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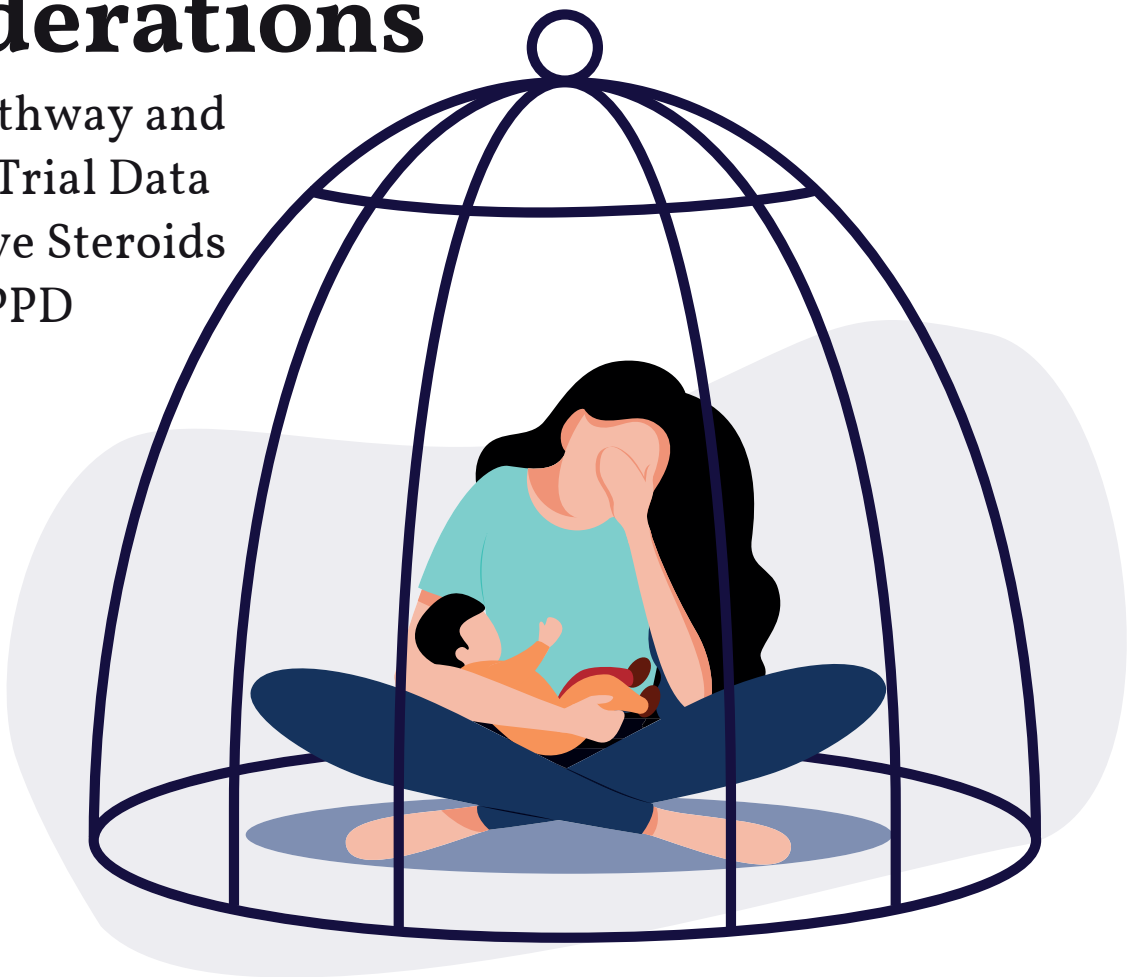
Patient-Specific Considerations

The GABA Pathway and New Clinical Trial Data on Neuroactive Steroids in MDD and PPD



Kristina M. Deligiannidis, MD
Northwell Health
Glen Oaks, NY

Anita H. Clayton, MD
University of Virginia School of Medicine
Charlottesville, VA

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CME Objective

After completing this educational activity, you should be able to:

- Highlight the inadequacies of suboptimal depression treatment related to adherence, adverse effects, persistent symptoms/lack of efficacy, polypharmacy, and treatment resistance
- Outline the underlying neurobiology of major depression and postpartum depression, with a focus on the GABAergic system
- Review the clinical trial data for approved and investigational GABAergic neuroactive steroid treatments

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Patient-Specific Considerations, the GABA Pathway, and New Clinical Trial Data on Neuroactive Steroids in MDD and PPD

Kristina M. Deligiannidis, MD, and Anita H. Clayton, MD

ABSTRACT

Major depressive disorder (MDD) and major depressive episode with peripartum onset, commonly referred to as postpartum depression (PPD), are among the most common psychiatric illnesses and are leading contributors to disability and suicide. Standard of care antidepressants are the cornerstone of MDD treatment; however, nonadherence to antidepressants has been widely recognized as one of the reasons for treatment failure in MDD. Delayed response in current therapies can take up to 4 or even 8 weeks for patients to experience therapeutic benefits. Low treatment response rates are seen in a considerable amount of patients, with early-stage treatment-resistant depression (TRD) affecting 50% of patients receiving first-line treatments and 30% developing into substantive TRD. Given these treatment gaps, there is an urgent need to develop novel antidepressants with a faster onset of action and shorter treatment course, which could improve adherence and treatment response rates. The neurobiology of depression is multifactorial, with different pathways converging on the development of the neurocircuit dysfunction characteristic of depression. Neuroactive steroids play an important role in modulating acute and chronic stress via their phasic and tonic inhibitory effects on select $GABA_A$ receptors, ultimately modulating neurocircuit function. With clinical recognition of the importance of neurosteroids in the modulation of $GABA_A$ signaling pathways, researchers have developed novel neuroactive steroid–based pharmacotherapies that have been tested in clinical studies. Given their rapid onset of action and shorter treatment course, these novel antidepressants have the potential to change the treatment paradigm for MDD and PPD.

