Staying Up to Date With Evolving Postpartum Depression Pathophysiology and Treatment Research

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Perinatal depression (PND) is one of the most common medical conditions associated with pregnancy, with 1 in 7 women impacted by PND symptoms[1] and 1 in 13 meeting criteria for major depressive disorder,[2] and with prevalence rates higher in low-income populations.[3] Unfortunately, half of postpartum depression (PPD) cases begin during pregnancy but are not diagnosed until postpartum.[4] Delayed diagnosis and treatment of PND lead to poor outcomes for both mother and child. Untreated PND is associated with low birth weight in infants, impaired maternal-infant bonding, and child neurodevelopmental delays and behavioral differences.[5] The cost of untreated depression with mother-baby dyads was estimated at $14.2 billion in 2017.[6]

Early diagnosis is critical, and the American College of Obstetricians and Gynecologists recently updated its recommendation that screening for perinatal depression and anxiety occur at the initial prenatal visit, later in pregnancy, and at postpartum visits using standardized validated instruments followed by a further diagnostic evaluation when necessary.[7] Continuation of effective medication through pregnancy is also recommended to prevent depressive episodes, as are psychotherapy, sleep hygiene, exercise, and childcare support.[8]

Several hypotheses have been developed to explain the pathophysiology of PND, including endocrine, epigenetic, synaptic transmission, neural network, neurosteroid, stress, and inflammatory mechanisms,[9]and researchers believe that the answer lies in a synthesized mechanism of all of these models.[10] Novel and emerging therapeutics are focusing on the neurosteroid mechanism within the integrated hypothesis.

Neuroactive steroids (NAS) are metabolites of progesterone that are made in astrocytes in the brain as well as peripherally in the gonads, adrenal glands, and placenta.[11] They act on the brain with inhibitory γ-aminobutyric acid (GABA) and excitatory glutamate neurotransmitter receptors and regulate inhibition-excitation balance within neural networks. They have been localized throughout the stress neurocircuit and have important roles in hypothalamic-pituitary-adrenal axis response in both acute and chronic stress conditions.[12]

It is theorized that NAS are implicated in PND due to the vast fluctuations in progesterone in the peripartum and postpartum periods, which result in large physiological shifts in the NAS progesterone metabolite allopregnanolone (ALLO) and changing $GABA_A$ receptors ($GABA_AR$) and/or GABA and glutamate concentrations.[13] The neuroplasticity of the GABAergic system is compromised and unable to adapt to the steroid level changes, leading to a dysfunctional affective state.[13] Endogenous NAS set a baseline affective tone, and ALLO can modulate network states in brain-wide altered functional connectivity and improve behavioral states. It is hypothesized that ALLO acts on delta subunit–containing $GABA_AR$ to shift the network to a healthy state.[14] Many NAS are GABA positive allosteric modulators (PAMs) and bind both synaptically and extrasynaptically, generating both phasic and tonic effects, creating a longer effect.[14]

Brexanolone is an IV-administered synthetic ALLO $GABA_AR$ PAM that was approved for the treatment of PPD in 2019 based on 3 placebo-controlled randomized controlled trials (RCTs) that showed in 60 or 90 μg/kg/h doses a change from baseline in the Hamilton Depression Rating Scale (HDRS-17) of −17.0 vs −12.8 in placebo, with maintenance of response at 30 days.[15] Brexanolone carries a black box warning for the risk of excessive sedation and loss of consciousness (LOC),[16] requiring a Risk Evaluation and Mitigation Strategy (REMS).[17] For lactating patients, the relative infant dose (RID) is 1.3%.[16] The investigational once-daily oral drug zuranolone is

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a synthetic analog of ALLO that has an RID of 0.314%.[18] In a pivotal placebo-controlled RCT, the 30-mg dose showed a change from baseline in HDRS scores of −12.5 vs −9.8 in placebo at day 3 and a maintenance of −19.2 vs −15.1 in placebo at day 45.[19] Adverse events included somnolence, dizziness, sedation, and headache but not LOC. Zuranolone is also showing promising results for the treatment of MDD in both men and women, indicating a broader impact of NAS on depression.[20]

Other NAS under investigation for the treatment of PPD include BRII-296, an extended-release injectable formulation of brexanolone that is expected to undergo future phase 2 trials,[21] and NORA520, an oral prodrug hydrolyzed to brexanolone with 2 promoieties, one to enhance oral absorption and one to prolong half-life.[22] It is in phase 1 development, nearing phase 2. LYT-300 is an oral prodrug of ALLO developed to bypass the first-pass metabolism in the liver via the lymphatic system that is currently advancing to phase 2.[23]

NAS are changing the understanding of the pathophysiology of depression and PPD, and novel and emerging therapeutics with new mechanisms of action based on these findings are impacting the treatment paradigm for this widespread and burdensome disorder, with an eye toward medication with faster onset and lasting effects.

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