ÖSSZEFOGLALÓ KÖZLEMÉNY

REVIEW ARTICLE

An update on approved and emerging drugs for the treatment of postpartum depression

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Depression, anxiety and psychotic disorders are common perinatal mental health disorders in the postpartum period. Depressive symptoms that occur postpartum are also present in the prenatal period in 50% of patients. Risk factors for the development of postpartum depression include poor relationship with the partner, lack of social support, mother's low socioeconomic status and multiparity. It has been determined that reproductive hormones change significantly during peripartum. Progesterone is one of these hormones and acts on the central nervous system starting from the fetal period; neurogenesis, neuromodulation, sedation are some of these effects. It has also been observed that progesterone has positive effects on learning, memory and mood. Progesterone exerts its effects on the central nervous system by converting into its metabolite allopregnanolone. Allopregnanolone is one of the neuroactive steroids, and found in similar amounts in the circulation of pregnant women and fetuses. It acts on synaptic and extrasynaptic γ-aminobutyric acid type A ($GABA_A$) receptors and is a positive allosteric modulator of the $GABA_A$ receptor. Allopregnanolone increases both the receptor's opening frequency and its open duration and improves GABAergic current. Low serum allopregnanolone levels in the second trimester are predictive of postpartum depression. Each 1 ng/mL increase in serum allopregnanolone level reduces the risk of development of postpartum depression by 63%. Brexanolone and zuranolone are synthetic allopregnanolone

A szülés utáni depresszió kezelésére engedélyezett és újonnan megjelenő gyógyszerek – aktuális helyzet

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A depresszió, a szorongás és a pszichotikus zavarok gyakori perinatalis mentális zavarok a szülés utáni időszakban. A szülés után jelentkező depressziós tünetek a betegek 50%-ánál a szülés előtti időszakban is jelen vannak. A szülés utáni depresszió kialakulásának kockázati tényezői közé tartozik a partnerrel való rossz kapcsolat, a szociális támogatás hiánya, az anya alacsony társadalmi-gazdasági státusza és a több gyermek. Megállapították, hogy a reproduktív hormonok jelentősen megváltoznak a peripartum alatt. A progeszteron az egyik ilyen hormon, és a magzati időszaktól kezdve hat a központi idegrendszerre; a neurogenezis, a neuromoduláció, a szedáció néhány ilyen hatás. Azt is megfigyelték, hogy a progeszteron pozitív hatással van a tanulásra, a memóriára és a hangulatra. A progeszteron a központi idegrendszerre gyakorolt hatását allopregnanolonná történő átalakulás után fejti ki. Az allopregnanolon a neuroaktív szteroidok közé tartozik, és hasonló mennyiségben található meg a terhes nők és a magzatok keringésében. A szinaptikus és extraszinaptikus γ-aminovajsav A-típusú ($GABA_A$) receptorokra hat, és a $GABA_A$-receptor pozitív alloszterikus modulátora. Az allopregnanolon növeli mind a receptor nyitási frekvenciáját, mind a nyitás időtartamát, és növeli a GABAerg áramot. A második trimeszterben mért alacsony szérumallopregnanolon-szint előre jelzi a szülés utáni depressziót. A szérumallopregnanolon-szint minden egyes 1 ng/ml-es emelkedése 63%-kal csökkenti a szülés utáni depresszió kialakulásának kockázatát.

preparations approved by the FDA for use in female patients with postpartum depression. They act via positive allosteric modulation on the $GABA_A$ receptor. Brexanolone is administered via intravenous infusion at varying infusion rates in a healthcare facility over 60 hours. Its effect starts immediately after treatment and continues until the 30th day of follow-up, and depressive mood does not recur. Zuranolone was developed for oral use, and administered as a single dose of 50 mg after a fatty meal. Their effectiveness has been demonstrated in patients with treatment-resistant depression. The development of other novel agents that act on the $GABA_A$ receptor and other pathways for the treatment of postpartum depression is in progress.

