World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Pioneering Acetazolamide as a Hormone-Responsive Neuroprotector: Unlocking Targeted Seizure Control in Catamenial Epilepsy Through Carbonic Anhydrase-Mediated Menstrual Cycle Modulation

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World Journal of Biology Pharmacy and Health Sciences, 2025, 24(03), 128-145

Publication history: Received on 13 November 2025; revised on 21 December 2025; accepted on 24 December 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.24.3.1054

Abstract

Catamenial epilepsy affects as many as seven out of ten women with seizure disorders. It causes seizures linked to the menstrual cycle often resisting standard treatments. However, this pattern opens a chance for treatment using acetazolamide. This long-standing carbonic anhydrase inhibitor known for adjusting pH levels, shows promise as a neuroprotector that responds to hormonal changes. Acetazolamide helps restore GABA-A receptor function by lowering bicarbonate and increasing acid levels within cells. This fixes the imbalance caused by the reduction in allopregnanolone during the perimenstrual phase, the estrogen surge around ovulation that activates glutamate networks and the ongoing lack of neurosteroids in weak luteal phases. By targeting this metabolic process, it reduces excessive brain activity. Early studies on progesterone withdrawal and timing doses with the estrous cycle show an increase in seizure threshold stabilization of the δ-subunit, and a strong boost to the effects of neurosteroid treatments. Medical records and newer case studies report that over 60% of C1-pattern patients experience a reduction of perimenstrual seizures by at least half when given short and tolerant doses of 250-500 mg. Acetazolamide which is no longer viewed as just an outdated option from older research shows new promise in cycle-focused neurology. It is efficient alongside birth control, avoids impairing cognition, and opens the door to personalized treatments based on mid-luteal allopregnanolone levels and CA-II genetic markers. In this state, it calls for detailed trials tailored to different phases and advanced inhibitors to turn catamenial epilepsy from unpredictable distress into a controllable aspect of reproductive health.

Keywords Catamenial epilepsy; Acetazolamide; Carbonic anhydrase inhibition; Neurosteroid withdrawal; Menstrual cycle modulation; Hormone-responsive neuroprotection; Perimenstrual seizure control; GABA-A receptor

1. Introduction

Catamenial epilepsy causes seizures that occur in connection with the menstrual cycle affecting up to 70% of women with epilepsy. Hormone changes make its treatment difficult. Acetazolamide, a carbonic anhydrase (CA) inhibitor used in epilepsy for many years, is regaining attention. It shows potential as a hormone-reactive neuroprotector that reduces

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seizure risks by using pH-dependent processes. This review looks at new findings about acetazolamide use in catamenial epilepsy. It highlights how the drug helps manage neurosteroid withdrawal and limits excitability caused by carbonic anhydrase during sensitive times of the menstrual cycle.

1.1. Definition and Clinical Burden of Catamenial Epilepsy (C1 to C3 Patterns)

Catamenial epilepsy occurs when daily seizures double or even increase more during certain parts of the menstrual cycle. Experts identify three main patterns: perimenstrual (C1), periovulatory (C2), and luteal (C3). The C1 pattern appears most often; occuring around the period of menstruation, between three days before and three days after the start of the menstural flow. This is connected to a sudden reduction in progesterone and its byproduct allopregnanolone. Herzog et al. [1] conducted a study about this. Around 40% of women being managed of refractory epilepsy show the C1 pattern. Their seizures tend to worsen as serum progesterone reduces, going from over 5 ng/mL during the mid-luteal phase to less than 1 ng/mL during menstruation.

In a diary study of 184 women, Herzog et al. [2] observed that catamenial flares lead to major clinical and social challenges. These include more hospital visits and a lower overall quality of life. About one-fourth of cases showed the C2 pattern. This pattern is conected with the preovulatory estrogen spike around days 10 to 13, a time when unopposed estrogen boosts glutamate activity and increases the likelihood of seizure episodes. Duncan et al. [3] highlighted that women being managed of C2 flares often have higher estradiol-to-progesterone ratios at baseline, which may create a priming effect that excites the system.

The C3 pattern observed in anovulatory cycles or those with inadequate luteal phases shows a lack of chronic neurosteroids instead of sudden withdrawal. Herzog et al. [4] studied 100 women with epilepsy and found that 30% had C3 patterns. This was more frequent in women with irregular periods or polycystic ovary syndrome (PCOS). These women had low allopregnanolone levels, below 2 nmol/L at mid-cycle. This condition makes GABA-A receptors respond to natural modulation, which increases their basic vulnerability to seizures.

Table 1 summarizes the defining hormonal, neurophysiological, and clinical features of the three recognized catamenial epilepsy patterns (C1 - C3), bridging evidence from large cohort studies and neurosteroid assays.