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Psychiatric illnesses are major causes of disability and death worldwide. In the US, mental illness accounts for at least one-third of all disabilities.[1] Patients with severe psychiatric disorders die considerably earlier than expected,[1] with causes of death including metabolic and cardiovascular illnesses, violence, and suicide. In the US, the suicide rate has risen over the past 20 years, and suicides claim more than 40,000 lives per year.[1] Major depressive disorder (MDD) and anxiety disorders are among the most common psychiatric illnesses and are leading contributors to disability and suicide.[2–4] Postpartum depression (PPD), a major depressive episode (MDE) with onset during pregnancy or after delivery, is one of the most common medical complications in the perinatal period.[5] Numerous psychosocial risk factors are associated with PPD, including stressors during pregnancy, lower socioeconomic status, history of sexual abuse, and history of MDD, which remains the strongest predictor of PPD.[6] The severity of these disorders requires early detection and rapid treatment. Current therapy options have delayed time to response and require chronic treatment that may be associated with persistent side effects. Investigating novel targets for treatment may address these challenges.

BURDEN OF MDD AND PPD

Depression is a significant contributor to the global disease burden and affects all communities, requiring better treatment options. The World Health Organization estimates that depression will be the largest contributor to the global disease burden by 2030, affecting approximately 300 million people.[7,8] It has been estimated that 30.1% of women and 17.4% of men have lifetime histories of a major depressive episode.[9] MDD causes severe functional impairment and adversely affects interpersonal relationships, lowering quality of life (QoL).[10] A worldwide survey reported 41.6% of individuals with 12-month major depression also had 1 or more anxiety disorders over the same 12-month period, and higher proportions of respondents with 12-month anxious than non-anxious MDD reported severe role impairment (64.4 vs 46.0%) and suicidal ideation (19.5 vs 8.9%).[11] Depression often worsens medical comorbidities such as diabetes, hypertension, chronic obstructive pulmonary disease, and

coronary artery disease. Patients with MDD are 40% more likely to develop a comorbid medical diagnosis than the general population.[10]

Economic costs associated with depressive disorders are estimated at $210.5 billion annually, with direct costs (eg, costs of treatment) and indirect costs (eg, work absences and decreased productivity) contributing to the economic burden.[12] The impact of the costs associated with MDD is substantial, and treatment optimization is necessary to mitigate these costs. Approximately 30% of people treated for MDD will not achieve remission after 2 or more treatment trials of adequate antidepressant doses used for an adequate duration, thus meeting diagnostic criteria of treatment-resistant depression (TRD).[13] It is unknown if inadequate treatment leads to the development of TRD or if failure of treatment reveals preexisting TRD.

MDD affects approximately 8% of pregnant women and 8% of postpartum women.[5] While recognized by the US Department of Health and Human Services as a high-priority public health issue, PPD remains underdiagnosed and undertreated: nearly 50%–70% of women with PPD may go undiagnosed, and approximately only 16% receive treatment.[14] When untreated, PPD can persist for more than 3 years.[15] Anxious symptoms are prominent in women with PPD and are associated with more severe depression.[16] Comorbid anxiety symptoms are additionally associated with a longer time to treatment response[17] and an increased risk of self-harm ideation.[16,18] In a meta-analysis of the prevalence of maternal anxiety in the antenatal and postnatal periods, antenatal and postnatal anxiety disorders were diagnosed in 15.2% of women during pregnancy and 9.6% of women post-birth.[19]

A systematic review found that PPD has negative consequences for mothers and children up to 3 years of age.[20] PPD impacts maternal psychological health, QoL, and interactions with their infant, partner, and relatives. The review showed that the health of infants and children is intimately associated with the health of their mothers, and maternal depression may have direct and indirect negative effects on the child's development.[20] PPD may also lead to suicide, and suicide is a leading cause of pregnancy-related maternal mortality.[21,22] Therefore, detecting and treating PPD as early as possible is essential to ensure maternal, child, and family health.

CURRENT MDD AND PPD TREATMENT LIMITATIONS

Response

MDD may present as a single episode, recurrent episodes, or chronic depression (ie, >2 years in duration). The Sequenced Treatment Alternatives to Relieve Depression trial examined outcomes of traditional antidepressant therapy and found that the cumulative remission rate was 67% after 4 trials of antidepressant treatment.[23] Additionally, after >2 treatments of adequate dose and duration (considered TRD), over 30% of patients with MDD remained symptomatic, with persistent depressive symptoms affecting coping skills, interpersonal functioning, and QoL.[24]

Patients who experience 3 or more episodes of depression often require long-term therapy with the current SOC antidepressants. Oral antidepressants generally take weeks to become effective and may take significantly longer to reach maximum efficacy. Response takes 4 weeks on average and remission, 6 weeks; however, remission can take up to 12 weeks, and physicians typically wait 6 to 8 weeks to determine possible recovery.[25] In addition, some patients do not experience full remission of depression, while others experience unacceptable adverse effects.

Stop to Watch the Discussion

Adherence

SOC antidepressants are the cornerstone of MDD treatment; however, nonadherence to antidepressant medication has been widely recognized as one of the reasons for treatment failure in MDD. Monitoring adherence to antidepressants is difficult, but nonadherence may account for a significant number of patients being incorrectly classified as having TRD.[26] One study evaluated barriers and facilitators of adherence among outpatients with MDD and found patient-specific barriers such as medication side effects.[26] Another study examined claims of 4,312 patients with newly diagnosed MDD and evaluated adherence to antidepressant treatment regimens.[27] Adherence in the acute treatment phase (the first 16 weeks) was 51%, which dropped to 42% in the continuation phase of treatment (17–33 weeks). Lower adherence was associated with younger patient age, older-generation antidepressants, comorbid substance abuse or cardiovascular or metabolic conditions, and living in low-income neighborhoods.[27] Another study observed 6-month adherence to antidepressants in an outpatient setting and found that only 44% of patients continued therapy for 6 months. Among those who discontinued their initial antidepressant, 63% of patients did so without consulting their physician.[28]

Therefore, a better understanding of the barriers to adherence in patients with MDD is crucial to identify

effective interventions to facilitate adherence and improve patients' clinical outcomes.

