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Narrative Review

Role of Neurosteroids in Catamenial Epilepsy

Areej Khalid [1*], Aysha Asif [2], Wajiha Aftab [2], Muhammad Najeeb [3], Asiya Najam [2], Abdul Hannan [2]

[1] HITEC Institute of Medical Sciences, Islamabad, Pakistan
[2] Dow International Medical College, Islamabad, Pakistan
[3] CMH Lahore, Islamabad, Pakistan

*** Corresponding Author:** Areej Khalid, HITEC Institute of Medical Sciences, Islamabad, Pakistan. E-mail: areejsyedkhalid141104@gmail.com

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Abstract

Catamenial epilepsy is a hormonally influenced seizure disorder where conventional antiepileptic drugs (AEDs) often show limited efficacy. Neurosteroids—endogenously synthesized modulators of GABAergic inhibition—represent a promising, mechanism-based alternative. During hormone-sensitive phases of the menstrual cycle, compounds like ganaxolone may help restore inhibitory balance and enhance seizure control. Its safety profile appears favorable, with only mild side effects. However, more comprehensive studies are required to confirm its long-term safety and potency in comparison with traditional antiepileptic drugs (AEDs).

Keywords: Seizures, Allopregnanolone, GABA-A Receptor Agonists, Menstrual Cycle/Physiology

Introduction

Epilepsy is a chronic non-transmissible neurological disorder, marked by recurrent seizures stemming from excessive neuronal discharge in the brain.[1] Approximately 50 million people worldwide suffer from this disease.[2] As per data provided by the National Health Inspection Survey (NHIS) in 2021, nearly 2.9 million US adults reported active epilepsy.[3] Despite its manifestation across all age groups, its prevalence peaks in childhood and undergoes a secondary surge in the elderly.[4] Individuals diagnosed with epilepsy have more than twice the mortality rate in comparison with the rest of the population— Standardized Mortality Ratio (SMR) 2.25; 95% Cl, 2.22-2.28.[5]

The frequency and intensity of seizures are affected by various factors, including a genetic predisposition, environmental triggers, and even the levels of different hormones in the bloodstream.[6,7] Women specifically may experience a significant impact of hormones on seizure patterns. Fluctuations of estrogen and progesterone during different phases of the menstrual cycle may increase the likelihood of seizures, a condition known as catamenial epilepsy, affecting more than 40% of epileptic females.[8,9] Research shows a positive association between the serum estradiol/ progesterone ratio and seizure frequency.[10] In the days preceding ovulation and menstruation, there experience a soar in this ratio, and it has a steep decline during the early and mid-luteal phase.[10] The NIH progesterone trial showed that day 1 (average daily seizure frequency: 0.68) of the menstrual cycle averaged double the seizure frequency in comparison with day −8 (0.30).[11]

Despite its prevalence, research on catamenial epilepsy remains limited. There have been few animal trials, and there is no FDA-approved treatment for the condition as of yet.[12] Current drug treatments mostly involve the use of conventional AEDs, but research shows that catamenial seizures are often quite resistant to available drug treatments.[13] Neurosteroids are steroids synthesized within the brain that exert various effects by adjusting neuronal excitability. There is a growing body of evidence that suggests that natural and synthetic neurosteroid analogs may prove to be a potent pharmaceutical intervention for this condition in the future, given their propensity to act as anticonvulsants via gamma-aminobutyric acid (GABA) A receptor modulation.[13]

Different Therapies of Treatment for Epilepsy

Treatment of epilepsy is categorized based on the type of seizures the patient has. Ethosuximide, an

