralimbic (ventral frontal and anterior insula), and neocortical (prefrontal and parietal) abnormalities have been identified in depression [6]. Presumably a relatively simplistic mapping of symptoms onto brain regions would be as follows: the motivational deficits lying in the mid-brain–striatal–anterior cingulate/frontal projections, cognitive deficits reflect hypofunction within lateral prefrontal cortex, affective manifestations result from disordered paralimbic activity, anhedonia results from hypofunction within the ventral striatum, slowed motor manifestations arise from the interface of motor systems with the dorsal striatum or thalamus, amygdalar hyperactivity/ hypersensitivity may underlie a tendency toward comorbid anxiety and misperception of danger signals, and the hypothalamus probably mediates disturbances in sleep, appetite, and neuroendocrine regulation [7]. In humans, Lorberbaum et al. [8] demonstrated that the midbrain, hypothalamus, septal region, thalamus, dorsal and ventral striatum, lateral paralimbic regions, anterior and posterior cingulate and medial prefrontal cortex may be important in healthy maternal brain behaviour and social bonding/attachment. Abnormal activity has been reported in depressed subjects in these regions as well.

There is a significant unmet need for new treatment options in PPD, for mothers suffering from the disorder, as well as their children and families. Women with PPD may be more likely to have a response to serotonergic agents, such as selective serotonin-reuptake inhibitors [9] and venlafaxine [10] than to nonserotonergic tricyclic antidepressants [11]. Oestradiol has been evaluated as a treatment for PPD [12]. In this study, comparing transdermal 17 β -oestradiol (200 μ g per day) with placebo, the oestradiol-treated group had a significant reduction in depression scores during the first month. However, nearly half the women also were treated with antidepressants, so the effect of

oestradiol alone remained uncertain [12]. Currently, none of the available pharmacologic treatment options for PPD do not target the underlying mechanism or biology. Because of the serious adverse impact that depression can have on the mother, infant, and family, a medication that acts quickly is extremely important. Psychotherapy and antidepressants can often take weeks to months to be effective. Symptoms can begin as early as the beginning of the third trimester or in the acute postpartum period and may persist well beyond the perinatal period if left untreated. The prevalence of severe PPD ranges from 5% to 10% of all cases of PPD, and is a leading cause of maternal mortality. Feelings of guilt, shame, or fear can make it difficult for women to speak up about their symptoms, so it is essential for clinicians/psychiatrists to be proactive and encourage open and honest conversations about this condition. Partners, family, and friends should recognize signs and symptoms that their loved one might be experiencing and seek help from their healthcare providers.

Allopregnanolone, a potent positive allosteric modulator of synaptic and extra-synaptic GABA-A receptors has been shown to have profound effects on anxiety and depression in animal models [13]. Plasma allopregnanolone concentrations rise in concert with progesterone throughout pregnancy, reaching the highest physiological concentrations in the third trimester. After childbirth, these concentrations decrease abruptly. Failure of GABA-A receptors to adapt to these changes at parturition has been postulated to have a role in triggering PPD [14].

Brexanolone (SAGE 547) is a neuroactive steroid and positive allosteric modulator of both synaptic and extra-synaptic GABA-A receptors. Brexanolone showed promising results in a small, but diverse sample of women with severe PPD, in a recently published double-blind, randomized, and placebo-controlled study [15]. In this double-blind, randomized, controlled trial, researchers assigned 21 women with severe PPD (Hamilton Depression Rating Scale [HAM-D] score of at least 26) to a 60-hour, continuous intravenous dose of brexanolone or placebo. In order to make the sample as representative as possible, the researchers recruited patients from urban, suburban, and rural settings in the United States to receive treatment at four research sites. The study's primary efficacy endpoint was the mean change from baseline in the 17-item HAM-D total score in subjects who received brexanolone compared with subjects who received placebo at the 60-hour time point. By 60 hours, seven (70%) women had achieved remission (HAM-D total score of ≤ 7) compared with one (9%) in the placebo group. Brexanolone-treated subjects demonstrated a mean reduction in HAM-D total score of 20.97 points, a 12.2-point difference [95%CI, -20.77 to -3.67] from placebo ($p = .008$). The effect

was statistically significant from 24 hours after initiation of treatment (-19.37 vs. -8.12, $p = .006$) until the 30-day follow-up (-20.77 vs. -8.84, $p = .010$). Furthermore, mean HAM-D scores for the women who received brexanolone remained significantly lower for a follow-up period of 30 days compared with the placebo group. Change from baseline in MADRS total score showed similar results to those obtained with the HAM-D score. The observed improvement in symptoms of PPD following brexanolone administration also extended beyond core depressive symptoms, as evidenced by the significant treatment difference observed for CGI-I response. Two patients in the brexanolone group who had reported active suicidal ideations with a specific plan at baseline did not report the same feelings or behaviour at the post-treatment assessment. Brexanolone was found to be generally well tolerated among the study participants. There were no deaths, other serious adverse events, or discontinuations. Overall, fewer patients who received brexanolone experienced adverse events compared with placebo (4 of 10 on brexanolone and 8 of 11 on placebo). The most commonly reported adverse events in the trial were dizziness (two brexanolone-treated subjects; three placebo-treated subjects) and somnolence (two brexanolone-treated subjects; no placebo-treated subjects) and an equal number of patients reported the cluster of dizziness, sedation, or somnolence (three in brexanolone group and three in the placebo group).

The rapid and marked antidepressant response associated with brexanolone administration contrasts with the 4–6 weeks needed (and low remission rates) that have been reported with SSRIs [9] and other antidepressants [10,11] in the management of patients with PPD. The rapid onset of action and duration of effect observed in this study compared to placebo suggested that brexanolone had the potential to address unmet needs in the treatment of patients suffering from PPD. Neuroactive steroids such as allopregnanolone might function as behavioural switches, suggesting a potentially crucial role in treatment of reproductive and endocrine-related mood disorders, particularly PPD.

Primary care and family physicians must expect that one out of eight new mothers would have PPD. In women with previous episodes of PPD, the risk of recurrence is one in four. The goal of treatment is complete normalization of mood and physiologic and social functioning. Women with PPD may also respond to interpersonal psychotherapy. The results of the Kanes et al.'s study [15] supported the rationale for targeting GABA-A receptors in the development of therapies for the estimated 10–20% of birth mothers who suffer from PPD. While these results are encouraging, an ongoing phase 3 clinical program would further evaluate the safety and efficacy of

brexanolone. The study's potentially important implication for our understanding of the pathophysiology of postpartum mood disorders, but also raised questions such as whether the medication is a treatment for postpartum episodes specifically or could be used generally in treatment-resistant depression. Together with preclinical and clinical studies suggesting a role for neuroactive steroids and GABA-A receptor regulation in the pathophysiology of PPD, Kanes et al.'s findings [15] also reinforced the rationale for further examining brexanolone in patients with PPD.

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