Molecular Science

AIMS Molecular Science, 10 (2): 70–78.
DOI: 10.3934/molsci.2023006
Received: 28 November 2022
Revised: 14 February 2023
Accepted: 01 March 2023
Published: 13 March 2023

http://www.aimspress.com/journal/Molecular

Editorial

What do we need to know about neurosteroids and emotions?

Flavia di Michele[1,*], Elena Romeo[2]

[1] Policlinico Tor Vergata Foundation, Dept. Psychiatry; Neuropsychoendocrinology Lab IRCCS S. Lucia, Rome, Italy
[2] Bocconi University, Milan, Italy

* **Correspondence:** Email: flavia.dimichele@gmail.com; Tel: 00390656485204.

Abstract: Neurosteroids are essential endogenous compounds which modulate numerous brain-related functions. Neurosteroids affect both the excitatory (glutamate) and the inhibitory (γ-aminobutyric acid, GABA) systems in the brain allowing for the modulation of a wide array of emotions and behaviors. Their synthesis is increased in response to stress, helping the organism to return to homeostasis. Alterations of neurosteroid concentrations therefore have a role in the pathophysiology of stress and stress-related conditions, such as mood (therefore acting on sadness and anger) and anxiety (fear) disorders. Here, we summarize the action of some neuroactive compounds, such as allopregnanolone, pregnanolone, pregnenolone, pregnenolone sulfate and dehydroepiandrosterone, in regulating emotions and outline their current pharmacological use in different pathologies.

Keywords: neurosteroids; emotions; 3α,5α-THP; GABAA receptors

This editorial focuses on the current concepts related to the key role of neurosteroids in modulating emotions. We start from pre-clinical studies to arrive at human studies, especially considering that neuroscience comparisons are necessary in discovering continuities, and that the limbic brain that serves to mediate emotions is highly conserved across species. We then discuss the exciting and innovative therapeutic perspectives related to using neurosteroid compounds, representing new targets for psychiatric treatments, such as those for post-partum depression (PPD), anxiety, panic disorders and epilepsy. The development of synthetic neurosteroids for PPD is a milestone, considering that untreated PPD has important consequences on the health of the mother-newborn dyad, with adverse effects on child emotional, cognitive and behavioral development.

Ever since Aristotle, humanity has been trying to identify the different types of emotions. Later on, Darwin, in an essay on emotions in humans and animals, first explained that emotions are universal.

Although, to date, no scientific agreement on a definition exists, emotions are states of mind brought on by neurophysiological modifications, coupled with feelings, thoughts and behavioral responses [1–4]. There is cross-talk between emotions and mood, temperament, personality, disposition and creativity [5].

Emotions include positive or negative experiences associated with a specific pattern of physiological function. Emotions produce different physiological, behavioral and cognitive changes. Their trigger function for the genesis of adaptive behavioral responses is what allowed and allows species to learn, survive, reproduce themselves and identify kin [6].

Emotions also have a relational function (communication to others about their own physiological reactions) and an autoregulatory function (insight into inner psychophysiological changes and internal state) [7,8].

Anger, fear, sadness and joy are considered the basic emotions [1]. The representations of basic emotions may be supported by large-scale functional connectivity networks in the brain (i.e., the limbic brain).

According to the diencephalic theory by Cannon [9] and Bard [10], the emotional stimulus, which can be either an event (internal or external), a scene, a facial expression or a particular voice tone, is expressed in the subcortical brain the limbic system, particularly the amygdala, receiving information directly from posterior nuclei of thalamus and provokes a first autonomic and neuroendocrine reaction in order to activate the arousal system. The autonomic reaction, under the control of the autonomic nervous system, is associated with various visceral changes, such as variations of the heart rate, increased sweating, faster breathing, piloerection, modifications in muscular tension and dryness of the mouth. This orthosympathetic activation exerts an analgesic effect [11].

Additionally, the neuroendocrine reaction to the emotional trigger is mediated by the hypothalamic-pituitary-adrenal (HPA) axis, which is the major neuroendocrine system involved in the response to stress by releasing cortisol, through the corticotropin-releasing factor (CRF), increasing emotional behaviors such as fearfulness and avoidance of competition [12,13]. Besides this, neurosteroids (synthesized in the brain) represent an endogenous complementary system to HPA, which is active in stressful conditions, making them able to rapidly modulate the balance between the excitatory and inhibitory synaptic activity of the brain [14,15]. Indeed, the 3α,5α-reduced metabolite of progesterone (3α,5α-THP; or 3alpha,5alpha-tetrahydroprogesterone; or allopregnanolone) is the most potent endogenous agonist at the γ-aminobutyric acid A ($GABA_A$) receptors ($GABA_A$-R). Even its isomers pregnanolone and tetrahydrodeoxycorticosterone are effective in the positive modulation of $GABA_A$-R, with significant regional differences [16].