Keywords: postpartum depression, $GABA_A$ receptor, allopregnanolone, brexanolone, zuranolone

A brexanolon és a zuranolon az FDA által befogadott szintetikus allopregnanolon-készítmények, amelyeket szülés utáni depresszióban szenvedő nőknél alkalmaznak. A $GABA_A$-receptor pozitív allosztérikus modulációjával fejtik ki hatásukat. A brexanolont intravénás infúzióval, változó infúziós sebességgel, 60 órán keresztül, egészségügyi intézményben adják be. Hatása közvetlenül a kezelés után kezdődik, és 30 napig tart, a depresszív hangulat nem ismétlődik. A zuranolont szájon át történő alkalmazásra fejlesztették ki, és egyszeri 50 mg-os dózisban, zsíros étkezés után kell bevenni. Hatékonyságukat bizonyították kezelésre rezisztens depresszióban szenvedő betegeknél. A $GABA_A$-receptorra és más útvonalakra ható egyéb új szerek fejlesztése a szülés utáni depresszió kezelésére folyamatban van.

Kulcsszavak: szülés utáni depresszió, $GABA_A$-receptor, allopregnanolon, brexanolon, zuranolon

Psychiatric symptoms in the postpartum period have attracted attention since prehistoric times. Hippocrates hypothesized that postpartum symptoms were caused by the suppression of puerperal discharge or the flow of milk from the breast to the brain or the flow of blood into the breast tissue/milk ducts[1].

General approach to psychiatric symptoms during and after birth

Perinatal mental diseases are conditions that are frequently encountered during pregnancy and postpartum period and can have fatal consequences. These clinical conditions include depression, anxiety and psychosis[2]. In addition, it has been found that many mothers experience baby blues, although they do not belong to the group of clinical depressive disorders. The term motherhood blues was first defined by *Moloney* at 1952. According to the first definition, crying, difficulty in thinking and fatigue in the postpartum period are called third-day depression. However, baby blues is not a permanent condition and gets better on its own within a few weeks[3]. According to the literature, when cultural and geographical contexts are taken into account, an overall prevalence of 39% has been found for baby blues, ranging from 13.7% to 76%[4].

Definition for postpartum depression

It is understood that postpartum depression does not differ etiologically from depressive disorders that developed in other ways. For the ICD11 classification, after the appropriate diagnosis is made there are three other diagnostic codes to indicate that the medical condition is related to pregnancy, labour or postpartum period. These are: 1) 6E20: Mental or behavioural disorders associated with pregnancy, childbirth or the puerperium, without psychotic symptoms; 2) 6E21: Mental or behavioural disorders associated with pregnancy, childbirth or the puerperium, with psychotic symptoms; 3) 6E2Z Mental or behavioural disorders associated with pregnancy, childbirth or the puerperium, unspecified; respectively. Although it varies depending on the postpartum follow-up period, it is estimated that 3-6% of women will experience a major depression episode during or in the weeks/months after pregnancy. Approximately 50% of major depressive episodes referred to as postpartum actually begin before birth. Therefore, these periods can be collectively referred to as "peripartum". To use the peripartum indicator, mood symptoms are expected to appear during pregnancy (even if they do not meet all diagnostic criteria) or within four weeks after birth.[5] Women with

periods of peripartum depression often experience severe anxiety or even panic attacks. According to prospective studies, women experiencing baby blues are more likely to experience major depression[5].

Postpartum psychosis

Mood episodes that begin around the time of labour may have psychotic features. Psychotic symptoms may occur in the postpartum period even without these specific features. Postpartum mood episodes with psychotic features (major depression or mania) occur once in 500-1000 births. The following features are present in the psychiatric histories of women who experience mood episodes accompanied by psychotic features: a) Previous postpartum depression, b) Major depressive and bipolar affective disorder, regardless of the peripartum period, and c) Women with a family history of bipolar disorder. For women who have experienced postpartum depression with psychotic features, there is a 31% chance of relapse with each subsequent birth[6].

