Neurosteroids for the Treatment of Major Depressive Disorder (MDD) and Chronic Pain

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Abstract

Neurosteroids are endogenous steroids within the brain that act as modulators in neurotransmission. Among their targets are the gamma-aminobutyric acid (GABA) receptors, which are responsible for inhibitory signaling in the brain. The interaction between neurosteroids and GABA receptors is complex, influencing mood regulation and pain perception. Endogenous neurosteroids have been used in conditions such as postpartum depression (PPD), where fluctuation in neurosteroid levels contribute to the onset of depressive systems. Conversely, exogenous neurosteroids, such as brexanolone and zuranolone, have emerged as therapeutic agents for PPD. These compounds act as positive allosteric modulators (PAMs) on GABA receptors, enhancing inhibitory neurotransmission and alleviating symptoms of depression. In addition, neurosteroids and GABA receptors can influence chronic pain pathways. There is a shared neurobiological substrate between major depressive disorder (MDD) and chronic pain, involving the dysregulation of GABAergic neurotransmission. Brexanolone and zuranolone offer a dual mechanism of action for treating both MDD and chronic pain. In conclusion, the modulation of neurosteroids and GABA receptors presents a novel therapeutic avenue for addressing the complex process between MDD and chronic pain. Agents like brexanolone and zuranolone offer a targeted approach to alleviate symptoms in both psychiatric and pain management domains.

1. Neurosteroids

Neurosteroids are a group of molecules that function as endogenous steroids within the central nervous system (CNS).[1] These molecules are derived from cholesterol and synthesized within the brain itself, in regions such as the hippocampus, cerebral cortex, and cerebellum. They can act as potent neuromodulators, influencing processes such as cognition, mood regulation, stress response, and neuroprotection.[2] Various neurological and psychiatric disorders have been implicated from a dysregulation in neurosteroid levels, highlighting their significance in maintaining proper brain function and mental health. Understanding the intricate mechanisms regulating neurosteroid synthesis and action holds promise for the development of novel therapeutic strategies for treating neuropsychiatric conditions ranging from anxiety and depression to epilepsy and neurodegenerative diseases.[3]

2. Neurosteroids and GABA Receptors

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter that facilitates its neuronal activity by binding it to its receptors. These receptors are complex, pentameric structures composed of various subunit types, and their diversity results in a wide array of receptor subtypes, each with distinct functional properties. The two primary receptor types are GABAB and GABAA as shown in **Figure 1** below with their respective pathways. GABAB receptors utilize metabotropic signaling pathways involving G-proteins. Activation of these receptors opens potassium channels, resulting in neuronal hyperpolarization. In contrast, GABAA receptors (GABAA_Rs) employ an ionotropic mechanism, which means they directly regulate ion flow.[4] This occurs via enhancing the influx of chloride ions to decrease the cellular

electrical potential and cause neuronal hyperpolarization. [1-4] This inhibitory pathway mediated by GABAA_Rs manifests in two distinct modes, phasic and tonic inhibition. Phasic inhibition occurs through intrasynaptic receptors following synaptic events, whereas tonic inhibition is facilitated by extra synaptic receptors, providing a sustained source of inhibition.[4]

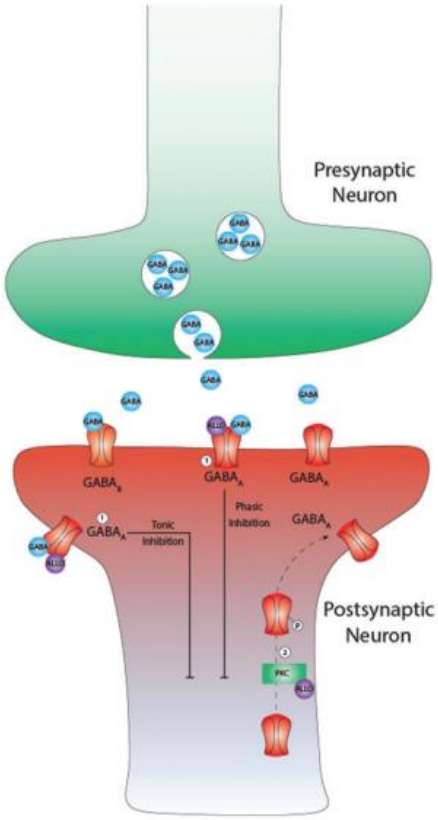

Figure 1: A schematic highlighting the function of GABA receptors and synaptic transmission in the CNS. (Adapted from Hecking, J.; Davoudian, P.A.; Wilkinson, S.T. Emerging therapeutics based on the amino acid neurotransmitter system: an update on the pharmaceutical pipeline for mood disorders. *Chronic Stress* 2021.)