On the other hand, dehydroepiandrosterone sulfate and pregnenolone sulfate represent antagonists to this receptor, increasing the neuronal excitability [17]. Therefore, neurosteroids can be considered a key system for homeostasis sustenance of the organism.

The development of multiple physical and psychiatric conditions can be considered maladaptive responses to stress. Focusing on stress-related biologic alterations can not only help from a diagnostic perspective, but also for the development of new pharmacological interventions.

Acute stress increases both the hypothalamic CRF and the GABAergic neurosteroid 3α,5α-THP. Moreover, the 3α,5α-THP itself regulates the release of CRF in a sex- and brain region-dependent manner. Indeed, recent studies in rats have shown that the initial exposure to a stress

stimulus increased circulating cortisol levels in both males and females, but 3α,5α-THP attenuated the cortisol response only in females after restraint stress. On the other hand, 3α,5α-THP decreased the CRF stress response after a forced swimming test in both males and females [18].

Therefore, 3α,5α-THP is a molecule that markedly increases $GABA_A$-R responses, modulates the HPA axis and also exerts neuroprotective effects, increasing neurogenesis via the enhancement of the production of brain-derived neurotrophic factor, decreasing apoptosis and inflammation [19].

The physiological relevance of 3α,5α-THP as an anxiolytic is supported by the fact that this neuroactive steroid not only increases the inhibitory signals resulting from the release of GABA acting on $GABA_A$-R, but it also exerts a permissive role in fine-tuning the efficacy of direct receptor agonists (i.e., muscimol), or that of other positive allosteric modulators of GABA action at $GABA_AR$, such as benzodiazepines and barbiturates [20–24].

Besides the anxiolytic effect of 3α,5α-THP, its role in the aggressive and impulsive behavior is being investigated. A stressful paradigm such as social isolation elicits impulsive, aggressive and anxiety-like behaviors. Recent studies have demonstrated that 4-week-long socially isolated mice evidenced a reduction in the responsiveness of $GABA_A$-R to the administration of GABA mimetic drugs at $GABA_A$-R and a downregulation of the synthesis of 3α,5α-THP in corticolimbic regions [25]. Moreover, it has been shown that finasteride, which inhibits the enzyme 5α-reductase, which catalyzes the main rate-limiting step in 3α,5α-THP synthesis, increases suicide-related aggressive behaviors [26].

GABAergic mechanisms are therefore involved in the control of aggressiveness, thereby indicating a role for 3α,5α-THP in this behavior; namely, its biosynthesis would reduce signs of aggression, decrease fear responses and facilitate pro-social behavior [25].

Post-partum disorders occur because of a disequilibrium between glutamate and GABA homeostasis. In rodents, region-specific changes in GABAergic inhibition occur in the peri-partum period [27]. While the post-partum period is characterized by decreased 3α,5α-THP and enhanced neuronal GABA synthesis, raising brain GABA concentrations in regions is important to maternal care. Altered peri-partum 3α,5α-THP concentrations could affect cortical GABA concentrations via their interaction with GAD or phasic and tonic cortical inhibition through $GABA_A$-R [28].

The development of major depressive disorder (MDD) is associated with a chronic, repeated stress exposure, while an intense traumatic event in combination with chronic stressful conditions may determine the occurrence of anxiety spectrum disorders or posttraumatic stress disorder (PTSD).

In humans, a role for cerebrospinal fluid (CSF) or serum 3α,5α-THP concentrations has been found in several psychiatric disorders, namely, anxiety spectrum disorders, including panic disorders, PTSD, depressive disorders such as MDD and PPD, premenstrual dysphoria and schizophrenia [19,29–36].