Risk factors for postpartum depression

Major risk factors include rural settlement, neurotic personality, low self-esteem, experiencing postpartum baby blues, life events that cause stress, problematic/weak marital relationship, domestic violence (verbal, physical, sexual), poor social relationships and lack of social support, low socioeconomic class, single parenthood, unwanted pregnancy, multiparity, obstetric (congenital) problems, baby problems (colic baby, etc.), mother's low educational level, and low family income[7]. It has been determined that women with postpartum-onset major depression are more sensitive to the mood effects of reproductive hormones, whose levels decrease significantly after birth[8]. No relationship was found between the mother's age at birth and age at marriage and postpartum depression. It has been found that the rate of postpartum depression is lower in breastfeeding mothers[8].

Treatment of postpartum depression

When left untreated, perinatal-onset depression reduces the mother's ability to care for herself and the baby and disrupts the baby's cognitive, behavioral and emotional development. In addition, depression can cause the mother to use substances and lead to problems such as preeclampsia, preterm birth or low birth weight in the newborn. Postpartum depression has been shown to negatively affect mother-child bonding. The severity and chronicity of the mother's depressive episodes will put the child at risk of receiving inadequate care. Spouses of female patients with postpartum depression are also at a 24-50% risk of experiencing paternal depression[9].

Treatment of postpartum depression is similar to other depressive disorders, as there is a consensus that its etiology is not different. The first step is psychotherapy and antidepressant treatment. It has been observed that many mothers prefer psychotherapy before pharmacotherapy due to lactation[10]. In the pharmacological treatment of postpartum depression, selective serotonin reuptake inhibitors (SSRIs) are the first choice among antidepressants. Among SSRIs, sertraline and paroxetine are preferred as the first line treatment due to their compliance with lactation[11, 12]. If SSRIs are insufficient, the effective dose is reached by augmentation with serotonin-noradrenaline reuptake inhibitor (SNRI)[13] or noradrenergic and specific serotonergic antidepressant (NaSSAs) mirtazapine[11]. In cases where there is no response to treatment, clinicians often increase the drug dose (titration), use combination, augmentation or drug substitution methods. Once the effective dose is reached, treatment continues for 6-12 months.

Treatment is determined according to the patient's complaints and other symptoms accompanying depression. In patients with psychotic signs and symptoms, second generation (atypical) antipsychotic agents are added to the treatment. If the patient has uncontrolled psychotic symptoms or severe anxiety and behavior that harms herself and her environment (especially the baby), treatment is provided with benzodiazepines[10]. Transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT) are nonpharmacological treatment options for treatment-resistant patients.

Current agents in the treatment of postpartum depression

Progesterone and the GABA receptor

Although the mechanism of postpartum depression is not fully known, dysregulation of stress response pathways (e.g. hypothalamic-pituitary-adrenal axis, HPA) and dysfunctional GABA signaling are among the possible mechanisms[9, 14, 15]. It has been found that the $GABA_A$ receptor density, which decreases during pregnancy, in patients with postpartum depression does not return to its previous level in the postpartum period[16, 17]. This is thought to be the cause in approximately 12% of patients with postpartum depression[16]. Mice genetically deficient in the $GABA_A$ receptor delta subunit exhibited postpartum depression-like behavior[14]. Neuroactive steroids (progesterone metabolites, etc.) with positive allosteric modulatory activity on GABAergic signaling and the $GABA_A$ receptor may act on the paraventricular nucleus of the hypothalamus to regulate the HPA axis[9]. Neuroactive steroids are synthesized from cholesterol and are

