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ASCP Corner

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Investigational Treatment of Depressive Disorders With Neuroactive Steroids:

Potential Implications for Premenstrual Dysphoric Disorder

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The pathophysiology of premenstrual dysphoric disorder (PMDD) has been the subject of investigation for years.[1] PMDD is defined as an increase in 5 or more mood symptoms, such as mood lability, irritability, and anxiety, during the week before menses that resolve after the onset of menses and cause significant distress or impairment,[2] and it affects up to 6% of women.[3,4] Past theory postulated that PMDD was due to an abnormal response to normal hormonal changes.[5] More recent schema implicates changes in the production and/or signaling of ovarian-produced steroids during the menstrual cycle as a possible contributing mechanism.[6–8] In a prior ASCP Corner, Carlini and Deligiannidis[9] reviewed evidence-based treatments for PMDD, which include selective serotonin reuptake inhibitors (SSRIs) and combination drospirenone–ethinyl estradiol oral contraceptives. Importantly, despite these first-line treatments, many women with PMDD have residual or treatment-resistant symptoms, and more options are needed. In fact, gonadotropin-releasing hormone agonists are sometimes used, although the data are mixed, and they have potential for adverse effects.[4,5,8,9] Hence, novel therapeutics are still needed for PMDD, and neuroactive steroids are an emerging class of medications of interest for the treatment of PMDD.

Neuroactive steroids are synthesized in the brain and endocrine organs to modulate behavior—including reproductive behavior—but also other essential neuroactivity including the hypothalamic pituitary adrenal (HPA) axis, neuroprotection, and immune function.[7,10] By definition, neurosteroids are produced in the brain and can have effects on both excitatory and inhibitory neurotransmission.[10] They can rapidly induce anxiolytic and sedative effects via positive allosteric modulation of γ-aminobutyric acid A ($GABA_A$) receptors,[11,12] but they can have other effects depending on brain region and specific neurosteroid.[10] Acute stress increases the synthesis of neurosteroids, and due to their lipophilic nature, they cannot be stored and must be produced de novo.[13] They are capable of passing through the blood-brain barrier.[12,13] Progesterone-derived neuroactive steroids include allopregnanolone (ALLO) and its stereoisomer pregnanolone,[14] and ALLO levels in brain and plasma parallel that of progesterone.[10,15] In reproductive-age women, the ovary is responsible for increased ALLO during the luteal phase of the menstrual cycle, specially via production by the corpus luteum.[15,16]

A number of investigators have compared changes in mood with ALLO during the menstrual cycle. Prior to the addition of PMDD to the *Diagnostic and Statistical Manual of Mental Disorders* in 2013,[2] researchers commonly studied premenstrual syndrome (PMS) in its stead.[3] PMS has been described as a disorder of mood and somatic symptoms during the luteal phase of the menstrual cycle that resolves at or soon after the onset of menstruation[5] and does not require any specific symptom nor number of symptoms.[4] Wang and colleagues[17] measured serum progesterone and ALLO during the luteal phase in women with PMS for 2 consecutive cycles. When compared with heathy women, the women with PMS had lower progesterone but no difference in ALLO. Among only the women with PMS, the participants with higher ALLO had lesser PMS symptom ratings. Similarly, Monteleone et al[18] sought to determine basal progesterone and ALLO levels in women with PMS. In comparison to healthy women, women with PMS had significantly lower progesterone and ALLO during the luteal phase, but only progesterone was lower during the follicular phase.[18] Both studies indicate that lower ALLO was associated with increased symptoms for the women with PMS.

Several more complex studies demonstrated alterations in women with PMDD after repeat ALLO measurement or in response to its administration. Girdler and colleagues[19] measured ALLO in women with PMDD and healthy women during both follicular and luteal phases and then repeated ALLO assessment 17 minutes after a stressor. Compared with healthy women during the luteal phase, the women with PMDD had higher ALLO at baseline, but stress increased ALLO 83% in the healthy women compared with only 42% in the women with PMDD, indicating a dampened response in the women with PMDD. Upon additional analysis of the PMDD cohort, the authors determined an inverse

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relationship between premenstrual anxiety and irritability in comparison with ALLO during the luteal phase.[19] Timby et al[20] did not observe any difference in ALLO between women diagnosed with PMDD when compared with healthy women during either the follicular or luteal phases. However, women with PMDD exhibited increased sensitivity to administration of intravenous ALLO during both phases of the menstrual cycle compared with the healthy women, but this response was reduced during the luteal phase.[20] All together, these studies demonstrate inconsistent patterns regarding the impact of ALLO on PMDD but suggest alterations that parallel mood and sensitivity changes during the luteal phase in a subgroup of susceptible women.