First-Line Switching

First-line treatment options (eg, selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs]) for MDD present an initial challenge due to acute adverse effects and slow onset of action. Switching from one antidepressant to another is frequently indicated due to inadequate treatment response or unacceptable adverse effects. A patient is unlikely to respond to treatment if there has been no improvement after 3 or 4 weeks on an adequate dose of an antidepressant.[29] After confirming the correct diagnosis, optimal dose and duration, and treatment adherence in patients with an inadequate response, a change of antidepressant drug is indicated. Specific adverse effects from chronic use of antidepressants, such as sexual dysfunction, weight gain, emotional blunting, and sleep disturbances, may also necessitate a change in therapy if deemed unacceptable by the patient or lead to medication discontinuation. Approximately 60% of patients taking antidepressants experience at least 1 adverse effect during treatment.[30]

Conservative switching strategies involve tapering the first antidepressant, followed by a washout period, and initiating a new antidepressant.[7] Unfortunately, conservative switching often takes considerable time, leaving the patient at risk of depressive episodes. Rapid or cross-taper switching is generally preferred but increases the possibility of drug toxicity, including serotonin syndrome; however, this is rare, and immediate switching has been demonstrated in several medications, eg, duloxetine, as well-tolerated.[31] Dose reduction or cessation of antidepressants can also result in relapse or exacerbation of psychiatric illness.[7] The requirement for chronic use of conventional antidepressants is complex, especially if patients have had numerous episodes of depression while taking medication.

Treatment Resistance

Treatment resistance represents one of the most important clinical challenges in the pharmacologic management of MDD. Many patients with MDD do not respond adequately to antidepressant monotherapy, and current treatment guidelines recommend switching of medications or a combination of medications after partial response or nonresponse with a SOC antidepressant.[32] A multicenter, cross-sectional study showed that approximately 60% of patients with MDD receive augmentation or combination strategies, receiving 2 or more psychiatric drugs simultaneously, suggesting that add-on medications for MDD are increasingly utilized.[33] Polypharmacy has become a common clinical practice for many psychiatric conditions, with up to one-third of patients treated in outpatient psychiatric settings prescribed 3 or more psychotropic drugs.[34] Polypharmacy may provide better symptom relief and disease management, but it increases the risk of adverse effects and drug interactions. However, clinical titration protocols are not appropriately available.[35] There is a high prevalence of polypharmacy, particularly in the elderly population, which poses risks of increased adverse drug reactions and harmful drug-drug interactions that must be considered when adding medications to therapy regimens. Patients with TRD have higher rates of comorbidities, suicide risk, and functional disability; additionally, they have a reduced likelihood of future treatment response and, notably, a longer duration of untreated depression.[7] Guidelines typically integrate a stepped-care algorithm of treatment where treatment intensity is based on initial response and disease severity.[7]

PPD

Similar adherence barriers are seen in patients with PPD, including adverse effects, yet additional factors influence the use of SOC antidepressants in this patient population. Approximately one-third of women prescribed an antidepressant choose not to take it due to concerns about potential side effects for their nursing infant[36]; this is consistent with another study that reported approximately one-third of peripartum women would "definitely not" take medication while breastfeeding,[37] despite an antidepressant's relative compatibility with breastfeeding.[38] With novel therapies utilizing shorter treatment courses for acute PPD episodes, women may be able to pause breastfeeding during treatment and resume upon treatment completion, if necessary.

GABAERGIC SYSTEM IN THE NEUROBIOLOGY AND TREATMENT OF DEPRESSION

The etiology of MDD is multifactorial, including genetic, neurobiologic, environmental, and psychosocial factors (**Figure 1**).[39] Historically, the primary etiology of MDD was considered to be due to abnormalities in neurotransmitters, particularly serotonin, norepinephrine, and dopamine, evidenced by the use of various antidepressants such as SSRIs, SNRIs, and norepinephrine-dopamine reuptake inhibitors in the treatment of depression. With continued progress in neuroscience, it has become evident that the underlying pathophysiology of MDD and PPD is complex and involves the interaction of several systems that ultimately manifest as the signs and symptoms of clinical depression. For a more comprehensive review of this literature, we recommend reviews by Dean and Keshavan[39] and Li et al.[40] Here, we outline a few of the main systems, focusing on the role of the GABAergic system.