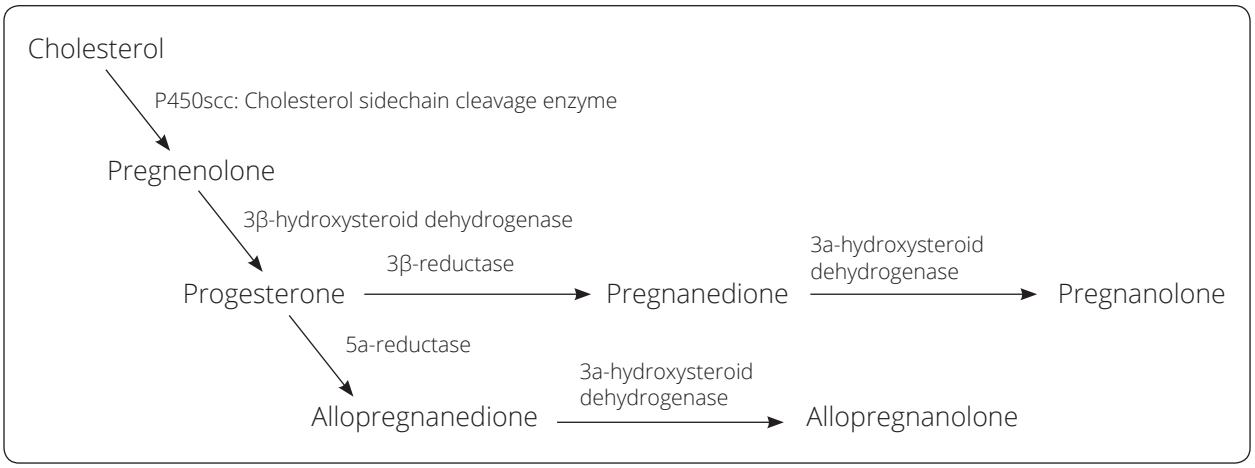

Figure 1. *In order to synthesize neuroactive steroid allopregnanolone, cholesterol is internalized to inner mitochondrial membrane by acute steroidogenic regulatory protein. As a next step after progesterone production, different enzymes are involved in the formation of pregnanolone and allopregnanolone by pregnanedione and allopregnanedione, respectively. Created with BioRender.com*

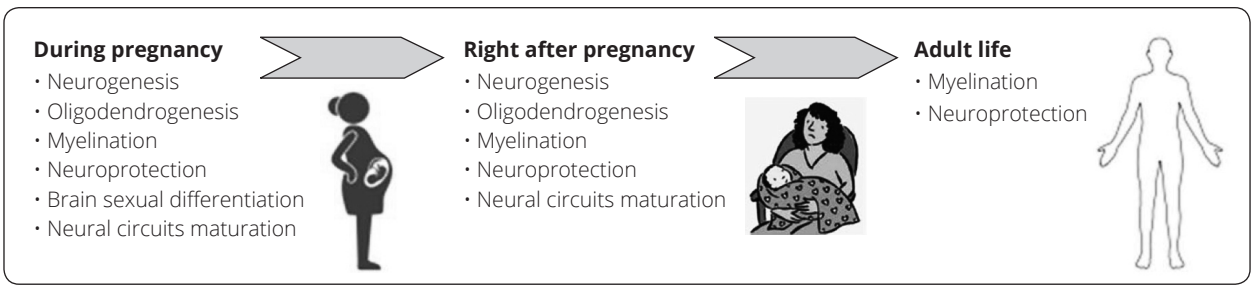

Figure 2. *Progesterone is a hormone that is effective in the neurodevelopment of the fetus during the perinatal period, starting from fertilization. First, it acts on neurogenesis and oligodendrogenesis. In later periods, myelination affects the gender-specific differentiation of the brain and the maturation of neural circuits. It continues to show myelination and neuroprotective properties in postnatal life. Created with BioRender.com*

effective in the brain and other central nervous system tissues **(Figure 1)**.

In order to adequately suppress stress-induced HPA axis activation via GABAergic signaling, the K^+/Cl^- cotransporter (KCC2), a neuron-specific membrane protein, must function effectively[15]. Depressive symptoms were observed in the postpartum period in mice lacking the KCC2 gene as they were unable to suppress stress-induced HPA axis activation properly[15]. Unlike classical agents, some progesterone-derived agents that act directly on the GABA receptor have been developed for the use of patients suffering from postpartum depression.

Progesterone is a hormone that has sedative, neuroprotective, neuromodulatory and anxiolytic effects on the CNS **(Figure 2)**[18]. It also has positive effects on learning, memory and mood.