The distinct modes of inhibition mediated by GABAA receptors, including phasic and tonic inhibition, highlight the multifaceted nature of GABAergic signaling and its role in neuronal activity.[4-5] Since it holds such significance in inhibitory neurotransmission in places like the CNS, neurosteroids act as potent modulators of GABAergic signaling and have emerged

as new targets for therapeutic intervention.[1] Neurosteroids modulate GABAA_Rs through structure-specific interactions.[3] These molecules augment GABAergic responses via mechanisms like direct gating alterations and positive allosteric modulation.[1-2] This interplay between neurosteroids and GABA receptors offers valuable insights into potential therapeutic interventions for various neurological and psychiatric disorders characterized by dysregulated neurotransmission.[5] Elucidating these mechanisms opens pathways for developing targeted treatments to restore neuronal balance and alleviate symptoms associated with such conditions.

3. Endogenous Neurosteroids and PPD

Endogenous neurosteroids play a crucial role in regulating mood and emotional well-being. Among these neurosteroids, allopregnanolone (alloP), derived from progesterone, has garnered significant attention for its involvement in postpartum depression (PPD).[6] PPD is a type of depression that affects individuals after childbirth, particularly within the first few weeks to month post-delivery. It is characterized by consistent feelings of hopelessness, fatigue, and sadness, often accompanied by changes in sleep disturbances, appetite, and difficulty bonding with the newborn.

During pregnancy, alloP levels rise significantly, contributing to the emotional stability characteristic of the perinatal period. However, after childbirth, there is a rapid decline in these levels, which has been linked to the onset of PPD in susceptible individuals. This allopregnanolone fluctuation during the perinatal period is presumed to influence GABAergic neurotransmission, particularly through its action as a positive allosteric modulator of GABAA receptors as shown in **Figure 2** below.[3,6] GABAergic signaling plays a crucial role in maintaining emotional stability and regulating stress responses. Therefore, the sudden decrease

in allopregnanolone levels postpartum contributes to the development of PPD symptoms such as anxiety, mood swings, and feelings of despair.

