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Guest Editorial

Neurosteroid treatment of postpartum depression and beyond

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Depression occurring during pregnancy or after delivery is one of the most common complications of childbirth and is associated with maternal morbidity and mortality. Here we review the breakthrough development of the first neuroactive steroid-based antidepressants approved for postpartum depression in the USA and their potential in other psychiatric illnesses.

Keywords
Postpartum depression; neurosteroid; brexanolone; zuranolone.

Perinatal depression (PND) defined as a depressive episode occurring during pregnancy and the postpartum period, has a global pooled prevalence of 14% and is one of the major complications of childbirth. PND has been associated with poor quality of life and lactation difficulties as well as persistent adverse effects on infant motor, cognitive, language, social and emotional development, including a seven-fold increased prevalence of depression in offspring at 18 years of age. Mental health conditions including PND are the leading cause of pregnancy-related deaths in the USA, and completed suicide is a leading cause of direct maternal mortality in the first postpartum year in the USA, the UK and Ireland. The use of rapidly efficacious PND treatments is critical to improving the lives of women and their families.

Neuroactive steroid research spans at least 80 years. Allopregnanolone's discovery in the adrenal glands was reported in 1938, the term 'neurosteroid' introduced in 1981 and the term 'neuroactive steroid' characterised in 1992. Neuroactive steroids include both neurosteroids (molecules derived from cholesterol and synthesised in the brain) and steroids synthesised in the periphery, including the adrenal glands, ovaries and placenta, which act on the brain. Subsequent research identified allopregnanolone's biosynthesis pathway in the brain and its actions at specific $GABA_A$ receptor (R) subtypes, the relationship between fluctuating peripartum allopregnanolone brain concentrations and $GABA_AR$ neuroplasticity and the integral role of neuroactive steroids in the regulation of the hypothalamic–pituitary–adrenal (HPA) axis during stress and non-stress conditions. Many neuroactive steroids bind specific synaptic $GABA_ARs$ that contribute to low-affinity phasic inhibition and extrasynaptic $GABA_ARs$, which contribute to high-affinity tonic inhibition, and result in changes in the excitatory–inhibitory balance of those neural networks. The literature demonstrates that females susceptible to postpartum depression (PPD) have higher sensitivity to stress during phases of neuroactive steroid variability and that this sensitivity corresponds to altered allopregnanolone-dependent functioning at the $GABA_AR$ in the hypothalamus. Other person-level variables, including genetic or epigenetic modifications of the $GABA_AR$, may contribute to a woman's sensitivity to allopregnanolone and interact with the social context (i.e. stressors and supportive factors). Consequently, synthetic neuroactive steroids and their analogues became a target of research as potential therapeutics for PPD.

As neuroactive steroids research in PPD progressed, analogous preclinical and clinical research was underway in other psychiatric and neurologic disorders, and before the testing of synthetic neuroactive steroids and their analogues as potential therapeutics in PPD, neuroactive steroids and related molecules were evaluated in the treatment of schizophrenia, bipolar disorder, smoking relapse prevention, post-traumatic stress disorder and refractory status epilepticus with limited success. Recently, four clinical trials assessing the safety and efficacy of zuranolone for major depressive disorder (without peripartum onset) were completed, with mixed results.

In December 2015, clinical development of Food and Drug Administration (FDA)-approved medications for PPD began with an open-label study of brexanolone, a $GABA_AR$ positive allosteric modulator (PAM). Four patients diagnosed with PPD and onset of symptoms very proximal to delivery who had been admitted to the University of North Carolina at Chapel Hill Perinatal Psychiatry Inpatient Unit were treated with brexanolone, a proprietary formulation of allopregnanolone, developed by Sage Therapeutics.[1] In this initial open-label study, rapid onset of action and marked improvement in clinical symptoms was observed in the four study participants who achieved remission (Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$) score ≤ 7) over the course of a 60 h infusion.[1] This robust treatment response in the open-label trial provided the rationale for continued development and study in subsequent phase II and III clinical trials of brexanolone in PPD.