antiepileptic drug, is used to treat absence seizures.[14] Status epilepticus is treated by administering intravenous benzodiazepines. If that does not improve the symptoms, phenytoin, valproate, levetiracetam, lacosamide, and phenobarbital can be used.[15] Approximately 80% of children with epilepsy have grand mal (tonic-clonic) seizures; phenytoin and valproic acid are the primary treatment options. Carbamazepine, on the other hand, is used for patients with brain damage, whether related to epilepsy or not. Treatment is typically maintained for 2 to 4 years until the patient is symptom-free, after which it is gradually tapered off over several months.[16] Refractory epilepsy is a type of epilepsy that is resistant to drug treatment, with nearly one-third of patients with epilepsy falling into this category. For these patients, alternative treatments are used, which include deep brain stimulation, vagus nerve stimulation, and responsive neurostimulation.[17] Surgical treatment options are available for refractory epilepsy, but fewer than 1% of patients opt for these procedures. These options may include surgical resection of the epileptic foci, radiofrequency thermocoagulation, and laser interstitial thermal therapy (LiTT), which, while not yet approved in Europe, is performed in the United States for small lesions.[17] Temporal lobe epilepsy is another type associated with hippocampal sclerosis. Temporal lobe seizures are among the most drug-resistant forms of epilepsy, and surgical intervention can be an effective treatment option, particularly for those with confirmed hippocampal sclerosis.[17] Juvenile myoclonic epilepsy is another type that requires careful consideration in treatment. Clinical trials have shown that valproic acid is effective for this condition, demonstrating good tolerability and superiority compared to other antiepileptic drugs.[18] Catamenial epilepsy is associated with seizures related to the menstrual cycle. Treatment is determined by the regularity of the cycle: for regular cycles, progesterone derivatives can be utilized, while for irregular cycles, non-hormonal options such as acetazolamide may be recommended. For women who cannot predict their cycles, GnRH analogs may be used to halt menstruation.[19]

Neurosteroids vs Traditional Antiepileptic Drugs

Neurosteroids such as allopregnanolone and tetrahydro -deoxycorticosterone (THDOC) act via GABA receptor modulation, enhancing GABAergic signaling within the brain, a process explained in detail later on in this review.[20] This is significant with regard to catamenial epilepsy, in which neurosteroid fluctuation is linked to seizure exacerbation in different phases of the menstrual cycle. Traditional AEDs like phenytoin, valproate, and carbamazepine target sodium or calcium ion channels to reduce neuronal firing or modulate neurotransmitter release.[21] Benzodiazepines may also act on GABA-A receptors, but they are less selective for extrasynaptic sites in comparison to neurosteroids.[22]

Neurosteroids are particularly effective in treating catamenial epilepsy, where traditional AEDs may not prove as potent in the therapy of hormone-related epilepsy patterns.[13]

Moreover, AEDs have a variable frame of action, with some drugs like valproate requiring regular dosage to maintain an effective therapeutic profile.[23] Neurosteroids, meanwhile, are produced endogenously and may be administered exogenously as well.[20,24] This allows for targeted administration during menstrual phases when neurosteroid levels are lowest.

Mechanism of Action of Neurosteroids and its Clinical Applications

Biosynthesis of Neurosteroids

The synthesis of neurosteroids begins with P450scc enzyme-dependent cleavage of cholesterol to yield pregnenolone, which is the rate-limiting step in the biosynthesis of neurosteroids within the brain. Then either 17α-hydroxypregnenolone or progesterone is produced from pregnenolone.[26] These steroid precursors are converted to derivatives that interact with neurotransmitter receptors (e.g., GABA-A and NMDA receptors, glycine receptors, and opioid σ1 receptors). There are two types of neurosteroids: nonsulfated (e.g., allopregnanolone and THDOC), which potentiate GABA-A receptor function, and sulfated, which increase neuronal excitability by acting as negative GABA-A modulators and enhance glutamatergic activity. However, sulfated neurosteroids can also negatively modulate glutamate transmission, depending on the receptor subunit composition.[12]

Modulation of GABA-A Receptors

Neurosteroids such as allopregnanolone are positive allosteric modulators that bind to discrete sites on the GABA-A receptor, causing direct activation.[27] GABA receptors are widely distributed throughout the brain

and spinal cord and constructed from different combinations of subunits (α, β, γ, δ, and ε).[28] Neurosteroid activity at GABA-A receptors increases both the frequency and duration of GABA-mediated chloride channel openings, facilitating neuronal hyperpolarization and decreased excitability.[29]

Neurosteroids, such as allopregnanolone, modulate GABA-A receptor activity by enhancing both synaptic (phasic) and extrasynaptic (tonic) inhibition. Tonic inhibition results from the continuous activation of extrasynaptic receptors by low levels of ambient GABA, particularly those with δ- and α5-subunits, while phasic inhibition is characterized by synaptically released GABA, which generates brief inhibitory signals.[12,30,26] Neurosteroids enhance tonic inhibition to lessen excitability and susceptibility to seizures in periods of hormonal fluctuation, as seen in catamenial epilepsy.[12,28]