Given the paucity of data specific to ALLO and PMDD, some inferences can be drawn from the literature regarding ALLO in other psychiatric disorders. Multiple investigators have implicated alterations in GABA neurotransmission in the pathogenesis of major depressive disorder (MDD)[21] and specifically in women.[22] In several small studies, ALLO was reduced in individuals with MDD compared with healthy controls, but it was raised to normal levels after successful treatment of depression with SSRIs.[23–25] In a cohort of pregnant women, there was no relationship between second or third trimester plasma ALLO with MDD, but pregnant women with lower ALLO during the second trimester of pregnancy were more likely to develop symptoms of postpartum depression (PPD) compared with women who did not.[26] In a subsequent study, lower ALLO during the second trimester of pregnancy was significantly associated with increased anxiety at 6 weeks postpartum, and lower ALLO during the second trimester trended toward increased depressive symptoms at 6 weeks postpartum.[27] Hence, it is plausible that ALLO plays a role in the mechanism of psychiatric illness in a subset of individuals with underlying biologic vulnerability.

ALLO acts to positively modulate $GABA_A$ receptors and produces potent anxiolytic effects.[11] Several pharmaceutical agents that mimic or oppose the action of ALLO are currently under investigation as treatment for depressive disorders including PPD and PMDD. In a randomized, placebo-controlled study, brexanolone—an intravenous, synthetic formulation of ALLO—resulted in significant reduction of depressive symptoms for women with PPD.[28] Although it is the only FDA-approved medication for PPD, the treatment is a single 60-hour intravenous infusion, and available follow-up data are limited to 30 days post-infusion. Additionally, participation in a risk and evaluation mitigation strategy program is required due to risk of excessive sedation and sudden loss of consciousness.[29] In contrast to the mechanism of brexanolone, isoallopregnanolone (also known as isopregnanolone) is an endogenous, negative allosteric modulator of $GABA_A$ receptors.[30] Bixo and colleagues[31] administered isoallopregnanolone (UC1010) subcutaneously to women with PMDD on the second day of the luteal phase to test if ALLO inhibition would alter their symptom course. Although some of their results were confounded by women with comorbid psychiatric disorders, the participants with pure PMDD experienced a 75% reduction in symptoms with isoallopregnanolone administration.[31] These significant mood improvements in women with pure PMDD indicate a need to further clarify the utility of $GABA_A$ receptor modulation for this specific illness. To our knowledge, no other synthetic neuroactive steroid has been investigated specifically for PMDD.

Several oral medications are under investigation as treatment for PMDD, MDD, and postmenopausal depression, but limited bioavailability of the oral neuroactive steroids has been suggested as a limitation to their efficacy.[32] Recently, Comasco et al[33] treated women with PMDD in a double-blind, randomized, placebo-controlled trial with a selective progesterone receptor modulator, ulipristal acetate (UPA), which acts as a progesterone antagonist. The women who received UPA 5 mg daily for 3 months had a significant reduction of symptoms as measured by the Daily Record of Severity of Problems. In fact, 85% of the women treated with UPA had partial or complete remission of symptoms.[33] Dichtel and colleagues[34] published results of an open-label pilot study of an oral analog of ALLO, ganaxolone (225 or 450 mg twice daily), as adjunctive treatment for postmenopausal depression. All participants were treated with an antidepressant for at least 6 weeks prior to enrollment, and duration of ganaxolone administration lasted between 7 and 10 weeks. Prior to treatment, the authors determined a positive association with baseline ALLO level and greater depression severity, although the majority of participants (6 of 10) had undetectable levels. As anticipated, ganaxolone reduced depressive symptoms, and while the participants had significant improvements in overall sleep, they also experienced daytime sleepiness.[34] In a randomized, placebo-controlled trial, another synthetic neuroactive steroid, SAGE-217, was orally administered to both men and women with moderate-to-severe depression for 14 days at a dose of 30 mg once daily. At day 15, the treatment arm had a statistically significant reduction of depressive symptom severity, but the authors did not collect data beyond that time point. Similar to the trials with ganaxolone, participants experienced sedation from SAGE-217.[35] In a subsequent study with over 300 male and female participants, SAGE-217 30 mg administered daily for 2 weeks did not demonstrate a difference in depression symptoms at day 15, but the investigators noted a high placebo response and lack of measurable drug concentration for 9% of participants.[36] Further investigation is required to determine duration of treatment response, appropriate dosing given lower than expected drug concentrations for both oral agents, and ideal target population(s) with careful consideration of sex and disorder. Additionally, it may prove important to perform data collection with consideration of menstrual cycling.