The 60 h continuous intravenous treatment protocol developed in the open-label study was preserved in the phase II double-blind randomised placebo-controlled trial. In the phase II study, a total of 21 women with severe PPD ($HAM\text{-}D_{17}$ score ≥ 26) were randomised: ten women received brexanolone and 11 received placebo. Women with a history of bipolar disorder, schizophrenia or other psychosis were excluded. The $HAM\text{-}D_{17}$ mean reduction from initial baseline was 21.0 points in the active drug group compared to 8.8 points in the placebo group at the 60 h primary end-point.[2] Subsequently, there were two positive double-blind randomised placebo-controlled phase III trials conducted at many research sites in the USA with a total of 246 study participants. In the first phase III trial, the women enrolled had severe PPD ($HAM\text{-}D_{17}$ score ≥ 26) and in the second trial, a slightly less severe $HAM\text{-}D_{17}$ baseline score of 20–25 was required for study enrolment. In both trials, the least-squares mean reduction in $HAM\text{-}D_{17}$ scores showed statistically and clinically meaningful reductions in the active drug groups compared to placebo.[3] The positive phase II and III clinical trials led to brexanolone becoming the first US FDA-approved medication for PPD in 2019. In all clinical trials of brexanolone for PPD, the drug was administered intravenously over 60 h and rapid onset of action in the initial 24 h of the infusion was observed, with continued remission of symptoms at hour 60. Further, sustained maintenance of the treatment response was observed over the 30-day follow-up period.[3]

Common adverse effects observed included dry mouth, flushing/hot flashes or sedation and sleepiness. Any observed sedation was

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readily managed by decreasing the dose of the brexanolone infusion. The potential risk of severe sedation of loss of consciousness with intravenous drug administration led to the requirement for a Risk Evaluation and Mitigation Strategy requirement at the time of FDA approval. Since becoming commercially available, brexanolone demonstrated good efficacy with rapid onset of action and reassuring safety data. However, the drug was expensive, widespread uptake was challenging as it had to be administered intravenously in a medically supervised setting and obtaining insurance authorisation could be time consuming, which created treatment delays. In October 2024, Sage Therapeutics announced plans to sunset brexanolone and focus on zuranolone in PPD.

Zuranolone is a synthetic analogue of allopregnanolone, an extrasynaptic and synaptic $GABA_AR$ PAM and a neuroactive steroid. The ROBIN study was the first phase 3 randomised, double-blind, placebo-controlled out-patient trial in females with severe PPD.[4] An acute 14-day course of oral zuranolone (30 mg daily) showed rapid (by day 3), clinically meaningful and sustained response as compared to placebo. There was a significantly greater reduction from baseline in HAM-D_{17} total score with zuranolone compared with placebo at day 15 and sustained differences in HAM-D_{17} scores favouring zuranolone were observed from day 3 to day 45. The SKYLARK study was an additional phase 3 randomised, double-blind placebo-controlled out-patient trial in severe PPD.[5] The antidepressant effects of oral zuranolone were rapid, evident at day 3. Treatment with zuranolone (50 mg daily) compared with placebo resulted in statistically significant improvement in depressive symptoms at day 15 with significant improvement in depressive symptoms also reported at days 28 and 45. Approved in 2023, it is the only FDA-approved oral medication for treatment of PPD in adults.

Zuranolone is not approved by any medicines regulatory agency for the treatment of major depressive disorder (without peripartum onset). Recent systematic reviews and meta-analyses of individual trial data reported that zuranolone was associated with significant improvements across several measures of depression during the treatment period (14 days) but not the follow-up period.[6] The positive results observed in the zuranolone PPD trials versus the mixed results observed in the major depressive disorder (MDD) trials[7,8] are interesting and suggest that there may be a differential response to neuroactive steroids in women with PPD as compared to persons with MDD more broadly.