Stop to Watch the Discussion

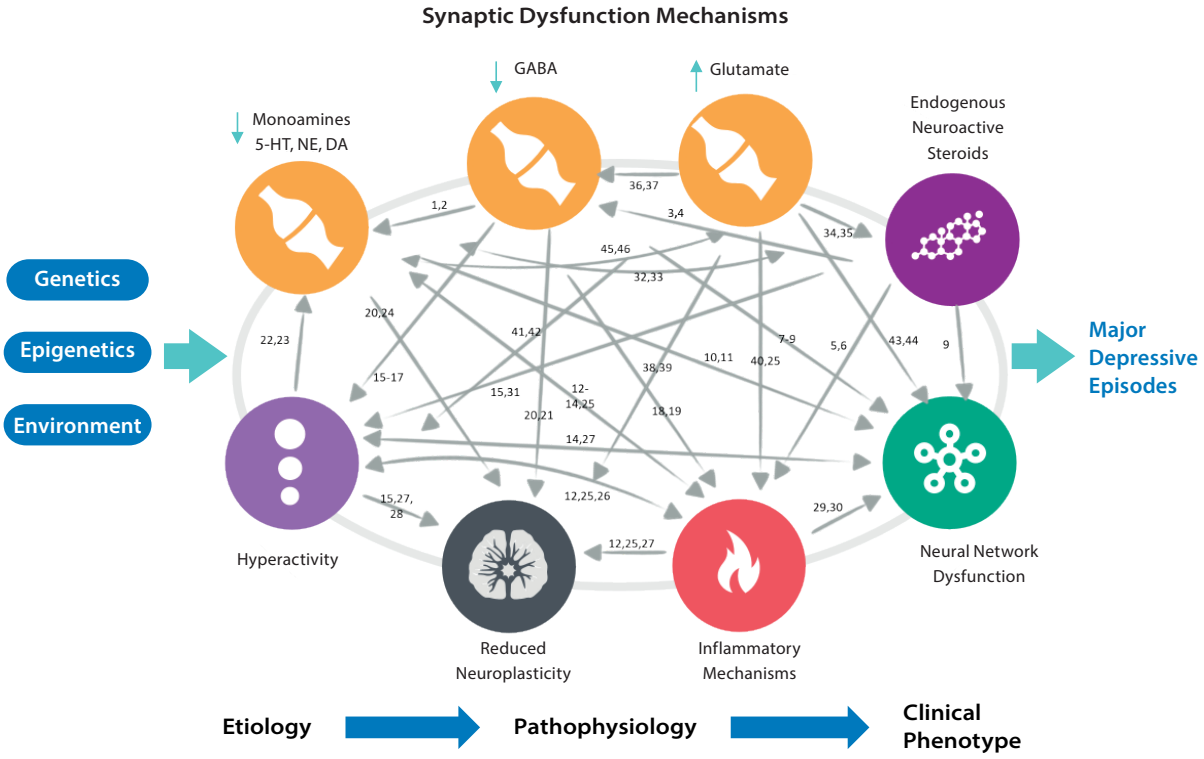
Stress/HPA Axis

Stress is considered a causative or a contributing factor to depression. Stress is defined as a disruption of homeostasis that causes an adaptive reaction to re-establish homeostasis.[41,42] The stress neurocircuit represents a subcortical-cortical neural system within the hypothalamic-pituitary-adrenal (HPA) axis that regulates arousal, neuroendocrine, and affective responses. Long-term or chronic stress can lead to hyperactivity of the HPA axis and promote the secretion of hormones, including cortisol, adrenocorticotropic hormone, corticotropin-releasing hormone, arginine vasopressin, and vasopressin.[41,42] Mounting evidence has shown that stress-induced abnormality of the HPA axis is associated with depression and cognitive impairment due to the increased secretion of cortisol and the insufficient inhibition of glucocorticoid receptor regulatory feedback.[43,44]

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain and spinal cord. GABAergic and glutamatergic (GLU) signaling play a central role in the neurobiological effects of stress.[41,42] GABAergic signaling controls corticotropin-releasing hormone (CRH) neurons, which govern the activity of the HPA axis, mediating the body's neuroendocrine response to stress.[45] Reduced GABA action in the paraventricular nucleus of the hypothalamus indicates hyperactivity of this nucleus and implies diminished inhibition to CRH-producing cells that may lead to an activation of the HPA axis.[46]

Globally, women are nearly twice as likely as men to experience depression,[47,48] and this risk is elevated during the reproductive years from menarche through post-menopause. There is evidence that the increase in prevalence correlates with female reproductive hormone changes during puberty, across the menstrual cycle, during the perinatal period, and across the menopausal transition, as has been demonstrated in macaque and rodent studies.[47,48] While most women experience mild, transient changes in mood following pregnancy, MDE with peripartum onset, or PPD, is a serious and persistent

Figure 1. Unified Theory of Depression[a]



[a]Adapted from Dean and Keshavan.[39]
Abbreviations: 5-HT = serotonin; NE = norepinephrine; DA = dopamine; GABA = gamma-aminobutyric acid.

disorder affecting up to 8% of women in the perinatal period, with onset during gestation and up to 4 weeks after delivery.[5]

Stress is a risk factor for PPD as well as for MDD,[49,50] and dysfunction of the HPA axis is thought to be involved in the underlying neuropathology of PPD.[51] This risk is increased in patients with previous adverse life events,[52] as adverse life events can alter HPA axis function and lead to increased vulnerability to PPD.[49] Those exposed to repeated stress during pregnancy exhibit elevated levels of corticosterone.[53] Based on evidence for stress and HPA axis dysfunction in PPD, chronic stress during pregnancy[54] and elevated levels of corticosterone during the postpartum period/lactation induce depression-like behaviors,[55] and elevated levels of corticosterone can be attributed to the disinhibition of CRH neurons.[56] In contrast, blocking CRH signaling decreases depression-like behaviors.[57]

Disruption in HPA axis function could also influence the levels of reproductive hormones, and it is suggested that dysregulation of reproductive hormones could dysregulate the levels of stress hormones.[58] Based on the onset of symptoms of PPD occurring at a time of dramatic hormone fluctuations, hormone withdrawal in pseudopregnancy animal models is sufficient to induce depression-like behavior in rats.[59] An abrupt rather than gradual decline in hormone levels has been shown to induce increased stress reactivity and precipitate abnormal depression-like behaviors.[60] Estrogen signaling is known to impact HPA axis function, and experiments demonstrate estrogen treatment is capable of exerting antidepressant effects,[61] while higher progesterone levels are correlated with worse depression scores.[62]

The evidence for HPA axis dysfunction in both MDD and PPD suggests that normalizing HPA axis function may be a therapeutic treatment approach for these disorders.