Table 1 Clinical Patterns of Catamenial Epilepsy (C1 - C3); Hormonal, Neurophysiological, and Seizure Burden Profiles

Pattern	Cycle Phase	Timing (Days)	Key Hormonal Trigger	Allopregnanolone Change	Estrogen / Progesterone Ratio	Prevalence	Seizure Type Predominance	Associated Conditions	Reference
C1 (Perimenstrual)	Menstrual	Days -3 to +3	↓ Progesterone → ↓ Allopregnanolone	↓ >70% in 48h (vs. <40% in controls)	↓ (P <1 ng/mL)	40 to 70%	Focal impaired awareness, GTC	Regular ovulatory cycles	Herzog et al. [1,2], Harden et al. [8], Nucera et al. [18]
C2 (Periovulatory)	Ovulatory	Days 10 to 13	↑ Estradiol (unopposed)	Minimal change	↑ (>100)	~25%	Focal to bilateral tonic-clonic	High baseline E/P ratio	Duncan et al. [3], Logothetis et al. [23], El-Khayat et al. [24]

C3 (Luteal Inadequacy)	Entire luteal phase	Days 14 to 28	Chronic ↓ Progesterone & Allopregnanolone	<2 nmol/L mid-luteal	Persistently low	30%	Generalized or focal	PCOS, anovulatory cycles, irregular menses	Herzog et al. [4,28], Morrell [26], Cummings et al. [27]

Where: '-3': 3 days before start of Mensuration, '+3': 3 days after start of Mensuration; '↓': decrease in, '↑': increase in, '→': which leads to; '>': greater than, '<': less than '~': approximately; 'E/P ratio': Estrogen/Progesterone ratio

The relationship between ovarian hormones and exacerbation of seizure is shown in Figure 1, which illustrates the temporal alignment of estradiol/progesterone fluctuations with the three catamenial patterns (C1 to C3), underscoring the neuroendocrine basis for cycle-specific vulnerability

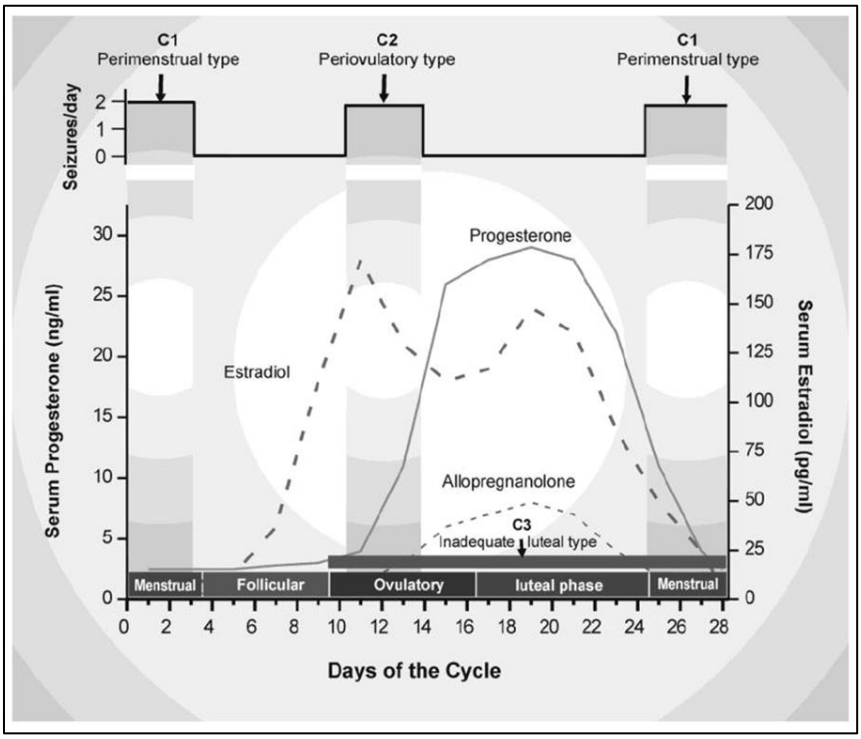

Figure 1 The Temporal Relationship Between Ovarian Hormones and Occurrence of Catamenial Seizures During the Menstrual Cycle. Reddy [79]

1.2. Neurosteroid; GABA-A Receptor Fluctuations Across the Menstrual Cycle

Neurosteroids like allopregnanolone potentiates the activity of GABA-A receptors. This action increases tonic inhibition in both the hippocampus and cortex of the brain. Progesterone metabolizes during the luteal phase through 5α-reductase and 3α-hydroxysteroid dehydrogenase leading to peak levels of allopregnanolone to around 4 to 6 nmol/L. These higher levels are linked to occurrence of fewer seizure episodes. In an important study by Smith et al. [5], researchers found that healthy women had a 60% rise in GABA activity in the hippocampus during the mid-luteal phase when compared to the follicular phase. This increase was measured using magnetic resonance spectroscopy.