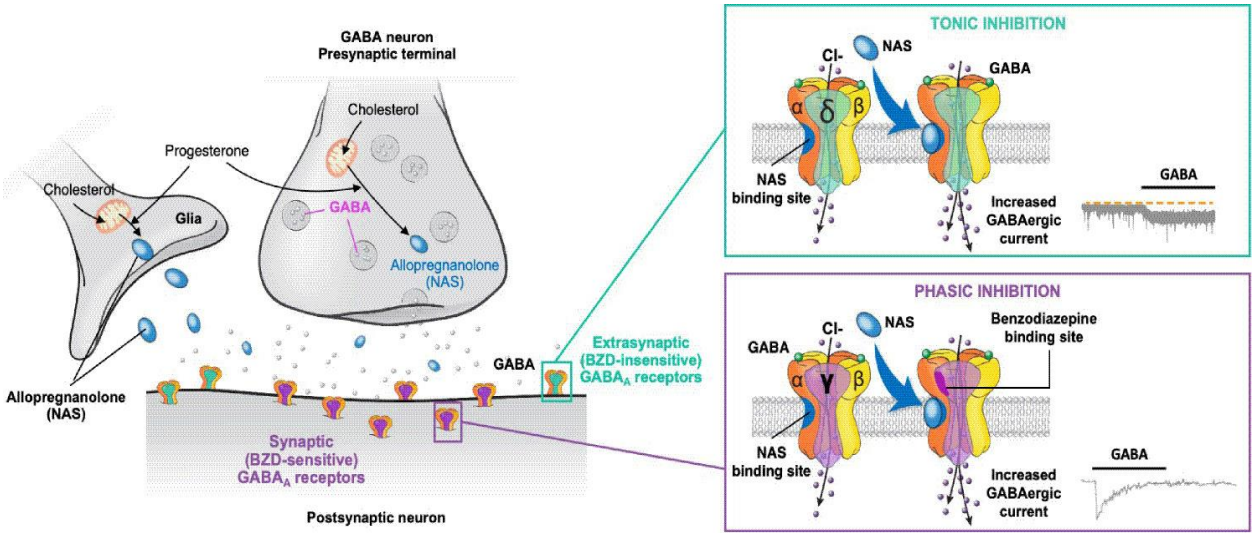

Figure 2: The schematic shows the mechanism of action of the positive allosteric modulator allopregnanolone on synaptic and extra synaptic GABAA receptors involving binding to both types of receptors. Allopregnanolone functions as a positive allosteric modulator, enhancing the frequency and duration of channel opening. This action leads to an increase in hyperpolarizing GABAergic current, impacting neurotransmission. Key terms include BZD for benzodiazepine, GABA for γ-aminobutyric acid, GABAA for γ-aminobutyric acid type A, and NAS for neuroactive steroid.
(Adapted from Gunduz-Bruce, H.; Takahashi, K.; Huang, M.Y. Development of neuroactive steroids for the treatment of postpartum depression. *Journal of neuroendocrinology* 2022, *34*, e13019.)

Through understanding the role of endogenous neurosteroids in PPD, biological mechanisms underlying the condition become clearer.[2-3,6] As a result, scientists can more readily study the potential novel therapeutic interventions for treating PPD symptoms. Research into modulating neurosteroid levels or enhancing GABAergic neurotransmission has encouraged the development of more effective PPD pharmacotherapies, offering hope for mothers who do experience this challenging condition.[6]

4. Exogenous Neurosteroids and PPD

Exogenous neurosteroids refer to synthetic or externally administered versions of neurosteroids that occur naturally within the brain.[7] These compounds are obtained because they can supplement or mimic the function of endogenous neurosteroids, which may be dysregulated or deficient in certain conditions.[8] By introducing exogenous neurosteroids, physicians aim to restore normal levels of these compounds. This would inherently modulate neurotransmitter systems and potentially alleviate symptoms associated with various neurological and psychiatric disorders.[7-8] Exogenous neurosteroids offer a unique avenue for therapeutic intervention, providing targeted modulation of brain function to address specific symptoms and improve mental health outcomes overall. The following exogenous neurosteroids have been developed and approved for the treatment of PPD.

a) Brexanolone

Brexanolone, marketed under the name ZULRESSO, is a new treatment for postpartum depression (PPD) in adult women, notable for its unique mechanism of action and administration method.[7] It is an aqueous formulation of allopregnanolone that was approved by the FDA on March 19, 2019, with breakthrough therapy designation, Brexanolone represents the first drug specifically for PPD.