GABA

A functional imbalance of the GABAergic and glutamatergic systems also contributes to the pathophysiology of depression. GABA is the primary inhibitory neurotransmitter that acts in the central nervous system (CNS).[41,63] Inhibitory neurotransmission is essential for brain function by balancing excitatory transmission.[40] GABA mediates its effects in the CNS through both $GABA_A$ and $GABA_B$ receptors. The $GABA_A$ receptor consists of 5 transmembrane subunits that form a channel permeable to chloride and is present at 30% of synapses in the brain. The binding of GABA to $GABA_A$ receptors opens the transmembrane channel, and an influx of chloride results in inhibition of the postsynaptic neuron. GABA can elicit CNS inhibition as either a short signal in response to $GABA_A$ synaptic receptor activation (ie, phasic inhibition) or a long-lasting inhibition response (ie, tonic inhibition) with extrasynaptic $GABA_A$ receptor activation.[64]

In euthymic mood states, GABAergic inhibition and glutamatergic excitation are balanced. Acute stress results in imbalances between GABAergic and glutamatergic signaling.[42] Stress-induced increases in glutamatergic signaling may lead to abnormal GABAergic transmission. In addition, stress-induced abnormalities in GABAergic inhibition can lead to chronic HPA axis activation.[42] Chronic stress leads to a gradual down-regulation of GLU receptors. Concurrent impaired GABAergic inhibition prevents the recovery of glutamatergic synapses once stressors resolve. During depression, GABAergic and glutamatergic transmission may be balanced, but signaling is at lower levels. GABAergic transmission is also important for hippocampal neurogenesis and neural maturation, and GABAergic deficits may lead to cognitive and memory deficits often seen in depression.[41]

Evidence supports a role for disruption in GABA signaling in the pathophysiology of PPD as well. The dramatic perinatal changes in circulating levels of allopregnanolone (AlloP) are one potential factor affecting GABAergic signaling and PPD development. These steroid hormones and neurosteroids have been shown to regulate the expression and function of $GABA_A$ receptors.[65] GABA levels have shown to be inversely correlated with depression scores in women at risk for developing PPD. GABA levels have been shown to be lower during the peripartum period,[66] while enhancing the inhibitory effects on $GABA_A$ receptors causes an acute decrease in anxiety levels and reduces depression symptoms.[41] GABAergic signaling has also been proposed to play a role in anxiolysis during the postpartum period, whereas dysregulation in GABAergic signaling is thought to negatively impact mood during this period.[67]

Neuroactive Steroids

Neuroactive steroids (NAS) are natural or synthetic steroids that rapidly alter the excitability of neurons by modulating the $GABA_A$ receptor and the *N*-methyl-D-aspartic acid classes of glutamate receptors. NAS can bind to both synaptic and extrasynaptic receptors, facilitating both phasic and tonic inhibition.[1,42] Alterations in NAS levels and GABAergic signaling are implicated as potential contributing factors to neuroendocrine dysfunction and vulnerability to MDD and PPD.[66,68] NAS likely have widespread effects on stress-sensitive circuits that can influence HPA axis function.[69]

In addition to NAS binding to $GABA_A$ receptors and allosterically enhancing the channel current, progesterone metabolites like AlloP can also bind to metabotropic G protein–coupled membrane progesterone receptors that increase protein kinase C and protein kinase A phosphorylation of different $GABA_A$ receptor subunits. When a specific subunit is phosphorylated, membrane insertion or stabilization of receptors in the membrane occurs, resulting in prolonged membrane accumulation of the receptors and increased inhibition.[70]

In PPD, endogenous NAS levels change due to stress and postpartum hormonal changes.[1] The peripartum period is accompanied by high levels of estrogen,

progesterone, and AlloP and elevated levels of stress hormones. In pregnancy, NAS levels rise, and GABA receptor expression decreases, which leads to stable inhibition. In the postpartum period, hormone levels are dramatically reduced, accompanied by a sudden decrease in NAS at birth. Recovery of GABA receptor expression lags, which creates a hyperexcitable state that may persist and precipitate symptoms of PPD.[1] These fluctuations in hormone levels and prolonged stress can lead to chronic dysregulation of the HPA axis[71] as well as a state of NAS deficiency.[1] One study demonstrated that increased depression severity was associated with decreased plasma GABA concentrations in women at risk for PPD.[66] Some studies indicate that reduced levels of AlloP are associated with increased depressive symptoms, and increased levels of AlloP correlate with decreased risk of developing PPD, though studies are mixed.[72–74] AlloP-mediated signaling has been identified as an important therapeutic target, and utilizing novel therapies like AlloP or AlloP analogs has the potential to address the treatment gap for MDD and PPD.

NEW CLINICAL TRIAL DATA ON NEUROACTIVE STEROIDS, AND THEIR ANALOGUES, FOR MDD AND PPD

New data exist for NAS targeting the $GABA_A$ receptors in MDD and PPD that could alter treatment algorithms. Rapid onset of action may improve levels of functional impairment[75] and reduce the duration of symptoms and depression severity. The short duration of treatment and overall good tolerability seen with NAS treatments (eg, adverse effects of somnolence, dizziness, dry mouth) differentiates these novel treatments from current antidepressant therapy. Thus, rapid response to a short course of therapy with maintenance of effect would represent a paradigm shift in the treatment of PPD and MDD.

Stop to Watch the Discussion

Brexanolone is an intravenous formulation of AlloP, a NAS and positive allosteric modulator (PAM) of $GABA_A$ receptors, approved in 2019 for treating PPD in adults. Unlike benzodiazepines, which target only synaptic $GABA_A$ receptors, brexanolone targets both synaptic and extrasynaptic $GABA_A$ receptors. The efficacy and safety of brexanolone were demonstrated in 4 studies—1 proof of concept and 3 randomized, double-blind, placebo-controlled trials.[76–79] These studies showed that a single 60-hour infusion of brexanolone resulted in rapid and statistically significant improvements in depressive symptoms on the 17-item Hamilton Depression Rating Scale (HDRS) from baseline compared to placebo at the primary endpoint of hour 60.[76–79] Brexanolone continued to demonstrate improvement on the HDRS after 30 days of treatment in both NCT02942017 and NCT02942004 of the 3 randomized placebo-controlled studies.[78] The rapid onset of action of brexanolone is particularly advantageous over traditional therapy options due to the rapid response that is required for the severity of the disease.[76–78] Additionally, the duration of adherence is limited to the single 60-hour infusion.