Thus, targeting $GABA_A$ receptor signaling via neuroactive steroids may have therapeutic implications for multiple depressive disorders including PMDD, but more investigation is required to elucidate their utility. Practically speaking, oral compounds are generally preferred for patient self-administration, and some women prefer not to take

exogenous hormones. Additionally, bioavailability of oral neuroactive steroids is an important concern.[32] The adverse effect of sedation caused by these compounds could be utilized for benefit given likelihood of sleep disturbance in this population. Notably, the promising findings for MDD in men and women suggest a broader treatment effect beyond application to times of gonadal steroid changes in women. Larger, placebo-controlled trials are warranted to determine appropriate dose, timing of administration, and duration of these potential therapies by indication.

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Potential conflicts of interest: **Dr Freeman** has the following disclosures: investigator-initiated trials/research: JayMac, Sage; advisory boards: Otsuka, Alkermes, Sunovion, Eliem; independent data safety and monitoring committee: Janssen (Johnson & Johnson), Novartis; steering committee for educational activities: Medscape; educational activities: WebMD; employee of Massachusetts General Hospital (MGH) and works with the MGH National Pregnancy Registry (current registry sponsors: Teva [2018– present], Alkermes, Inc. [2016–present]; Otsuka America Pharmaceutical, Inc. [2008–present]; Forest/Actavis [2016–present], Sunovion Pharmaceuticals, Inc. [2011–present]); and as an employee of MGH, works with the MGH Clinical Trials Network and Institute, which has had research funding from multiple pharmaceutical companies and National Institute of Mental Health. **Dr Szpunar** reports no potential conflict of interest.