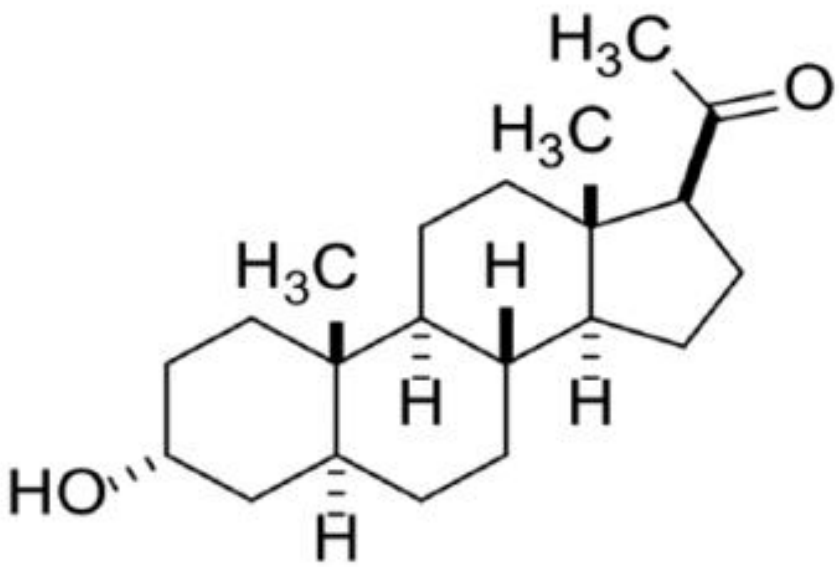

Figure 3: Chemical Structure of Brexanolone. Adapted from Powell, J.G.; Garland, S.; Preston, K.; Piszczatoski, C. Brexanolone (Zulresso): finally, an FDA-approved treatment for postpartum depression. *Annals of Pharmacotherapy* 2020, *54*, 157-163

The pharmacokinetics reveal dose-proportional behaviors and a need for strict adherence to a recommended dosing schedule.[8] This medication is only available as IV infusion and must be administered continuously over 60 hours as follows: 0-4 hours begin with 30 mcg/kg/h, then 4-24 hours increase to 60 mcg/kg/h, next 24-52 hours increase to 90 mcg/kg/h, 52-56 hours decrease dose to 60 mcg/kg/h, and then finishing up with 56-50 hours decrease dose to 30 mcg/kg/h.[7] Due to this type of administration, the patient would have to present to an inpatient or outpatient clinic and require constant supervision by healthcare professionals.

Along with its complicated administration technique, Brexanolone also has many adverse effects that are concerning for patients.[7-9] To begin, it has FDA black box warnings for loss of consciousness, central nervous system depression, and requirement of administration in a specialized care facility. This medication carries a risk of abuse and is classified as a schedule IV

therapy by the Drug Enforcement Agency (DEA). Participation in the brexanolone Risk Evaluation and Mitigation Strategy (REMS) is mandatory due to its addictive properties.[7-8] Brexanolone has major key drug interactions with opioids, antidepressants, benzodiazepines, alcohol, and other central nervous system depressants. The use of this medication with these may increase the severity and likelihood of sedation or somnolence.

Although Brexanolone has shown great therapeutic effects for the treatment of PPD, there are still so many limitations that make patient compliance and accessibility difficult with this drug.[10] Some limitations include predicted excessive costs of around $34,000, administration requirements, severe adverse events, the challenge for new mothers to spend 2.5 days away from their newborn babies, and the lack of long-term safety and efficacy data.[7-10] Brexanolone is the first drug to prescribed for the treatment of PPD, but along with it has many complications that need fixing before becoming the ideal drug of choice.

b) Zuranolone

In the treatment of Postpartum Depression, current antidepressants may take up to 2-4 weeks to show effects, showing the need for faster, effective treatments.[11] Zuranolone, a synthetic derivative of allopregnanolone targeting GABAA receptors, shows promise as a rapid, 14-day treatment for PPD. It was approved by the FDA on August 4, 2023, and is also marketed under the brand name Zurzuvae.[12] Like brexanolone, zuranolone is a neurosteroid with antidepressant activity and a novel mechanism of action as positive allosteric modulators of GABAA receptors. Zuranolone is available as a pill, while brexanolone is administered as an intravenous infusion. The drug alters both synaptic and extra synaptic GABAA conductance by attaching to a non-benzodiazepine site located on the receptor. Zuranolone was developed via an

extensive structure-activity relationship initiative aimed at refining the pharmacological, pharmacokinetic, and pharmacodynamic characteristics of neuroactive steroid GABA modulators within this class.[11-12]