The neural effects of progesterone are mediated by signaling pathways in which different receptors are activated. These receptors include intracellular progesterone receptors (PR); membrane-associated progesterone receptor membrane component 1 (PGRMC1); and membrane progesterone receptors (mPRs) and $GABA_A$ receptors[19]. Progesterone produces these effects by transforming into its metabolite, allopregnanolone, in the brain tissue. Allopregnanolone is one of the neuroactive steroids, and present in both the peripheral circulation and the brain of the pregnant woman and the fetus. Allopregnanolone is effective in cell proliferation and overall brain growth. The level of allopregnanolone in the brain varies depending on the endocrine state[20]. In a mouse study in which allopregnanolone synthesis was experimentally disrupted, cerebellar white matter abnormalities and autism-like behaviors have emerged[21]. Allopregnanolone acts through synaptic (containing the gamma subunit) and extrasynaptic (containing the delta subunit) $GABA_A$ receptors **(Figure 3)**.

Circulating levels of allopregnanolone rise dramatically with the progression of pregnancy. It is at its highest level at birth and decreases rapidly within a few days after birth[22–24]. The main source of allopregnanolone

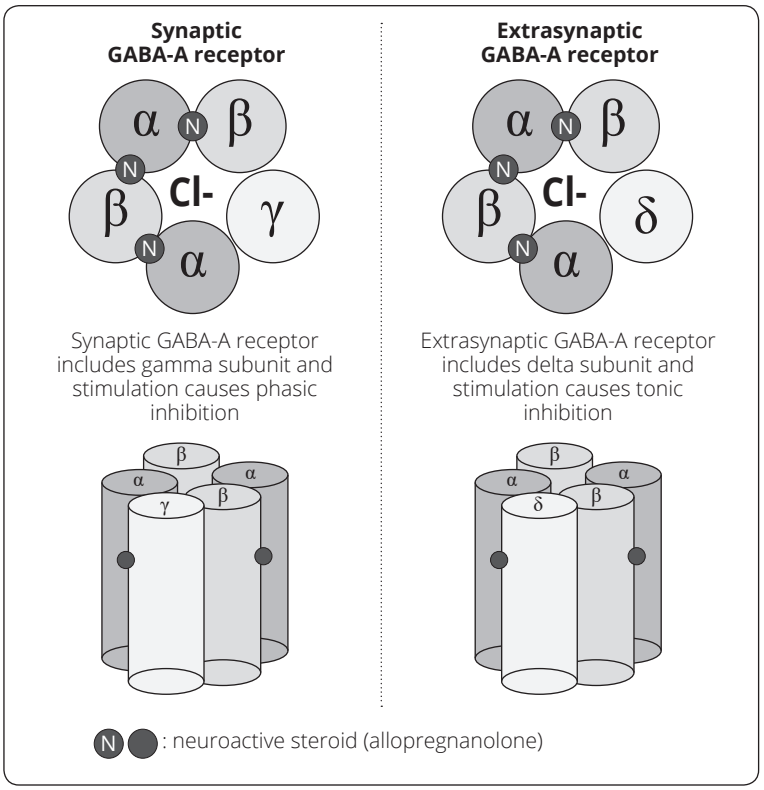

Figure 3. *Synaptic and extrasynaptic GABA-A receptors contain 5 subunits which differ in the last one. For the synaptic receptor, the last one is a gamma subunit, and stimulation of synaptic GABA-A receptor by GABA neurotransmitter or any other activating agent causes phasic inhibition. For the extrasynaptic receptor, the 5th subunit is a delta subunit, and when stimulated, extrasynaptic receptor causes tonic inhibition. Created with BioRender.com*

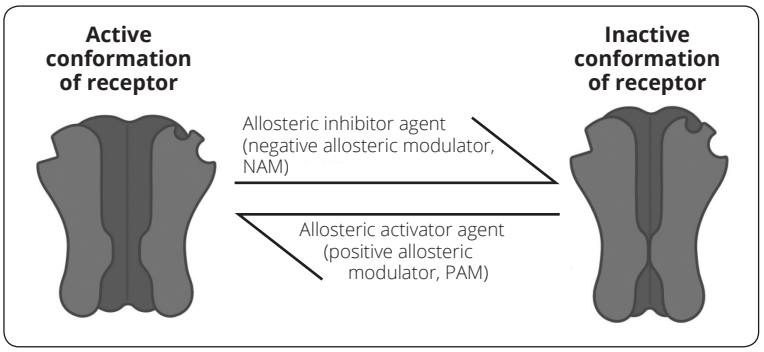

Figure 4. *An allosteric activator (also known as positive allosteric modulator, PAM) modulates the receptor's chiral structure and increases the activity by binding allosteric site. Vice versa for allosteric inhibitor (negative allosteric inhibitor, NAM). Created with BioRender.com*