It has been shown that the anxiolytic and antidepressant actions of fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) are related to an increase in 3α,5α-THP availability. Indeed, the 3α,5α-THP concentrations measured in the CSF of 15 patients with MDD before treatment with fluoxetine or fluvoxamine were about 60% lower (~15 fmol/ml) than the controls. After 8–10 weeks of treatment with fluoxetine or fluvoxamine, normalized CSF 3α,5α-THP content (to control values, ~40 fmol/ml) were found in patients with MDD. Interestingly, a statistically significant correlation existed between symptom improvement, as measured by the Hamilton Rating Scale for Depression, and the increase in CSF 3α,5α-THP after fluoxetine or fluvoxamine treatment. Moreover, the CSF levels of the precursors pregnenolone and progesterone were unaltered after SSRI treatment and did not correlate with the fluoxetine- or fluvoxamine-induced increment of CSF 3α,5α-THP [37].

Therefore, normalization of CSF 3α,5α-THP levels in MDD patients could at least in part explain the anxiolytic and antidysphoric actions of fluoxetine or fluvoxamine via its positive allosteric modulation of $GABA_A$-R [36]. Numerous other studies confirmed Uzunova's findings in the plasma of MDD patients following SSRI treatment [31,32,38–41].

Moreover, 3α,5α-THP is reduced in humans with status epilepticus and in children with a genetic type of epilepsy [42].

Concerning pregnancy, it is well known that peri-partum fluctuations in reproductive hormones occur.

On the other hand, it has been shown that pregnant women with lower levels of 3α,5α -THP in the second trimester of pregnancy were more likely to develop symptoms of PPD than women with higher levels [41]. This data confirmed a previous study indicating that hormone withdrawal only correlated with depressive symptoms in women with a history of PPD, suggesting an underlying predisposition to hormone fluctuations in these women [43].

Interestingly, in women with a history of PPD, GABA concentrations have been shown to be low during the peri-partum period [44]. Therefore, alterations in GABAergic signaling may be fundamental in the underlying neurobiology of PPD.

Besides 3α,5α-THP, another neurosteroid, such as dehydroepiandrosterone, in cooperation with other hormones and transmitters, significantly affects some aspects of human mood, and it modifies some features of human emotions and behavior. Indeed, although its properties are mainly evident from the perspective of cognitive and memory function, it has been reported that its administration can increase feelings of well-being and is useful in ameliorating atypical depressive disorders [45].

In panic disorder patients, a disequilibrium of neurosteroid composition has been shown. Particularly, during the panic attack, significant reductions in the plasma concentrations of 3α,5α -THP and 3α,5β-THP (the potent agonists on $GABA_A$-R) and a concomitant increase in the concentrations of the functional antagonistic isomer 3β,5α-THP have been observed. On the other hand, no changes in neuroactive steroid levels were observed after placebo administration in patients with panic disorder, or after placebo, sodium lactate or cholecystokinin tetrapeptide administration in healthy controls. Therefore, the altered neurosteroid composition found in these patients may represent a counter-regulatory mechanism against the occurrence of spontaneous panic attacks [29].

PTSD has a complex neurobiological substrate represented by abnormal structures and function in the brain circuitry underlying fear/threat processing and emotion regulation. This includes abnormalities in the frontolimbic system, such as an alteration in amygdala-prefrontal coupling, a reduction of hippocampal volume and increasing amygdala reactivity. The learning and memory mechanisms relevant to PTSD recovery, including extinction, extinction retention, reconsolidation of reactivated aversive memories and episodic non-aversive memory, have been the object of study in models of stress-related disorders. A potential involvement in these learning and memory mechanisms of hormonal changes, specifically GABAergic neuroactive steroids such as 3α,5α–THP and other pregnane compounds, have been investigated. Two studies on PTSD have evidenced that CSF 3α,5α-THP concentrations correlate negatively with PTSD and negative mood symptoms in both men and women, while the enzymatic blockade in the biosynthesis of these neuroactive steroids may be sex-specific [31,46].

Anger is an emotional experience and aggressiveness is an impulsive, directed behavior with harmful intention that is considered to be a dimension of several psychiatric conditions; moreover, it is a potential outcome of paranoia/belligerence and dysphoria/irritability. Increased aggressiveness and hostility in schizophrenic patients were associated with alteration of 3α,5α-THP plasma levels [35].

It has been shown that progesterone and 3α,5α-THP influence dopamine-mediated behavior, assuming their antipsychotic-like profile. Indeed, 3α,5α-THP, the most potent endogenous positive modulator of $GABA_A$-R, is capable of regulating dopaminergic release via GABA [19].