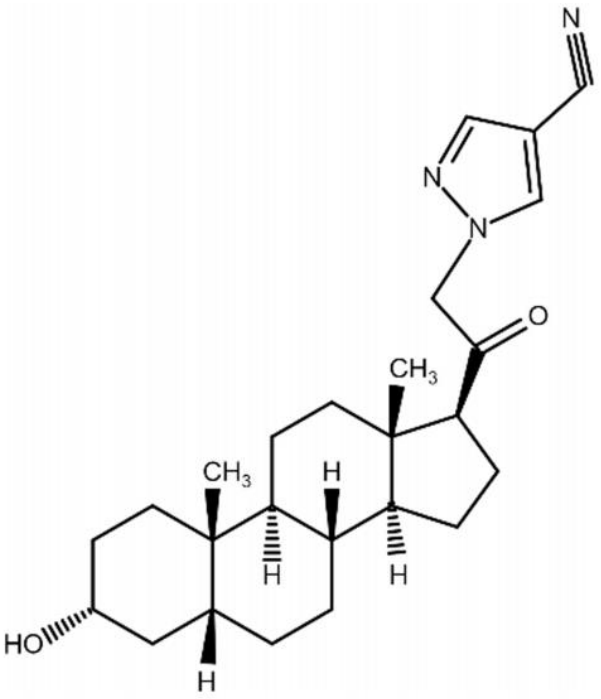

Figure 4: Chemical Structure of Zuranolone. Adapted from Marecki, R.; Kałuska, J.; Kolanek, A.; Hakało, D.; Waszkiewicz, N. Zuranolone–synthetic neurosteroid in treatment of mental disorders: narrative review. *Frontiers in Psychiatry* 2023, *14*.

The primary adverse effects noted in the cohort administered zuranolone consisted of drowsiness, headaches, vertigo, upper respiratory tract infections, gastrointestinal disturbances, and sedation.[12] The utilization of zuranolone has been linked to the risk of provoking suicidal thoughts and actions in individuals.[11] It is also not recommended for pregnant women as exposure during pregnancy may pose risks to fetal development. Caution should also be exercised when administering zuranolone alongside CYP3A4 inducers, such as rifampin, as this combination may lead to reduced efficacy in treating depression.[12] When this drug is

administered with potent CYP3A4 inhibitors like itraconazole, it is advisable to decrease the zuranolone dosage to 30 mg and closely monitor patients for potential side effects like somnolence or confusion, as there is a risk of zuranolone accumulation. In cases of severe hepatic impairment or moderate to severe renal impairment, it is recommended to reduce the daily dose to 30 mg as well. Zuranolone does not have any contraindications for use, but careful consideration of these factors and appropriate dosage adjustments are crucial to ensure safe and effective treatment.

Despite these limitations, zuranolone represents a promising short-course, rapid-acting oral therapy for PPD, differentiating it from traditional antidepressants that require extended periods to manifest effects.[11-12] The oral bioavailability of zuranolone has the potential to increase its usage as a drug on a broader scale. It shows indication not only for addressing postpartum depressive disorder but also for treating major depression, insomnia, bipolar disorder, and Parkinson's tremor.

5. MDD and Chronic Pain Share Similar Brain Mechanisms Involving GABA Receptor and Neurosteroids

Major depressive disorder (MDD), a leading contributor to global disability, presents a complex array of symptoms that severely impact an individual's daily functioning.[13] Identified by persistent low mood and anhedonia, MDD demands a multifaceted approach to comprehend its origins and treatment.[14] Recent data highlights the multifactorial nature of depression, involving genetic factors, environmental stressors, and changes in crucial neurotransmitter

systems. Theories concerning neurotransmitter imbalances including the monoamine, glutamatergic, and GABAergic hypotheses, offer insights into the biological mechanisms underlying depression, guiding the development of targeted therapies.[13] For instance, the GABAergic deficit hypothesis, supported evidence of diminished GABA levels and altered receptor expression, suggests potential treatments aimed at restoring neurotransmitter equilibrium.[14] As depicted in **Figure 5**, the intricacy of the GABA pathway and neurocircuitry underscores the complexity of depression. A comprehensive comprehension of this complexity highlights the necessity for innovative and effective therapeutic approaches to improve long-term outcomes for individuals afflicted by this incapacitating condition.