The ovarian cycle impacts behavior and seizure susceptibility through neurosteroid fluctuations that influence GABA-A receptor expression and tonic inhibition. Research indicates that during hormonally driven periods, females with higher levels of extrasynaptic δ-containing GABA-A receptors exhibit better seizure protection.[27]

Hormonal Influence on Seizure Activity

Neurosteroids play a significant role in modulating neuronal excitability and seizure activity by influencing brain neurotransmitter systems. In catamenial epilepsy, fluctuating levels of hormones, such as progesterone and estrogen, during the menstrual cycle, lead to changes in neurosteroid concentrations that affect seizure susceptibility During the early follicular phase, estrogen and progesterone levels are low, with estradiol peaking mid-cycle and progesterone rising in the luteal phase before menstruation.[13,25] Generally, progesterone and neurosteroids like allopregnanolone, pregnenolone, and androstanediol exhibit anticonvulsant properties, whereas estradiol, pregnenolone sulfate, DHEA sulfate, and cortisol tend to exhibit convulsive activity.[13,25,26]

Anticonvulsant Impact of Progesterone and Its Metabolites

Progesterone affects seizure susceptibility directly by interacting with progesterone receptors and indirectly by being converted into neurosteroids such as allopregnanolone, which act to modulate GABA-A receptors. Another discussed mechanism is the inhibition of excitatory glutamic transmission. Other progesterone-mediated regulatory mechanisms may oppose neuroprotective effects during pregnancy when seizure susceptibility is low due to high progesterone levels.[25,26,29,31] However, contrasting actions of progesterone and estrogen may mask anticonvulsant effects, and certain regulatory mechanisms may counteract neuroprotective effects.[32]

Progesterone is initially converted into 5α-dihydroprogesterone by an enzyme called 5α-reductase and then converted to allopregnanolone by an enzyme known as 3α-hydroxysteroid oxidoreductase.[25,26,28] This conversion may take place in the periphery either in the periphery or in the brain, where allopregnanolone accumulates. Additionally, some allopregnanolone is synthesized locally within the brain from cholesterol. Despite its low affinity for PRs, allopregnanolone may indirectly activate these receptors by being converted back to 5α-dihydroprogesterone, a moderately effective PR agonist, suggesting that PRs PRs may play a role in the longer-term effects of neurosteroids on seizure control.[25] However, studies show that progesterone's antiseizure effects are not linked to PR.[26]

Allopregnanolone mimics the anticonvulsant effects of progesterone, enhancing synaptic inhibition by GABA-A receptor modulation,[25,26,28] and significantly increases in conjunction with progesterone. At low concentrations, neurosteroids enhance GABA-A receptor currents, while at higher concentrations, they directly activate the receptor. Similar to barbiturates, neurosteroids increase both the frequency and duration of channel opening in GABA-A receptors.[32] These effects are especially relevant in the luteal phase, where increased progesterone contributes to an elevated level of neurosteroids.[25]

Higher levels of allopregnanolone in the brain as a result of local production have protective benefits against seizures. Progesterone's conversion to allopregnanolone is the main mechanism behind its anticonvulsant action, and withdrawal, particularly before menstruation, raises the risk of seizures.[25] Three different binding sites on GABA-A receptors have been proposed; however, the precise locations are still unknown. According to animal studies, receptor subunit plasticity may increase the risk of seizures in perimenstrual epilepsy.[27]

Role of THDOC in Seizure Control

The neurosteroid tetrahydrodeoxycorticosterone (THDOC), synthesized from deoxycorticosterone, fluctuates with the menstrual cycle and is typically elevated during the luteal phase. Women with catamenial epilepsy often display 30% lower serum THDOC levels, especially around menstruation, which correlates with increased seizure susceptibility.[33] As a potent positive allosteric modulator of GABA-A receptors, THDOC enhances chloride influx and neuronal hyperpolarization, reducing excitability.[28]

While animal studies have shown that THDOC effectively suppresses chemically or electrically induced seizures, clinical data on its role in catamenial epilepsy remain sparse. This limitation highlights a significant gap in understanding its therapeutic relevance. Given that THDOC is primarily produced in the adrenal gland and may be influenced by stress, future studies should investigate how its levels vary across hormonal states, its pharmacokinetics, and whether exogenous supplementation could provide clinical benefit during vulnerable menstrual phases.