There is growing literature regarding the potential therapeutic use of neuroactive steroids in schizophrenia. It has been shown that the precursor of progesterone (and hence of 3α,5α–THP), i.e., pregnenolone, elevates pregnenolone sulfate, which is a neurosteroid that positively modulates the excitatory dopamine N-methyl-D-aspartate (NMDA) receptors. Administration of adjunctive pregnenolone significantly reduced negative symptoms in schizophrenic patients in a pilot proof-of-concept randomized controlled trial, and increase of pregnenolone and 3α,5α–THP post-treatment were correlated with cognitive improvements [36]. Multiple actions for pregnenolone, including the amelioration of NMDA receptor hypofunction (via metabolism to pregnenolone sulfate) and the mitigation of GABA dysregulation (via metabolism to 3α,5α–THP) in schizophrenia, may be hypothesized [47]. Moreover, the use of pregnenolone as an add-on in antipsychotics has reduced positive symptoms, also making it possible to reduce the extrapyramidal effects of classic therapy [48].

Interestingly, certain antipsychotics, such as olanzapine and clozapine, as well as lithium, can increase the plasma concentration of neurosteroids. On the contrary, as we already mentioned, 5-α reductase inhibitors, such as finasteride and other molecules capable of decreasing the endogenous production of neurosteroids, have been associated with the onset of depressive symptoms [49,26].

Targeting $GABA_A$ receptor signaling via neuroactive steroids may have therapeutic implications for multiple depressive disorders. That means that targeting neurosteroidogenesis could be considered a novel antidepressant treatment. Therefore, normalization of 3α,5α-THP synthesis may be a new target for the development of agents effective for psychiatric disorders related to neuroactive steroid downregulation.

In order to gain further understanding of the potential therapeutic benefits of these neuroactive steroids, many trials have been carried out, especially for the treatment of PPD.

According to the recent evidence from clinical studies using the 3α,5α-THP formulation, brexanolone (an intravenous formulation of allopregnanolone) has been shown to produce an improvement in depressive symptoms, as measured by the administration of the Hamilton Rating Scale for Depression and Montgomery Ansberg Depression Rating Scale. Brexanolone, and its FDA approval for the treatment of PPD [50], underscore the therapeutic importance of neurosteroid signaling in the brain. A single dose of brexanolone infusion has demonstrated an ultra-rapid antidepressant effect in PPD patients, lasting up to 1 week [51]. Among the brexanolone side effects, the most frequently recorded were dizziness (two patients in the brexanolone group vs three patients in the placebo group) and somnolence (two vs none). Moderate treatment-emergent adverse events were reported in two patients in the brexanolone group (sinus tachycardia, n=1; somnolence, n=1) [52]. Also, headaches have been reported as a moderate side effect, while serious adverse effects of syncope, or loss of consciousness, was reported by 4% of patients. Therefore, the use of this agent may be advantageous compared to other antidepressant treatments for PPD patients for whom a rapid effect is required due to the severity of the clinical manifestations [53].

Stimulation of 3α,5α-THP biosynthesis through the development of selective neurosteroidogenic drugs or precursor administration may also be effective for the therapy of all stress-related disorders.

Moreover, 3α,5α-THP, as the most potent positive allosteric modulator of GABA at $GABA_A$-R in the central nervous system, can be considered an endogenous anxiolytic, as well as an antiepileptic compound. These notions have clinical translation in the possibility of using synthetic neurosteroids

as broad-spectrum anticonvulsants that are also effective in the prevention of crises related to the suspension of alcohol and drugs. To date, ganaxolone appears to be an effective therapy, and with less risk of iatrogenic side effects for catamenial epilepsy patients [54].

In conclusion, hormonal changes modulate the neurotransmitters and neural circuitry underlying negative emotions such as fear, anger and aggression. Neuroactive steroids exert a key role in the maintenance of homeostasis by tuning the inhibitory and excitatory brain systems. Acute and chronic stress conditions induce abnormal and maladaptive kinds of emotional regulation processes and the alteration of these steroidal compounds that accompany stress-related disorders. Targeting these neuroactive steroids represents a new avenue in the treatment of such pathological conditions.

Acknowledgments

The authors wish to thank Dr. Luchetti S. for her impressive research in the field of neuroactive steroids, and Dr. Cichetti D. for his first contribution to a scientific debate.

Conflict of interest

The authors declare no conflict of interest regarding the publication of this manuscript.