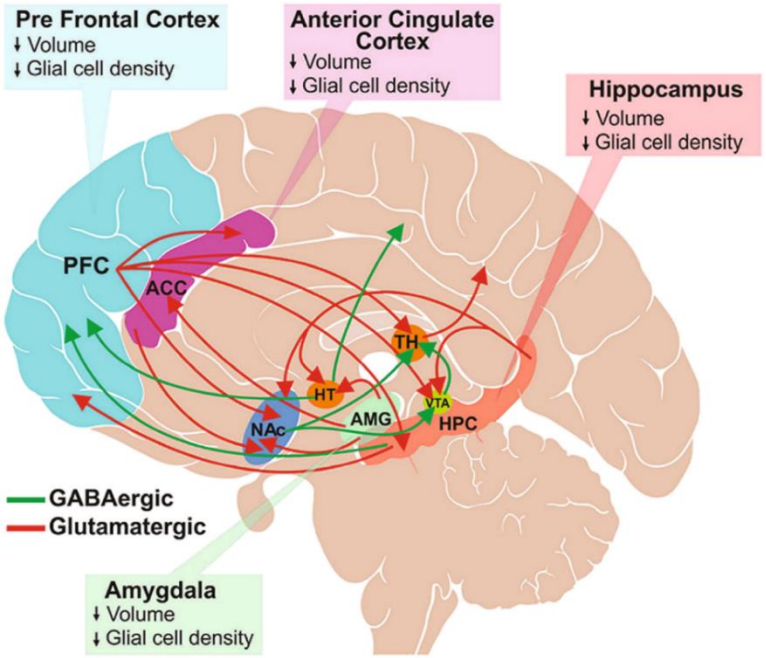

Figure 5: GABA pathway (green line) and neurocircuitry. Adapted from Cutler, A.J., Mattingly, G.W. & Maletic, V. Understanding the mechanism of action and clinical effects of neuroactive steroids and GABAergic compounds in major depressive disorder. *Transl Psychiatry* **13**, 228 (2023).

Neuroactive steroids (NASs) play a crucial role in brain function, synthesized either locally within neurons and glia or derived from circulating sterols.[13] They swiftly modulate neuronal excitability through non-genomic actions, influencing receptors of key neurotransmitters like GABA, NMDA, serotonin, and σ-1. This modulation is essential for maintaining the delicate balance between excitatory and inhibitory neurotransmission, which is pivotal for regulating mood, cognition, and pain perception. Notably, the prefrontal cortex, limbic system (including the amygdala and hippocampus), and the hypothalamic-pituitary-adrenal (HPA) axis are intimately involved in these processes, as seen in **Figure 6**.[15]