The potential infant exposure to antidepressants via excretion into breast milk is important to consider when discussing treatment options for PPD. One study evaluated the concentrations of AlloP in breast milk and maternal plasma from the start of a 60-hour infusion of brexanolone injection through 7 days. The results demonstrated that the maximum relative infant dose was estimated to be 1.3% of the maternal dose,[79] which is similar to or less than standard of care antidepressants, and well below the relative infant dose of < 10% that is generally considered compatible with breastfeeding.

The administration of brexanolone must be supervised by a health care provider in a certified medical setting. The FDA issued a boxed warning due to concern for excessive sedation and sudden loss of consciousness; therefore, patients must be monitored for 12 hours after receiving brexanolone. Because of these risks, brexanolone is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).[80] The most common side effects include somnolence, sedation, dry mouth, and dizziness.[81]

Zuranolone is a PAM of both synaptic and extrasynaptic $GABA_A$ receptors and a NAS, currently in clinical development as an oral, once-daily 14-day treatment for MDD and PPD. Zuranolone, a synthetic analog of AlloP, is being evaluated in the LANDSCAPE (MDD) and NEST (PPD) clinical development programs.

The LANDSCAPE and NEST programs evaluated the safety and efficacy of zuranolone in a once-daily 14-day treatment course of 30 mg or 50 mg of zuranolone compared to placebo. In addition, the studies assessed the improvement in depressive symptoms at the end of treatment (day 15) from change in baseline in HDRS-17 score. The primary endpoint of statistically significant

Table 1. Zuranolone Trials

LANDSCAPE	Trial Design	14 Day Course Dose	Efficacy Outcome Measurement Primary Endpoint	Outcome Results	Additional Findings
MDD					
MDD-201B[82]	DB, PC phase 2	30 mg	Change from BL in HDRS-17 day 15 vs placebo	−17 HDRS-17 points at day 15, $P < .001$	Mean BL HDRS-17 score was 25.2 vs 25.7 in the placebo group Least-squares mean (± SE) change in HDRS-17 score from BL to day 15 was −17.4 vs −10.3 points in the placebo group Reduction in HDRS-17 at day 15
MOUNTAIN[83]	DB, PC phase 3	20 mg	Change from BL in HDRS-17 day 15 vs placebo	No statistical difference vs placebo at any time point	
		30 mg		−12.5 HDRS-17 points at day 15, $P = .115$	Showed significant reduction in HDRS-17 scores vs placebo starting at day 3 ($P = .016$) and persisting through day 12 ($P = .018$), but not at day 15
WATERFALL[85]	DB, PC phase 3	50 mg	Change from BL in HDRS-17 day 15 vs placebo	−14.1 reduction in HDRS-17 vs −12.3 in placebo at day 15, $P = .0141$	Rapid onset seen at day 3 No difference in tolerability or efficacy in patients using zuranolone as monotherapy compared to those taking SOC antidepressant treatment; 30% of patients continued taking SOC AD throughout the study
SHORELINE[86,87]	OL, phase 3 Maintenance of effect	30 mg	Initial course responder—50% reduction from BL in HDRS-17 day 15; assessed for relapse with PHQ-9 every 2 weeks for 1 year for up to 5 repeat treatments	−15.2 HDRS-17 points at day 15 after initial dose	67.4% required initial course of treatment only or 1 additional course of treatment over 1 year
		50 mg		−16 HDRS-17 points at day 15 after initial dose	79.5% required initial course of treatment only or 1 additional course of treatment in 1 year. Mean time to second course was 250 days
CORAL[88]	DB zuranolone vs SOC AD phase 3	50 mg	Change from BL in HDRS-17 day 3 vs SOC ADs	−8.9 HDRS-17 points at day 3, $P = .0004$ −11.7 HDRS-17 points, $P = .0054$ mean change over course of treatment vs SOC AD	Initial results—significant reduction from BL in HDRS-17 at day 3 in 50 mg plus SOC compared to SOC plus placebo After 15 days, overall reduction in HDRS-17 continued statistically significant vs SOC AD Suggests potentially rapid reduction in depressive symptoms vs SOC AD
NEST	Trial Design	14 Day Course Dose	Efficacy Outcome Measurement Primary Endpoint	Outcome Results	Additional Findings
PPD					
ROBIN[89]	DB, PC phase 3	30 mg	Change from BL in HDRS-17 day 15 vs placebo	−17.8 HDRS-17 at day 15 vs placebo (−13.6), $P = .003$	Rapid statistically significant reduction vs placebo at day 3, ($P = .03$) Statistically greater change from BL in HDRS-17 by day 15 following 14 days of treatment vs placebo 75% of patients achieved response compared to placebo, $P = .0220$
SKYLARK[90]	DB, PC phase 3	50 mg	Change from BL in HDRS-17 day 15 vs placebo	−15.6 HDRS-17 at day 15 vs placebo (−11.6), $P = .0007$	Rapid reduction seen at day 3 vs placebo, $P = .0008$ Improvement over placebo continued through day 45, $P = .0067$ Clinically meaningful improvement in symptoms day 15 from BL vs placebo in HDRS-17 Well-tolerated, no withdrawal or increase in suicidal ideation

Abbreviations: AD = antidepressant, BL = baseline, DB = double-blind, HDRS = Hamilton Depression Rating Scale, PC = placebo-controlled, PHQ-9 = Patient Health Questionnaire-9, SOC = standard of care.

improvement in depressive symptoms with zuranolone at day 15 was met across all of the completed trials except for the MOUNTAIN study.[82,83,85–90] (**Table 1**). The LANDSCAPE program includes 5 studies: MDD-201B, MOUNTAIN, WATERFALL, SHORELINE, and CORAL. In every MDD study except for CORAL, in which SOC antidepressants were initiated, about 30% of patients were maintained on their pre-trial SOC antidepressant treatment dose.