References

1. Panksepp J (2005) *Affective neuroscience: the foundations of human and animal emotions*. Oxford Univ Press.
2. Damasio AR (1998) Emotion in the perspective of an integrated nervous system. *Brain Research Brain Res Rev* 26: 83–86. https://doi.org/10.1016/S0165-0173(97)00064-7
3. Ekman P, Davidson RJ (1994) *The Nature of emotion: fundamental questions*. New York: Oxford University Press, 291–293.
4. Cabanac M (2002) What is emotion? *Behav Processes* 60: 69–83. https://doi.org/10.1016/S0376-6357(02)00078-5
5. Averill JR (1999) Individual Differences in Emotional Creativity: Structure and Correlates. *J Personality* 67: 331–371. https://doi.org/10.1111/1467-6494.00058
6. Pinker S (1997) *How the mind works*. New York: WW Norton & Company, 342.
7. Wilson TD, Dunn EW (2004) Self-knowledge: its limits, value, and potential for improvement. *Ann Rev Psychol* 55: 493–518. https://doi.org/10.1146/annurev.psych.55.090902.141954
8. Barrett LF, Mesquita B, Ochsner KN, et al. (2007) The experience of emotion. *Ann Rev Psychol* 58: 373–403. https://doi.org/10.1146/annurev.psych.58.110405.085709
9. Cannon WB (1927) The James-Lange theory of emotions: A critical examination and an alternative theory. *Am J Psychol* 39: 106–124. https://doi.org/10.2307/1415404
10. Bard P (1928) A diencephalic mechanism for the expression of rage with special reference to the sympathetic nervous system. *Am J Physiol* 84: 490–515. https://doi.org/10.1152/ajplegacy.1928.84.3.490
11. Agnati LF, Tiengo M, Ferraguti F, et al. (1991) Pain, analgesia, and stress: an integrated view. *Clin J Pain* 7: S23–37. https://doi.org/10.1097/00002508-199108000-00005
12. Selye H (1956) The Stress of Life. 5 McGraw-Hill; New York, NY, USA.

13. Coste SC, Murray SE, Stenzel-Poore MP (2001) Animal models of crh excess and crh receptor deficiency display altered adaptations to stress. *Peptides* 22: 733–741. https://doi.org/10.1016/S0196-9781(01)00386-2
14. Baulieu EE (1991) Neurosteroids: a new function in the brain. *Biol Cell* 71: 3–10. https://doi.org/10.1016/0248-4900(91)90045-O
15. Paul SM, Purdy RH (1992) Neuroactive steroids. *FASEB journal* 6: 2311–2322. https://doi.org/10.1096/fasebj.6.6.1347506
16. Maksay G, Fodor L (2011) Differential effects of two major neurosteroids on cerebellar and cortical GABA(A) receptor binding and function. *Eur J Pharmacol* 650: 94–101. https://doi.org/10.1016/j.ejphar.2010.10.003
17. Majewska MD (1992) Neurosteroids: endogenous bimodal modulators of the GABAA receptor. Mechanism of action and physiological significance. *Prog Neurobiol* 38: 379–395. https://doi.org/10.1016/0301-0082(92)90025-A
18. Boero G, Tyler RE, O'Buckley TK, et al. (2022) (3α,5α)3-Hydroxypregnan-20-one (3α,5α-THP) Regulation of the HPA Axis in the Context of Different Stressors and Sex. *Biomolecules* 12: 1134. https://doi.org/10.3390/biom12081134
19. di Michele F, Caltagirone C, Spalletta G (2008) *Neurosteroid Perturbation and Neuropsychiatric Symptoms in Schizophrenia: From the Mechanisms to the Treatment.* Springer, Dordrecht ed. https://doi.org/10.1007/978-1-4020-6854-6_16
20. Matsumoto K, Uzunova V, Pinna G, et al. (1999) Permissive role of brain allopregnanolone content in the regulation of pentobarbital-induced righting reflex loss. *Neuropharmacol* 38: 955–963. https://doi.org/10.1016/S0028-3908(99)00018-0
21. Matsumoto K, Nomura H, Murakami Y, et al. (2003) Long-term social isolation enhances picrotoxin seizure susceptibility in mice: up-regulatory role of endogenous brain allopregnanolone in GABAergic systems. *Pharm Biochem Behav* 75: 831–835. https://doi.org/10.1016/S0091-3057(03)00169-2
22. Pinna G, Uzunova V, Matsumoto K, et al. (2000) Brain allopregnanolone regulates the potency of the GABAA receptor agonist muscimol. *Neuropharmacol* 39: 440–448. https://doi.org/10.1016/S0028-3908(99)00149-5
23. Guidotti A, Dong E, Matsumoto K, et al. (2001) The socially-isolated mouse: a model to study the putative role of allopregnanolone and 5α-dihydroprogesterone in psychiatric disorders. *Brain Res Rev* 37: 110–115. https://doi.org/10.1016/S0165-0173(01)00129-1
24. Puia G, Mienville J-M, Matsumoto K, et al. (2003) On the putative physiological role of allopregnanolone on GABAA receptor function. *Neuropharmacol* 44: 49–55. https://doi.org/10.1016/S0028-3908(02)00341-6
25. Pinna G (2010) In a mouse model relevant for post-traumatic stress disorder, selective brain steroidogenic stimulants (SBSS) improve behavioral deficits by normalizing allopregnanolone biosynthesis. *Behav Pharmacol* 21: 438–450. doi: https://doi.org/10.1097/FBP.0b013e32833d8ba0
26. Maurice-Gélinas C, Deslauriers J, Monpays C, et al. (2018) The 5α-reductase inhibitor finasteride increases suicide-related aggressive behaviors and blocks clozapine-induced beneficial effects in an animal model of schizophrenia. *Physiol Behav* 191: 65–72. https://doi.org/10.1016/j.physbeh.2018.03.036
27. Mostallino MC, Sanna E, Concas A, et al. (2009) Plasticity and function of extrasynaptic GABA(A) receptors during pregnancy and after delivery. *Psychoneuroendocrinol* 34: S74–83. https://doi.org/10.1016/j.psyneuen.2009.06.013