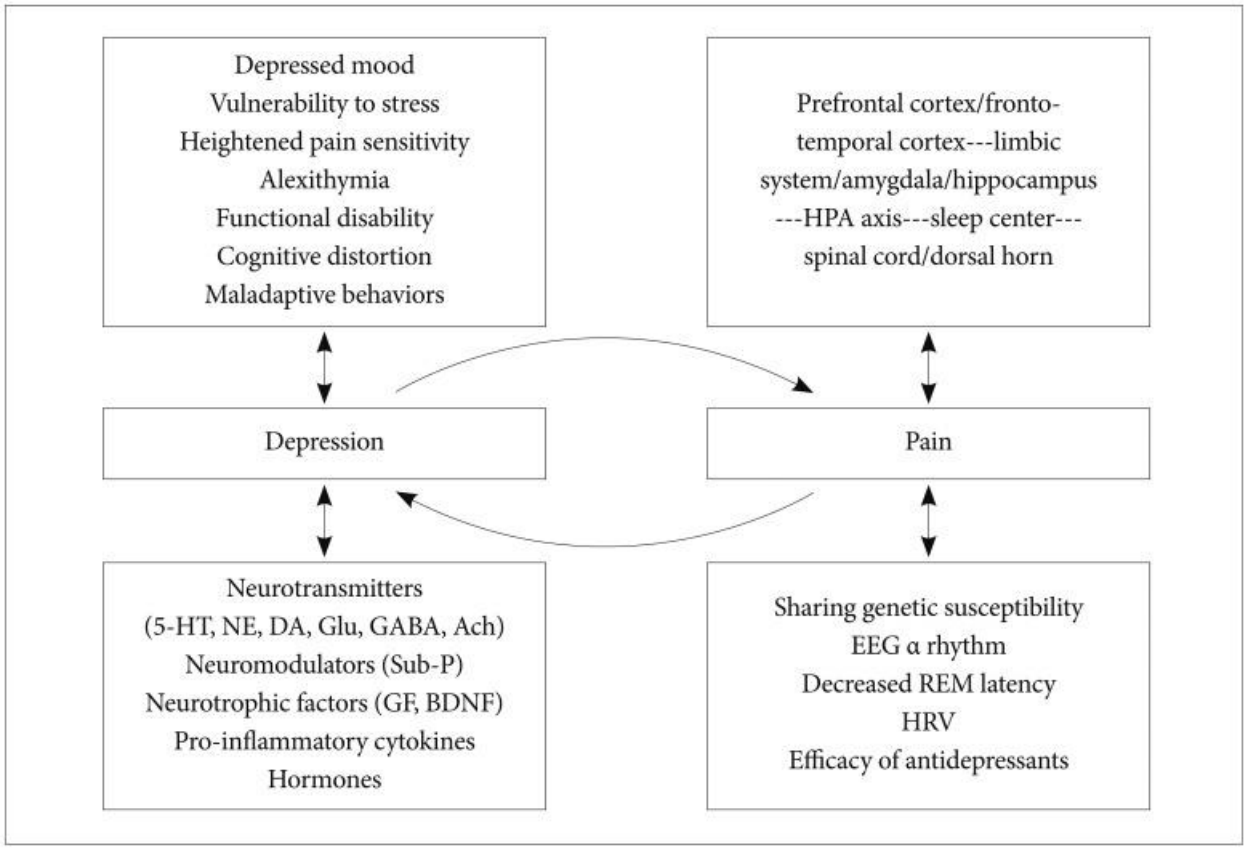

Figure 6: The schematic showing the comorbid relationship between MDD and chronic pain. GABA pathway and neurocircuitry. Adapted from Han C, Pae CU. Pain and depression: a neurobiological perspective of their relationship. Psychiatry Investig. 2015 Jan;12(1):1-8.

MDD and chronic pain often coincide, presenting a significant challenge to global health.[13-15] Emerging research reveals shared neurobiological pathways between these conditions, encompassing dysregulation in the GABA system and alterations in neurosteroid levels.[13] These shared pathways shed light on the sophisticated interplay between mood disorders and chronic pain, implicating brain regions like the prefrontal cortex and limbic system, which are integral for emotional regulation and pain processing.[15] Moreover, dysregulation of the HPA axis, a key player in stress response regulation, further complicates the relationship between MDD and chronic pain, contributing to their complex etiology and symptomatology.

Moreover, they present new avenues for therapeutic intervention, particularly with the emergence of neurosteroid-based treatments like brexanolone and zuranolone.[13-14] GABA, as the principal inhibitory neurotransmitter in the central nervous system (CNS), plays a crucial role in modulating neuronal activity and circuitry.[13-15] In both MDD and chronic pain, disruptions in GABAergic signaling contribute to the pathophysiology of these disorders.[13] Diminished GABA receptor expression and function have been noted in individuals with MDD and in animal models of chronic pain, suggesting a shared mechanism of impaired inhibitory control that may underlie the heightened emotional distress and altered pain perception observed in these conditions.[14] Neurosteroids, such as allopregnanolone, function as modulators of GABAA receptor activity, exhibiting anxiolytic, antidepressant, and analgesic effects.[13-15] Changes in neurosteroid synthesis or signaling have been implicated in both MDD and chronic pain, indicating a potential neurosteroid deficiency contributing to the emotional and physical symptoms experienced by individuals affected by these two important neuropsychiatric conditions.

6. Brexanolone and Zuranolone Can Be Used in MDD and Chronic Pain

Research suggests that depression is linked to reduced GABA levels and impaired GABAA receptor function.[1-3] Interestingly, treatments primarily targeting monoaminergic neurotransmission also affect the GABAergic and glutamatergic systems, highlighting the intricate interaction among neurotransmitter systems in mood regulation and indicating potential of neuroactive steroids in correcting dysregulated neurotransmission in psychiatric disorders, which is shown in **Figure 7**.[13,16-17] In clinical practice, the management of MDD encompasses various pharmacological options, including Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), and others. Brexanolone, a unique NAS targeting GABA neurotransmission, has shown promising results in postpartum depression (PPD), with rapid and sustained improvement in depressive symptoms.[7-8]