AP, THDOC, and androstanediol are among the neurosteroids shown to confer strong seizure protection. However, their efficacy may decline during low-progesterone phases of the menstrual cycle, increasing seizure susceptibility.[29] Notably, while THDOC exhibits robust efficacy in modulating GABA-A receptors, further research should explore its therapeutic window, optimal dosing, and potential synergy with other neurosteroids or AEDs.

Proconvulsant Effects of Neurosteroids

Estrogens play a complex function in seizure susceptibility; in people and animals, they often have proconvulsant qualities; however, in some situations, they may also have protective or anticonvulsant effects. Estradiol, which has been extensively researched in animal models of epilepsy, demonstrates highly variable effects on seizures based on parameters such as dosage, length of therapy, and hormonal state.[29,31] Estradiol is known to make seizures worse in women who have epilepsy. The follicular and luteal phases of the menstrual cycle are when plasma estradiol levels are at their highest. Research has indicated a positive relationship between the estrogen-to-progesterone ratio and seizure vulnerability, particularly during the premenstrual and periovulatory phases.[29] Neurons in areas such as the cerebral cortex and limbic system are impacted by estradiol. It affects glutamate receptor subtypes directly, especially NMDA receptors, and indirectly by making hippocampal neurons' dendritic spines denser. As demonstrated in animal models, this increase in spine density and excitatory synapses may improve the synchronization of neuronal firing and contribute to the convulsive effects of estradiol.[25]

Unopposed by progesterone, the midcycle spike in estrogen may be a factor in the worsening of seizures during these periods. Estrogen may have a proconvulsant impact by enhancing glutamate-mediated excitatory neurotransmission and reducing GABAergic inhibition, especially in the hippocampus; however, the precise mechanism is unknown.[25] By raising dendritic spine density and brain-derived neurotrophic factor (BDNF) levels, it also affects neuronal excitability, which in turn can raise hippocampus excitability.[26]

According to another study, the effect of estrogens on hippocampal seizure susceptibility is still controversial. Estradiol may have little impact or even be protective against seizures, although multiple studies show it to be a convulsant. Notably, neuroprotective advantages have been linked to modest levels of estradiol.[31]

In addition, the neurosteroid pregnenolone sulfate (PS), which possesses proconvulsant qualities in contrast to allopregnanolone, is secreted by the ovary. Whether administered systemically or directly in the brain, PS can cause seizures and status epilepticus. Moderate allosteric stimulation of NMDA receptors and inhibition of GABA A receptor function are part of its mechanism. PS can decrease GABAergic inhibitory transmission at physiological levels, even though its convulsant effects usually happen at concentrations far higher than the brain's normal levels. PS may further influence catamenial epilepsy by increasing seizure vulnerability when allopregnanolone levels are low. However, it is still unclear what part PS plays in catamenial seizures.[13,28]

Clinical Relevance of Neurosteroids in Catamenial Epilepsy Treatment

Neurosteroid actions in catamenial epilepsy highlight potential therapeutic strategies targeting hormonal fluctuation. By understanding the roles of specific neurosteroids, treatments can be tailored to address hormonal effects on seizure susceptibility.[32]

Clinical Efficacy

In a randomized, double-blind, phase 3 clinical trial, progesterone therapy was tested for its effectiveness in reducing seizures in women with catamenial epilepsy. While the initial results showed no significant difference between progesterone and placebo treatments, further post-hoc analysis revealed a key finding: women with perimenstrual catamenial epilepsy, which coincides with naturally lowered progesterone levels, responded significantly better to progesterone therapy.[34]

In a recent pilot study, ganaxolone was administered orally (300 mg/day) to two patients starting on day 21 of the menstrual cycle utill the third day after menstruation began. During four months of this pulse therapy, both patients showed a decrease in seizure frequency.[35]

Recent studies used a catamenial epilepsy model in female rats that had been made chronically epileptic through a lithium–pilocarpine treatment, causing them to experience ongoing, spontaneous seizures. These epileptic rats averaged around six seizures per day, each lasting about a minute. When neurosteroids were removed from their systems using finasteride, their seizure frequency spiked dramatically—over 10 times more than before.[36]

A large, randomized, double-blind, placebo-controlled, phase 2 study of ganaxolone as adjunctive therapy for uncontrolled partial-onset seizures in adults demonstrated that 1,500 mg/day ganaxolone resulted in a significant reduction in mean weekly seizure frequency compared with placebo.[37] While Ganaxolone is quite effective in other types of seizure, studies on its effectiveness in catamenial epilepsies are limited.