during pregnancy is the placenta[25]. By birth, serum allopregnanolone levels rise to approximately 50 ng/mL[26, 27]. Cord blood contains similar levels of allopregnanolone as maternal serum[26, 27]. Mood symptoms may occur as a direct effect of changing hormone levels, as an indirect effect due to changes in receptor concentration or configuration, or as a result of mediating factors such as changes in the immune system or HPA axis[25]. Allopregnanolone, detected at lower than average levels in the second trimester, is predictive of postpartum depression that is likely to develop in women with pre-existing mood disorders[28]. It was found that each additional 1 ng/mL increase of allopregranolon above the mean resulted in a 63% reduction in the risk of postpartum depression[27].

It has been observed that allopregnanolone and progesterone levels decrease in major depressive disorder, but isopregnanolone, the stereoisomer of allopregnanolone (3β,5α-tetrahydroprogesterone; 3β,5α-THP) levels increase[28]. Similarly, allopregnanolone levels in the cerebrospinal fluid of premenopausal women with post-traumatic stress disorder were found to be low, and their frequency of depressive symptoms increased[29]. Isopregnanolone has been shown to be an antagonist for 3a-reduced neuroactive steroids[30]. It is thought that selective serotonin reuptake inhibitors (SSRIs) and other antidepressant drugs such as mirtazapine normalize the allopregnanolone-isopregnanolone balance by acting on enzymes in the neurosteroidogenesis process and thus improve depressive symptoms[30].

In terms of receptors, it has been observed that the amount of synaptic GABA receptors decreases during pregnancy. The fact that the amount of receptors has not reached its previous level in the postpartum period is an important mechanism in the development of postpartum depression.[9] It has been determined that neuroactive steroids have a specific binding site on the GABA receptor, separate from the site for GABA, benzodiazepines, and barbiturates[31].

Only two agents, brexanolone and zuranolone, have been approved by the US Food and Drug Administration (FDA) for the treatment of postpartum depression in women. Both are positive allosteric modulators of the $GABA_A$ receptor. Positive allosteric modulation (allosteric activation) shifts the balance between the active and inactive conformational form of the receptor to the active form **(Figure 4)**[32]. In this way, it not only activates $GABA_A$ receptors tradition-