28. Zhao C, Gammie SC (2014) Glutamate, GABA, and glutamine are synchronously upregulated in the mouse lateral septum during the postpartum period. *Brain Res* 1591: 53–62. https://doi.org/10.1016/j.brainres.2014.10.023
29. Strohle A, Romeo E, di Michele F, et al. (2003) Panic attacks shift GABAA receptor modulatory neuroactive steroid composition. *Arch Gen Psychiatry* 60: 161–168. https://doi.org/10.1001/archpsyc.60.2.161
30. Rasmusson AM, Pinna G, Paliwal P, et al. (2006) Decreased cerebrospinal fluid allopregnanolone levels in women with posttraumatic stress disorder. *Biol Psychiatry* 60: 704–713. https://doi.org/10.1016/j.biopsych.2006.03.026
31. Romeo E, Ströhle A, Spalletta G, et al. (1998) Effects of antidepressant treatment on neuroactive steroids in major depression. *Am J Psychiatry* 155: 910–913. https://doi.org/10.1176/ajp.155.7.910
32. Ströhle A, Romeo E, Hermann B, et al. (1999) Concentrations of 3α-reduced neuroactive steroids and their precursors in plasma of patients with major depression and after clinical recovery. *Biol Psychiatry* 45: 274–277. https://doi.org/10.1016/S0006-3223(98)00328-X
33. Nappi RE, Petraglia F, Luisi S, et al. (2001) Serum allopregnanolone in women with postpartum "blues". *Obstet Gynecol* 97: 77–80. https://doi.org/10.1097/00006250-200101000-00016
34. Rapkin AJ, Morgan M, Goldman L, et al. (1997) Progesterone metabolite allopregnanolone in women with premenstrual syndrome. *Obstet Gynecol* 90: 709–714. https://doi.org/10.1097/00006250-200101000-00016
35. Spalletta E, Romeo G, Bonaviri G, et al. (2005) Preliminary evidence for association between aggression, hostility and 5alpha-3alpha-tetrahydroprogesterone levels in schizophrenia. *J Psychiatry Neurosci* 30: 49–52.
36. Marx CE, Keefe RS, Buchanan RW, et al. (2009) Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia. *Neuropsycopharmacol* 34: 1885–1903. https://doi.org/10.1038/npp.2009.26
37. Uzunova V, Sheline Y, Davis JM, et al. (1998) Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. *Proc Natl Acad Sci USA* 95: 3239–3244. https://doi.org/10.1073/pnas.95.6.3239
38. Eser D, Schüle C, Baghai TC, et al. (2006) Neuroactive steroids in depression and anxiety disorders: clinical studies. *Neuroendocrinol* 84: 244–254. https://doi.org/10.1159/000097879
39. Uzunova V, Sampson L, Uzunov DP (2006) Relevance of endogenous 3α-reduced neurosteroids to depression and antidepressant action. *Psychopharmacol* 186: 351–361. https://doi.org/10.1007/s00213-005-0201-6
40. Pinna G, Costa E, Guidotti A (2006) Fluoxetine and norfluoxetine stereospecifically and selectively increase brain neurosteroid content at doses that are inactive on 5-HT reuptake. *Psychopharmacol* 186: 362–372. https://doi.org/10.1007/s00213-005-0213-2
41. Osborne LM, Gispen F, Sanyal A, et al. (2017) Lower allopregnanolone during pregnancy predicts postpartum depression: an exploratory study. *Psychoneuroendocrinol* 79: 116–121. https://doi.org/10.1016/j.psyneuen.2017.02.012
42. Trivisano M, Lucchi C, Rustichelli C, et al. (2017) Reduced steroidogenesis in patients with PCDH19-female limited epilepsy. *Epilepsia* 58: e91–e95. doi: 10.1111/epi.13772. https://doi.org/10.1111/epi.13772
43. Bloch M, Schmidt PJ, Danaceau M, et al. (2000) Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry* 157: 924–930. https://doi.org/10.1176/appi.ajp.157.6.924