MDD-201B is a double-blind, placebo-controlled, phase 2 trial that evaluated the efficacy of zuranolone in patients with MDD.[82] Patients treated with zuranolone demonstrated a reduction in depressive symptoms at day 15. The least-squares mean change in the HDRS-17 score from baseline was 7 points more in the zuranolone group compared to placebo ($P < .001$). The MDD-201B trial prompted additional studies to determine the durability, dosing, and safety of zuranolone in MDD treatment.

The phase 3 MOUNTAIN study evaluated zuranolone 20 mg and 30 mg compared to placebo in the treatment for MDD.[83] Zuranolone 20 mg did not differ from placebo in reducing depression symptoms at any measured time point. Zuranolone 30 mg showed an initial significant reduction in HDRS-17 scores starting at day 3 and persisting through day 12 but was not statistically superior to placebo at the primary endpoint of day 15 ($P = .115$). The MOUNTAIN study results led to additional efficacy trials in the LANDSCAPE program. Patients were followed for maintenance of effect for 182 days.[84]

The phase 3 WATERFALL study assessed the safety and efficacy of zuranolone 50 mg given daily for 14 days for the treatment of MDD.[85] Zuranolone 50 mg produced a 14.1-point reduction in HDRS-17 scores compared to a decrease of 12.3 points with placebo ($P = .0141$) at day 15. Approximately 86% of patients who completed the zuranolone 50 mg course of therapy maintained a decrease in HDRS-17 scores 4 weeks after completing therapy (day 42). The WATERFALL study showed no difference in tolerability in patients using zuranolone as monotherapy compared to those taking SOC antidepressant treatment.[85]

The SHORELINE trial is an open-label phase 3 study evaluating the necessity for re-treatment with zuranolone (maintenance of effect study). Patients initially received zuranolone 30 mg or 50 mg a day for 14 days; responders were assessed every 2 weeks for 1 year to determine if retreatment was appropriate. Interim results showed that 45% of patients who responded to initial treatment with 30 mg of zuranolone and 50% receiving 50 mg of zuranolone did not require retreatment throughout the following year. Approximately 30% in both dose groups of patients required only 1 retreatment cycle, and 25% of patients needed more than 2 treatment cycles.[86,87]

The phase 3 CORAL study examined the safety and efficacy of zuranolone 50 mg for 14 days initiated concurrently with SOC antidepressant therapy.[88] The initial results demonstrated a significant reduction from baseline in HDRS-17 score at day 3 of treatment with zuranolone 50 mg plus SOC antidepressants compared to SOC antidepressants plus placebo ($P = .0004$). The overall reduction of HDRS-17 score after 15 days continued to be statistically significant compared to antidepressant therapy initiated with placebo, with day 42 showing equivalence to day 15. The most common side effects were somnolence, dizziness, headache, and nausea. The results of the CORAL study suggest the potential for patients to experience a rapid reduction in depressive symptoms compared to current antidepressants, which can take weeks or months to work.[88]

The NEST clinical development program for zuranolone treatment in PPD includes the SKYLARK and ROBIN studies. The ROBIN trial is a multicenter, randomized, placebo-controlled phase 3 study evaluating the efficacy and safety of zuranolone 30 mg in the treatment of PPD.[89] Patients were allowed to continue baseline antidepressant use if they had been on a stable dose for at least 60 days. The study showed a statistically greater least-squares mean change from baseline in HDRS-17 total score at day 15, following 14 days of treatment with zuranolone compared to placebo ($P = .0028$). Zuranolone demonstrated rapid reduction of symptoms as soon as day 3 of therapy.[89] Given that anxiety symptoms are often comorbid in PPD and are associated with longer time to treatment response, a recent secondary analysis of the ROBIN study examined rates of concurrent remission of depressive and anxiety symptoms.[89] Rates of concurrent remission of depressive and anxiety symptoms were higher with zuranolone versus placebo ($P < .05$) at days 3, 15, and 45; the rate of sustained concurrent remission (ie, at both days 15 and 45) was also higher with zuranolone ($P < .05$).

The SKYLARK study is a phase 3 double-blind, placebo-controlled trial that evaluated the efficacy and safety of zuranolone 50 mg as treatment for patients with severe PPD.[90] Women treated with zuranolone 50 mg demonstrated a statistically significant and clinically meaningful improvement in depressive symptoms at day 15 from baseline compared to placebo, measured by the HDRS-17 ($P = .0007$). Zuranolone was well tolerated and showed no evidence of withdrawal symptoms.[90]

The importance of breastfeeding to a new mother and her infant raises the question about how much medication is transferred into breast milk. An open-label study[91] evaluated concentrations of zuranolone in the breast milk of healthy lactating women. The study found very low concentrations (0.357%) of zuranolone in breast milk following the 5 days of administration of zuranolone.[91]

Although results varied across the completed trials, zuranolone was studied in over 1,000 patients and demonstrated overall rapid onset with good efficacy, safety, and tolerability with a 14-day course of 30 mg or 50 mg. If approved, zuranolone would be the first

rapid-acting, short-course oral treatment for MDD and PPD. An additional benefit of zuranolone compared with standard antidepressants was seen in a post hoc analysis of the MOUNTAIN trial in which sexual dysfunction was examined; there was no difference between sexual functioning after treatment initiation of zuranolone for either men or women compared to placebo.[92]

Ganaxolone, the 3β-methylated synthetic analog of AlloP, has been investigated for the treatment of unipolar PPD.[93,94] Ganaxolone, like AlloP, is an extrasynaptic and synaptic $GABA_A$ receptor PAM, but it differs significantly in its lack of affinity for estrogen or progesterone receptors. Trials of ganaxolone have included both IV and oral formulations, but its further development appears halted.