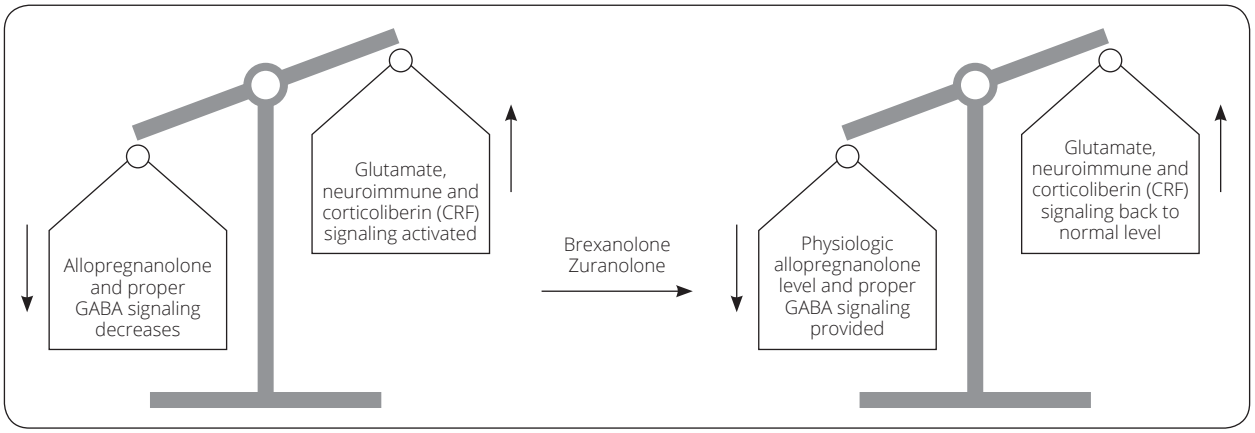

Figure 5. *The mechanism of postpartum depression development and results after allopregnanolone treatment. Unbalanced scales represent the depressive state of the patient: allopregnanolone level and proper GABAergic signaling decreases, in response to this, glutamergic activation, neuroimmune signaling and corticoliberin (corticotropin-releasing factor, CRF) release are stimulated. After treatment with allopregnanolone, imbalanced signal mechanisms and hormone levels are recovered and clinical improvement observed. Created with BioRender.com*

ally, but also increases the activity of GABA molecules in the medium through allosteric modulation[32].

Brexanolone

Brexanolone is the first agent specifically approved by the FDA in 2019 for intravenous use in the treatment of postpartum depression in women[33, 34]. Allopregnanolone, a metabolite of 3α,5α-progesterone, acts as a potent allosteric modulator of the γ-aminobutyric acid type A ($GABA_A$) receptor[35].

In the Phase 2 study (NCT02614547), the effectiveness, safety and pharmacokinetic parameters of brexanolone were examined[36]. This multicenter, placebo-controlled, and double-blind study showed that brexanolone provides a significant improvement compared to the placebo group according to the The Hamilton Depression Rating Scale (HAM-D) score[36].

Phase 3 consists of 2 studies (NCT02942004 and NCT02942017). It was conducted in 30 clinical research centers and specialized psychiatric units in the United States. In the first study, patients with a HAM-D score of 26 and above were accepted. Brexanolone at doses of 60 and 90 μg/kg/h and placebo were administered as an infusion for 60 hours. In the second study, those with a HAM-D score between 20 and 25 were included. In the second study, the results were compared with a brexanolone dose of 90 μg/kg/h and a placebo administered as a 60-hour infusion. As a result of Phase 3 studies, it was observed that brexanolone provided rapid onset of treatment and recovery without relapse. Symptoms of anxiety, somatization and insomnia significantly decreased from the 24th hour of infusion, and patients did not relapse until the 30th day of follow-up[37].

In a meta-analysis that indirectly compared brexanolone and the most commonly prescribed SSRIs in the treatment of postpartum depression, it was observed that the HAM-D score and the results stated by the patient and the clinician at the 3rd day, 28th day and end-of-treatment evaluations changed in favor of brexanolone[38].

Brexanolone poses a challenge for both patients and healthcare providers because it requires intravenous administration and monitoring in the healthcare facility. As approved by the FDA, brexanolone is given as a continuous intravenous infusion over 60 hours (2.5 days). The fact that the 60-hour practice period has to be spent in the health institution prevents the patient to do her daily work. Continuous intravenous infusion negatively affects the perception of and compliance with treatment of the patient, who is already depressed and pessimistic. Feelings of inadequacy may develop in postpartum women who feel that they cannot care for the baby during intravenous treatment, and this may support depressive feelings[39].

The most common side effects include sedation, dry mouth, loss of consciousness, and hot flushes[34]. Due to the risk of excessive sedation and sudden loss of consciousness, brexanolone is applied in certain centers within the Risk Evaluation and Mitigation Strategy (REMS) program[40]. Adverse effects that occurred depended on dosage and occurred regardless of time. In all patients, these symptoms disappeared completely within 60 minutes after stopping the drug[40].

Apart from the treatment of postpartum depression, studies are continuing with brexanolone in terms of postpartum psychosis, posttraumatic stress disorder (PTSD), psychosis, tinnitus, stress-triggered alcohol use, and perimenopausal depression. There is an average price of 7854 dollars for a single vial (December 2023)[41].