Safety and Tolerability

Ganaxolone, a neurosteroid metabolite of progesterone, has exhibited favorable results in several clinical trials as a therapeutic agent for intractable seizures.[38] A randomized, placebo-controlled phase 3 trial found that ganaxolone administration significantly reduced seizure frequency as compared to the placebo, and was well tolerated.[35] Despite its efficacy compared to intractable seizures, pretreatment with ganaxolone assessed in the low-dose pentylenetetrazol (PTZ) and the gamma-hydroxybutyric acid (GHB) model of absence seizure in rats was found to prolong seizures.[39]

Table 1. Studies Evaluating Efficacy or Safety of Neurosteroids in Treatment of Seizures

Author	Year	Study design	Aim	Sample size	Results
Knight EMP et al.	2022	Randomized placebo controlled clinical trial	Efficacy and safety of ganaxolone in CDKL5 deficiency disorder related refractory seizures	100 subjects	Ganaxolone significantly reduced seizure frequency and was well tolerated
Sperling MR et al.	2017	Randomized double-blind clinical trial	Efficacy and safety of ganaxolone for treatment of partial-onset uncontrolled seizures	147 subjects (131 completed study)	Ganaxolone was well tolerated and reduced seizure frequency
Herzog AG et al.	2012	Randomized double-blind clinical trial	Efficacy and safety of natural progesterone therapy vs placebo treatment of intractable seizures	294 subjects	No difference in primary outcome of ≥50% responders. Post hoc findings suggest progesterone may be clinically important for women with perimenstrually exacerbated seizures
Lawrence C et al.	2010	Randomized control animal trial	Role of endogenous neurosteroids in epilepsy (by blocking biosynthesus)	22 epileptic female rats	Inhibition of biosynthesis of neurosteroids caused seizure exacerbation
McAuley JW et al.	2001	Open label pilot study	Safety, tolerability and anticonvulsant activity of ganaxolone in patients of catamenial epilepsy	2 subjects	Lessened perimenstrual and non-perimenstrual seizure activity compared to baseline were observed with mild side effects
Snead OC	1998	Randomized control animal trial	Efficacy of ganaxolone in treatment of absence seizures	Rats (number unknown)	Ganaxolone exacerbated absence seizures by GABA-A receptor modulation

As mentioned above, a recent open-label pilot study evaluated ganaxolone for safety, tolerability, and efficacy in two patients with catamenial epilepsy over the course of 4 months. Mild side effects were reported.[35]

Another phase 2 placebo-controlled trial was carried

out to gauge the use of this drug for seizure therapy, most subjects of which were later enrolled in an open-label extension study.[40] Adverse side effects present in around 10% of patients were: headache (21%), convulsions (16%), fatigue (16%), falls (14%), nasopharyngitis (14%), dizziness (13%), contusion (12%), and nasal congestion (10%). As per authors, majority of the side effects ranged from mild to moderate in the group that was administered ganaxolone.[41]

Although no major adverse events have been reported, long-term safety remains uncertain. Potential concerns include hormonal disruption, tolerance development, or neuropsychiatric effects. Extended follow-up studies and post-marketing surveillance will be essential to fully evaluate these risks in chronic use.

Conclusion

In conclusion, this review article stresses the significant role that neurosteroids, in particular allopregnanolone and its synthetic counterpart ganaxolone, may play in the pharmaceutical management of catamenial epilepsy, a condition wherein seizure frequency is increased relative to hormonal changes during the menstrual cycle. Research suggests that neurosteroid administration enhances GABA-A receptor function to alter the excitability of neurons, thus providing a neurobiological basis for their anticonvulsant activity. These drugs have offered promising results in trials so far with regard to the alleviation of seizure susceptibility. Neurosteroid modulation might be a promising avenue that can be used in the future treatment of females with catamenial epilepsy. While neurosteroids such as allopregnanolone and ganaxolone show clear potential for targeted seizure control in catamenial epilepsy, clinical adoption remains premature. Large-scale randomized trials are urgently needed to validate their long-term safety, identify optimal treatment windows, and evaluate their efficacy in combination with established AEDs. These future efforts will be critical to translate neurosteroid research into individualized, hormone-informed epilepsy care.

Conflict of Interest

The authors declare no conflicts of interest.

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