The Magnolia study was a phase 2a, double-blind placebo controlled multiple-dose escalation study in women with severe PPD.[95] Part 1 of the study evaluated a 48-hour IV infusion of ganaxolone (60, 90, and 140 μg/kg/h), and part 2 evaluated a 6-hour IV infusion followed by a 28-day oral regimen (900 mg) compared to placebo. The efficacy endpoint for part 1 was the change from baseline in the HDRS-17 score at 60 hours post start of infusion and, for part 2, at day 29. In part 1, the high dose of 140 μg/kg/h was associated with a CFB in HDRS score of 16.9 at 60 hours post start of infusion. In part 2, patients treated with IV and then oral ganaxolone had a mean reduction from baseline in the HDRS-17 score of 13.6 points vs 11.5 points with placebo at day 29.[95]

The Amaryllis study was a phase 2, dose-optimization study in which patients with PPD received 675 mg of oral ganaxolone at dinner for 28 days (low dose) or patients received 675 mg of oral ganaxolone at dinner and bedtime for 2 days, followed by a dinnertime dose of 1,125 mg once daily for 26 days (high dose). The primary outcome measure was the change from baseline in HDRS score at day 29. The low dose showed a mean HDRS-17 reduction from baseline of 12.2 (SD 8.4) at day 29, and the high dose showed a mean HDRS-17 reduction of 14.5 (SD 7.64) at day 29.[96]

PRAX-114 is a $GABA_A$ PAM that has been investigated for the treatment of MDD.[93,97] A phase 2a non–placebo-controlled trial evaluated the safety and tolerability of PRAX-114 oral suspension over a 14-day treatment period with 3 different doses (40 mg, 60 mg, and 80 mg). A reduction of 15–19 points in HDRS-17 score was seen across the 3 dose groups.[93,97] The phase 2/3 double-blind, placebo-controlled ARIA trial evaluated the efficacy and safety of PRAX-114 using 40 mg as monotherapy for the treatment of MDD. The results showed that PRAX-114 did not separate from placebo on the primary endpoint of change from baseline in the HDRS-17 score at day 15 of treatment.[98] The double-blind, placebo-controlled Acapella MDD trial of 10 mg, 20 mg, 40 mg, and 60 mg was stopped after the interim analysis.[98] Further investigation of PRAX-114 was halted.

CONCLUSION

The initial results of the studies evaluating neuroactive steroid $GABA_A$ receptor positive allosteric modulators demonstrated promising results for the treatment of MDD and PPD. NAS therapies can potentially change the treatment paradigm with rapid onset, shorter duration of treatment, and overall good tolerability. Effect was maintained in 75%–80% (30 mg/50 mg) of initial responders with 1 or 2 doses over 1 year. NAS agents address gaps with current treatment therapies and have the ability to improve the QoL of patients with depression.[99]

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1. **Approximately what percentage of individuals remain symptomatic with persistent depressive symptoms after 2 or more traditional antidepressant treatment trials for MDD?**
   a. > 20%
   b. > 30%
   c. > 40%
   d. > 50%

2. **In euthymic mood states, GABAergic inhibition and glutamatergic excitation are balanced. Acute stress causes imbalances in GABAergic and glutamatergic signaling. When chronic stress causes a down-regulation of glutamatergic receptors, what happens to the GABAergic system?**
   a. Impaired GABAergic inhibition prevents the recovery of glutamatergic synapses once stressors resolve.
   b. GABAergic signaling increases, therefore inhibiting the production of corticotropin-releasing hormone cells.
   c. Impaired GABAergic inhibition increases the recovery of glutamatergic synapses once stressors resolve.
   d. GABA action in the paraventricular nucleus of the hypothalamus is reduced, indicating hypoactivity of this nucleus.

3. **Neuroactive steroids act by:**
   a. Binding to the sigma-1 receptor subunit on the $GABA_A$ receptor to downregulate allopregnanolone
   b. Binding to the serotonin transporter with high affinity to enhance serotonin in the CNS
   c. Modulating $GABA_A$ and *N*-methyl-D-aspartic acid (NMDA) classes of glutamate receptors to excite neurons
   d. Modulating $GABA_A$ to reduce brain-derived neurotrophic factor expression

4. **A 37-year-old single mother presents 2 weeks postpartum with symptoms of irritability, sadness, and anxiety. She has a history of diabetes, hypertension, and anxiety. She has no family support around her. This is her third child, and she discontinued use of sertraline 100 mg a year ago. She is looking for a treatment option that will address her postpartum depressive symptoms quickly. What is the best option for treating her postpartum depressive symptoms?**
   a. Sertraline and buspirone
   b. Brexanolone
   c. Dextromethorphan-bupropion
   d. Duloxetine

5. **The SHORELINE trial is an open-label phase 3 study evaluating the need for retreatment with zuranolone. Patients initially received zuranolone 30 mg/d or 50 mg/d for 14 days. Responders were assessed every 2 weeks for one year to determine if retreatment was appropriate.**
   a. 25% of responders to 30 mg/d required no retreatment during the year.
   b. 45% of responders to 30 mg/d and 50% of responders to 50 mg/d required no retreatment during the year.
   c. 60% of responders in both dose groups required 1 retreatment cycle during the year.
   d. 60% of responders in both dose groups required > 2 retreatment cycles during the year.

6. **PRAX-114 is a $GABA_A$ positive allosteric modulator (PAM). What was the endpoint result of its phase 2/3 double-blind, placebo-controlled ARIA trial using 40mg as MDD monotherapy?**
   a. A reduction of 13.1 points in HDRS-17 scores at day 15 compared to placebo
   b. A reduction of 13.1 points in HDRS-17 scores at day 8 compared to placebo
   c. A reduction of 11.4 points in HDRS-17 scores at day 15 compared to placebo
   d. No separation from baseline in HDRS-17 scores at day 15 between treatment and placebo

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