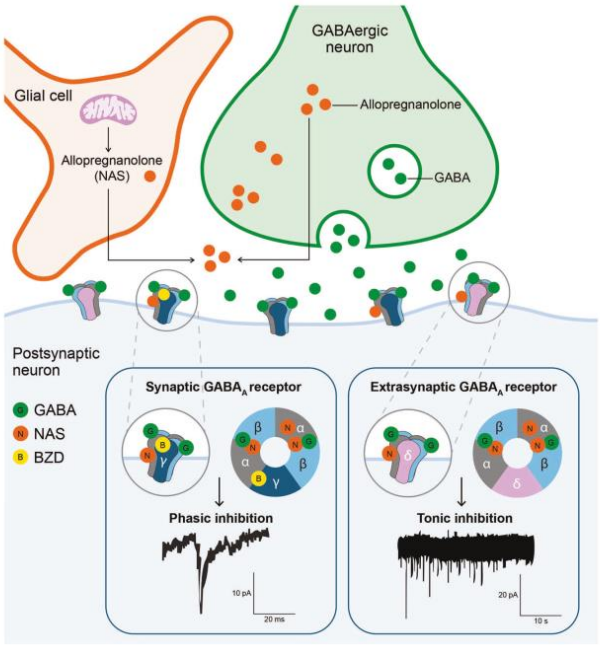

Figure 7: The schematic showing the role of GABA receptor modulation by neeurosterods. (Adapted from Cutler, A.J.; Mattingly, G.W.; Maletic, V. Understanding the mechanism of action and clinical effects of neuroactive steroids and GABAergic compounds in major depressive disorder. *Translational Psychiatry* 2023, *13*, 228.

Furthermore, there is a pressing need for innovative MDD treatments as existing oral antidepressants often have delayed effects, low response rates, and side effects.[13,16] Targeting the GABAA receptor with neuroactive steroid (NAS) GABAA receptor positive allosteric modulators (PAMs) presents a promising alternative. Recent research suggests that NAS GABAA receptor PAMs may provide rapid and enduring relief from depression symptoms with potentially improved safety and tolerability compared to conventional treatments.[16-17] This approach is particularly promising and novel strategy given the complexity of pathophysiology of MDD and the significant placebo effect observed in clinical trials, which complicates the approval of new therapies. The call for further investigation into NAS GABAA receptor PAMs represents a novel and effective approach for developing more effective and patient-friendly treatments for MDD, addressing a critical gap in mental health care.

Moreover, addressing pain management in MDD is crucial.[18] Neuroactive steroids have also shown potential in modulating pain perception through their interaction with GABAergic systems.[19] By focusing on these systems, neurosteroids can offer various approaches to treating depression and pain symptoms creating the potential to enhance overall therapeutic outcomes and patient well-being.[18-19] Therefore, investigating the involvement of neuroactive steroids in pain modulation alongside their antidepressant properties offers a effective pathway for future research and clinical interventions to tackle the elaborate relationship between mood disorders and chronic pain.[15-19]

7. Conclusions

Brexanolone, a synthetic form of allopregnanolone and positive allosteric modulator of GABA receptor in the brain, is approved for postpartum depression treatment, showcasing the efficacy of neurosteroid pathways in MDD . Its action on GABAA receptors suggests potential benefits in chronic pain due to shared neurobiology, targets and mechanisms, warranting further investigation. Zuranolone, another novel neurosteroid-based treatment with oral formulation, better patient compliance, and cost-effective targets GABAA receptors like brexanolone, offering the most promising approach for rapid relief in MDD and comorbid chronic pain. With overlapping mechanisms in MDD and chronic pain, zuranolone's impact on the GABAergic system may extend to analgesic effects, though research is ongoing.

The convergence of GABA receptor dysregulation and neurosteroid fluctuations in MDD and chronic pain suggests shared pathophysiology, opening new therapeutic avenues. Brexanolone and zuranolone, targeting these pathways, offer promising and novel strategies for MDD treatment, with implications for comorbid chronic pain management. Further research is needed to assess their efficacy and safety in chronic pain, optimize dosing, and identify biomarkers for personalized therapy. Integrating mental health and pain management services is crucial for holistic care for individuals with MDD and chronic pain in millions of people in the USA and the rest of the world.

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