Zuranolone

Zuranolone was approved in 2023 for use in the treatment of postpartum depression in women. It is the first drug approved for oral use in the treatment of postpartum depression[42]. It acts through positive allosteric modulation on synaptic (containing gamma subunit) and extrasynaptic $GABA_A$ receptors[4,3] It is selective to the $GABA_A$ receptor[44]. Its oral bioavailability is higher and its elimination half-life is longer compared to brexanolone (brexanolone: 9 hours, zuranolone: 16-23 hours). Zuranolone provides a significantly larger reduction than brexanolone in depressive symptoms and other somatic symptoms associated with depression after 14 days of oral use through increasing allopregnanolone levels, ameliorating GABA signaling, and decreasing glutamergic, neuroimmune and corticoliberin (CRF) signaling back to physiological levels **(Figure 5)**[45, 46].

In several studies, the zuranolone group showed a significantly larger change in the HAM-D score compared to the placebo group[43]. Additionally, improvement in depressive symptoms was reported on days 3, 28, and 45[43]. The most common side effects were somnolence, dizziness, and sedation[46]. There were no side effects such as loss of consciousness, withdrawal symptoms, or suicide[46].

Zuranolone can be administered as monotherapy or as an adjuvant to oral antidepressant therapy[46]. Zuranolone treatment showed also beneficial effects in patients with major depressive disorder,[45] insomnia[47, 48], tremor[48, 49], and bipolar disorder[48, 50]. The price of the 14-day treatment is calculated to be $15900.

HS-10353

HS-10353 is an isomeric modulator of the $GABA_A$ receptor. It aims to correct the imbalance between GABA-NMDA receptors by improving $GABA_A$ receptor dysfunction. It is expected that oral, nightly treatment will produce positive results on depressive symptoms and general well-being after 14 days. A phase 2 study on patients with postpartum depression is ongoing[51, 52].

Trazodone

Trazodone is a serotonin receptor antagonist and reuptake inhibitor[53]. While it simultaneously inhibits SERT, $5\text{-}HT_{2A}$, and $5\text{-}HT_{2C}$ receptors, it does not cause side effects such as sexual side effects, insomnia, and anxiety. A study comparing it to placebo for the treatment of postpartum depression is ongoing[54].

GH001

GH001 is the vaporized form of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT). Studies are ongoing for treatment-resistant depression (NCT05800860), bipolar II disorder (NCT05839509) and postpartum depression (NCT05804708)[55–57].

BRII-296, BRII-297

Both agents are positive allosteric modulators of the $GABA_A$ receptor. They are long-acting, injectable agents. Both agents are expected to have effects on postpartum depression and other depressive and anxiety disorders. A phase 1 study on healthy volunteers is ongoing for BRII-297[58].

Ganaxolone (SAGE-217)

Ganaxolone is another orally active allopregnanolone analog which is undergoing evaluation in clinical trials of postpartum depression[59, 60].

Conclusion

Mood episodes may have started during pregnancy or after birth. Positive social relationships buffer the stress experienced by psychiatrically vulnerable individuals against progression to depression or other affective disorders. In patients who receive proper physical and social support, the progression of baby blues to postpartum depression can be prevented, and even if postpartum depression develops, it can be milder.

Recent research on the proposed mechanism of action of neuroactive steroids for postpartum depression underscores the potential role of GABAergic signaling in the pathophysiology of depression. Data indicate that positive allosteric modulation of $GABA_A$ receptor by brexanolone and zuranolone may potentially offer rapid and sustained antidepressant benefits for individuals with postpartum depression. Further research is required to better understand the role of allosteric activation of $GABA_A$ receptor in postpartum depression.

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The editorial board and the publisher of *Clinical Neuroscience* are launching a call for application for the best publications in Hungarian written by young authors in 2024, with the prize(s) being awarded by the editorial board of the journal. Publications published in *Clinical Neuroscience* between January and December 2024 will be eligible if the author declares at the time of the application that he/she is under 35 years of age.

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The award(s) will be presented in 2025 at one of the conferences organised by the owners of *Clinical Neuroscience*.
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