Other neuroactive steroids are being investigated for PPD or other postpartum psychiatric disorders. Marinus Pharmaceuticals developed ganaxolone, a synthetic analogue of allopregnanolone, and completed clinical trials in PPD; however, results have not been published and further development appears halted. Brii Biosciences began drug development of BRII-296, a novel long-acting, single-injection formulation of a neuroactive steroid for PPD, but further development may be paused. Gerbera Therapeutics developed NORA520, an oral prodrug that is hydrolysed to brexanolone, which is currently in phase II clinical trials in PPD. An open-label study of IV brexanolone in postpartum psychosis was recently completed in ten patients enrolled at the University of North Carolina. This trial included patients with histories of bipolar disorder and active psychosis in the acute postpartum period, which is an entirely different patient population than that included in the PPD clinical trials. All patients were treated with the same infusion protocol used in the PPD clinical trials. Open-label results showed a positive treatment effect as presented at the Marcé International meeting in September 2024 in Barcelona, Spain.

The development of FDA-approved medications with a novel mechanism of action for PPD has been a game-changer for how we consider the future treatment of women's reproductive mood disorders. Since becoming commercially available, the oral drug zuranolone has seen increasing and widespread use in the USA, which represents an entirely new paradigm for how we treat PPD. A recent analysis compared the relative efficacy of postpartum treatment with zuranolone versus selective serotonin reuptake inhibitors (SSRIs) and combination therapies in the USA. Patients treated with zuranolone experienced greater symptom improvement as measured by the Edinburgh Postnatal Depression Scale compared to patients treated with SSRIs beginning at day 15, with largest mean difference at day 45,[9] and in the SKYLARK study, rapid antidepressant effects versus placebo were evident at day 3.

The lessons learned from the successful development of brexanolone and zuranolone provide an important roadmap for how we can address reproductive psychiatric disorders more broadly, and beyond reproductive psychiatry. These drugs were developed because of the significant morbidity and mortality associated with PPD and the recognition that successful treatment would have vital benefits for women, their children and their families. A similar approach should be applied to premenstrual dysphoric disorder and the perimenopause transition, which also cause profound suffering and often go unrecognised and untreated. Future research will further our understanding of their complex role in neuropsychiatric health and disease. For example, these synthetic neuroactive steroids may be used in preclinical mechanism of disease and action research, as preclinical therapeutic probes and in clinical proof of concept studies in other neuropsychiatric disorders.

PND treatment should be holistic in scope yet personalised, meeting the varied needs of all patients. Evidence-based approaches include individual and group psychotherapies, pharmacotherapies, family, social and peer support, neuromodulation, chronotherapies and sleep support and complementary and integrative approaches. Healthcare providers should encourage patients to be active in treatment planning so that their values, preferences and goals of treatment are known and respected by the healthcare team. Numerous barriers exist in PND detection and treatment and vary across healthcare settings globally. For PND treatment to be effective, patients must have access to treatment. To improve access, nations must address the myriad barriers to detection and treatment that span cultural, social, physical and systemic healthcare domains.

There is a great need for ongoing investment in women's mental health and an enormous opportunity for continued research that leads to improved treatments and outcomes. More research is needed to increase our understanding of who will respond to a given treatment based on an individual's underlying pathophysiology, and to increase our ability to offer targeted treatments that improve outcomes. There is still a long road ahead in realising the promise of precision medicine (or precision psychiatry); however, women's reproductive mood disorders that occur at times of hormonal flux provide an important window into elucidating some of the complexity that has made this challenging to apply in mood disorders broadly.

The overarching goal should be a population-based health approach that addresses the very real health disparities that exist during the perinatal period. We should ensure access to critical perinatal mental healthcare for all women that give birth and work to align policy and reimbursement of services with care delivery initiatives that improve outcomes. Ultimately, this investment will result in substantial cost savings. Without a doubt, the benefits of making mental health during the perinatal period a top priority has substantive impact across two generations and is worthy of investment.

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Author contributions

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