44. Deligiannidis KM, Kroll-Desrosiers AR, Mo S, et al. (2016) Peripartum neuroactive steroid and γ-aminobutyric acid profiles in women at-risk for postpartum depression. *Psychoneuroendocrinol* 70: 98–107. https://doi.org/10.1016/j.psyneuen.2016.05.010
45. Stárka L, Dušková M, Hill M (2015) Dehydroepiandrosterone: a neuroactive steroid. *J Steroid Biochem Mol Biol* 145: 254–260. https://doi.org/10.1016/j.jsbmb.2014.03.008
46. Rasmusson AM, King MW, Valovski I, et al. (2019) Relationships between cerebrospinal fluid GABAergic neurosteroid levels and symptom severity in men with PTSD. *Psychoneuroendocrinol* 102: 95–104. https://doi.org/10.1016/j.psyneuen.2018.11.027
47. Marx CE, Bradford DW, Hamer RM, et al. (2011) Pregnenolone as a novel therapeutic candidate in schizophrenia: emerging preclinical and clinical evidence. *Neuroscience* 191: 78–90. https://doi.org/10.1016/j.neuroscience.2011.06.076
48. Ritsner MS, Gibel A, Shleifer T, et al. (2010) Pregnenolone and dehydroepiandrosterone as an adjunctive treatment in schizophrenia and schizoaffective disorder: an 8-week, double-blind, randomized, controlled, 2-center, parallel-group trial. *J Clin Psychiatry* 71: 1351–1362. https://doi.org/10.4088/JCP.09m05031yel
49. Dazzi L, Seu E, Cherchi G, et al. (2004) Inhibition of stress-induced dopamine output in the rat prefrontal cortex by chronic treatment with olanzapine. *Biol Psychiatry* 55: 477–483. https://doi.org/10.1016/j.biopsych.2003.11.020
50. Powell JG, Garland S, Preston K, et al. (2020) Brexanolone (Zulresso): Finally, an FDA-Approved Treatment for Postpartum Depression. *Ann Pharmacother* 54: 157–163. https://doi.org/10.1177/1060028019873320
51. Zheng W, Cai DB, Zheng W, et al. (2019) Brexanolone for postpartum depression: A meta-analysis of randomized controlled studies. *Psychiatry Res* 279: 83–89. https://doi.org/10.1016/j.psychres.2019.07.006
52. Kanes S, Colquhoun H, Gunduz-Bruce H, et al. (2017) Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. *Lancet* 390: 480–489. https://doi.org/10.1016/S0140-6736(17)31264-3
53. Hutcherson TC, Cieri-Hutcherson NE, Gosciak MF (2020) Brexanolone for postpartum depression. *Am J Health Syst Pharm* 77: 336–345. https://doi.org/10.1093/ajhp/zxz333
54. Lattanzi S, Riva A, Striano P (2021) Ganaxolone treatment for epilepsy patients: from pharmacology to place in therapy. *Expert Rev Neurother* 21: 1317–1332. https://doi.org/10.1080/14737175.2021.1904895

AIMS Press