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REFERENCES

1. Rubinow DR, Schmidt PJ. Is there a role for reproductive steroids in the etiology and treatment of affective disorders? *Dialogues Clin Neurosci*. 2018;20(3):187–196.
2. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
3. Epperson CN, Steiner M, Hartlage SA, et al. Premenstrual dysphoric disorder: evidence for a new category for *DSM-5*. *Am J Psychiatry*. 2012;169(5):465–475.
4. Yonkers KA, Simoni MK. Premenstrual disorders. *Am J Obstet Gynecol*. 2018;218(1):68–74.
5. Schmidt PJ, Nieman LK, Danaceau MA, et al. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. *N Engl J Med*. 1998;338(4):209–216.
6. Bäckström T, Bixo M, Johansson M, et al. Allopregnanolone and mood disorders. *Prog Neurobiol*. 2014;113:88–94.
7. Schiller CE, Johnson SL, Abate AC, et al. Reproductive steroid regulation of mood and behavior. *Compr Physiol*. 2016;6(3):1135–1160.
8. Schmidt PJ, Martinez PE, Nieman LK, et al. Premenstrual dysphoric disorder symptoms following ovarian suppression: triggered by change in ovarian steroid levels but not continuous stable levels. *Am J Psychiatry*. 2017;174(10):980–989.
9. Carlini SV, Deligiannidis KM. Evidence-based treatment of premenstrual dysphoric disorder: a concise review. *J Clin Psychiatry*. 2020;81(2):9ac13071.
10. Paul SM, Purdy RH. Neuroactive steroids. *FASEB J*. 1992;6(6):2311–2322.
11. Bitran D, Hilvers RJ, Kellogg CK. Anxiolytic effects of 3 alpha-hydroxy-5 alpha[beta]-pregnan-20-one: endogenous metabolites of progesterone that are active at the $GABA_A$ receptor. *Brain Res*. 1991;561(1):157–161.
12. Lambert JJ, Belelli D, Peden DR, et al. Neurosteroid modulation of $GABA_A$ receptors. *Prog Neurobiol*. 2003;71(1):67–80.
13. Purdy RH, Morrow AL, Moore PH Jr, et al. Stress-induced elevations of γ-aminobutyric acid type A receptor-active steroids in the rat brain. *Proc Natl Acad Sci U S A*. 1991;88(10):4553–4557.
14. Rasmusson AM, Pinna G, Paliwal P, et al. Decreased cerebrospinal fluid allopregnanolone levels in women with posttraumatic stress disorder. *Biol Psychiatry*. 2006;60(7):704–713.
15. Genazzani AR, Petraglia F, Bernardi F, et al. Circulating levels of allopregnanolone in humans: gender, age, and endocrine influences. *J Clin Endocrinol Metab*. 1998;83(6):2099–2103.
16. Ottander U, Poromaa IS, Bjurulf E, et al. Allopregnanolone and pregnanolone are produced by the human corpus luteum. *Mol Cell Endocrinol*. 2005;239(1–2):37–44.
17. Wang M, Seippel L, Purdy RH, et al. Relationship between symptom severity and steroid variation in women with premenstrual syndrome: study on serum pregnenolone, pregnenolone sulfate, 5 alpha-pregnane-3,20-dione and 3 alpha-hydroxy-5 alpha-pregnan-20-one. *J Clin Endocrinol Metab*. 1996;81(3):1076–1082.
18. Monteleone P, Luisi S, Tonetti A, et al. Allopregnanolone concentrations and premenstrual syndrome. *Eur J Endocrinol*. 2000;142(3):269–273.
19. Girdler SS, Straneva PA, Light KC, et al. Allopregnanolone levels and reactivity to mental stress in premenstrual dysphoric disorder. *Biol Psychiatry*. 2001;49(9):788–797.
20. Timby E, Bäckström T, Nyberg S, et al. Women with premenstrual dysphoric disorder have altered sensitivity to allopregnanolone over the menstrual cycle compared to controls-a pilot study. *Psychopharmacology (Berl)*. 2016;233(11):2109–2117.
21. Duman RS, Sanacora G, Krystal JH. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. *Neuron*. 2019;102(1):75–90.
22. Zorumski CF, Paul SM, Izumi Y, et al. Neurosteroids, stress and depression: potential therapeutic opportunities. *Neurosci Biobehav Rev*. 2013;37(1):109–122.
23. Romeo E, Ströhle A, Spalletta G, et al. Effects of antidepressant treatment on neuroactive steroids in major depression. *Am J Psychiatry*. 1998;155(7):910–913.
24. Ströhle A, Romeo E, Hermann B, et al. Concentrations of 3 alpha-reduced neuroactive steroids and their precursors in plasma of patients with major depression and after clinical recovery. *Biol Psychiatry*. 1999;45(3):274–277.
25. Uzunova V, Sheline Y, Davis JM, et al. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. *Proc Natl Acad Sci U S A*. 1998;95(6):3239–3244.
26. Osborne LM, Gispen F, Sanyal A, et al. Lower allopregnanolone during pregnancy predicts postpartum depression: an exploratory study. *Psychoneuroendocrinology*. 2017;79:116–121.
27. Osborne LM, Betz JF, Yenokyan G, et al. The role of allopregnanolone in pregnancy in predicting postpartum anxiety symptoms. *Front Psychol*. 2019;10:1033.
28. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet*. 2018;392(10152):1058–1070.
29. Meltzer-Brody S, Kanes SJ. Allopregnanolone in postpartum depression: Role in pathophysiology and treatment. *Neurobiol Stress*. 2020;12:100212.
30. Lundgren P, Strömberg J, Bäckström T, et al. Allopregnanolone-stimulated GABA-mediated chloride ion flux is inhibited by 3beta-hydroxy-5alpha-pregnan-20-one (isoallopregnanolone). *Brain Res*. 2003;982(1):45–53.
31. Bixo M, Ekberg K, Poromaa IS, et al. Treatment of premenstrual dysphoric disorder with the $GABA_A$ receptor modulating steroid antagonist Sepranolone (UC1010)—a randomized controlled trial. *Psychoneuroendocrinology*. 2017;80:46–55.
32. Rasmusson AM, Marx CE, Jain S, et al. A randomized controlled trial of ganaxolone in posttraumatic stress disorder. *Psychopharmacology (Berl)*. 2017;234(15):2245–2257.
33. Comasco E, Kopp Kallner H, Bixo M, et al. Ulipristal acetate for treatment of premenstrual dysphoric disorder: a proof-of-concept randomized controlled trial [published online ahead of print December 10, 2020]. *Am J Psychiatry*.
34. Dichtel LE, Nyer M, Dording C, et al. Effects of open-label, adjunctive ganaxolone on persistent depression despite adequate antidepressant treatment in postmenopausal women: a pilot study. *J Clin Psychiatry*. 2020;81(4):19m12887.
35. Gunduz-Bruce H, Silber C, Kaul I, et al. Trial of SAGE-217 in patients with major depressive disorder. *N Engl J Med*. 2019;381(10):903–911.
36. Sage Therapeutic Reports Topline Results from Pivotal Phase 3 MOUNTAIN Study of SAGE-217 in Major Depressive Disorder [press release]. Business Wire website. December 5, 2019. https://www.businesswire.com/news/home/20191205005375/en/

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