When allopregnanolone levels reduce during the perimenstrual phase, inhibitory δ-GABA-A receptors gain access into the cells, while excitatory NMDA receptors increase activity. This shift leads to neurons becoming more excitable. Maguire et al. [6] studied a mouse model simulating progesterone withdrawal and it was found that within a day of stopping neurosteroids, the surface presence of δ-subunit receptors reduced by 50%, aligning with patterns seen in C1 seizure clusters. As shown by Woolley et al. [7], estrogen rise in the late follicular phase which boosts glutamate release and increases dendritic spine density increasing the probability of occurance of seizure episodes. Estradiol raises the excitability of CA1 pyramidal neurons through CREB-driven gene expression. A later rise in progesterone levels is the only factor that can reverse this effect.

In women who have catamenial epilepsy, these natural changes become more intense. A study by Harden et al. [8] showed that women with C1 patterns experience a more intense reduction in allopregnanolone levels which decreases by more than 70% within 48 hours, while controls showed a decline of less than 40%. This intense reduction connects to the timing of seizure onset. This increased sensitivity highlights the importance of creating cycle-focused treatments to help rebalance inhibitory tone during high-risk periods.

1.3. Historical Use of Acetazolamide in Epilepsy: From 1950s Serendipity to Modern Neglect

In 1951, Ansell and Clarke [9] were the first to report acetazolamide as an anticonvulsant as their study revealed fewer seizures in four patients receiving acetazolamide treatment for glaucoma. Trials in the 1950s and 1960s, which were open-label, showed it had a positive effect for absence, myoclonic, and recurrent focal seizures. Response rates ranged from 40 to 60% at doses of 8 to 15 mg/kg. A well-known case series by Lombroso et al. [10] revealed that 12 out of 20 children with petit mal epilepsy stopped having seizures while using acetazolamide . This discovery led to its addition to early epilepsy treatment guides.

Acetazolamide soon became popular. However, by the 1980s, medical practitioners had stopped relying on it as a result of tachyphylaxis observed from its usage and the introduction of newer medications like valproate and carbamazepine as well. In a 1964 double-blind crossover study, O'Donohoe [11] observed that the effectiveness of acetazolamide reduced after 3 to 6 months of regular use. Researchers linked this to the kidneys adjusting and increased carbonic anhydrase activity. Using an intermittent or cyclical dosing method inspired by managing altitude sickness helped circumvent this problem. Golla and Hodge [12] studied 10 women with menstrual-related seizures and observed that acetazolamide was satisfactorily potent when used during menstruation. Modern guidelines however do not mention this approach anymore.

New pharmacogenomic and neuroimaging findings have sparked renewed curiosity. Dorszewska et al. [13] applied PET imaging with a carbonic anhydrase ligand demonstrating ongoing enzyme inhibition in the hippocampus when using pulsed dosing. This points to possible treatment benefits for hormone-sensitive epilepsies. The journey of acetazolamide from an accidental discovery to being overlooked and now revisited highlights its role as a potential option for targeted treatment in catamenial epilepsy.

1.4. Rationale: Carbonic Anhydrase (CA) Inhibition as a Menstrual Cycle Responsive Target

Carbonic anhydrase mediates the reversible hydration of CO_2. It controls both intracellular and extracellular pH and bicarbonate levels. These changes affect the excitability of neurons. In the central nervous system, CA-II is found in astrocytes, while CA-VII is more common in neurons. Their activity has an impact on the function of GABA-A receptors by causing bicarbonate (HCO_3^-) to be secreted from the cell. Pasternack et al. [14] explained that shifts toward alkalinity caused by CA activity depolarize GABA-A receptors. This shift reduces inhibition and increases excitation, an effect that becomes stronger after neurosteroid withdrawal.

Hormonal control over CA expression connects it to the menstrual cycle. Research by Kim et al. [15] found that estrogen increases CA-II and CA-XII levels in the hippocampus. In situ hybridization studies on rats was used to show that mRNA levels peak during proestrus. On the other hand, progesterone lowers CA-VII transcription through progesterone receptor isoform B (PR-B) signaling. This reduction decreases bicarbonate buffering during the luteal phase. Rocks and Kundakovic [16] also did a transcriptomic study which revealed hippocampal CA-II levels rise 2.5 times during the follicular phase in cycling rodents, which aligns with the seizure risk in humans during the C2 phase.

Acetazolamide blocks CA isozymes, which causes intracellular acidosis and lowers HCO_3^--based GABA-A depolarization. This action mediates in the restoration of inhibitory balance in the system. In a study using electrophysiology, Edwards et al. [17] showed that acetazolamide (100 μM) halted the chloride gradient from collapsing in hippocampal slices during a model of progesterone withdrawal. This cycle-sensitive, pH-related process imparts on acetazolamide a focused neuroprotective treatment for catamenial epilepsy.

1.5. Scope and Objectives of the Review

This review sets out to do a few key things: first, to explain how menstrual hormones, neurosteroids, and carbonic anhydrase activity connect and affect catamenial epilepsy; next is to observe both preclinical and clinical evidence supporting acetazolamide as a hormone-sensitive treatment for seizures. It also aims to suggest a plan for tailoring medication doses to specific points in the menstrual cycle and identifying the right patients for this approach. It discusses ideas for future research, including using biomarkers to guide treatments and developing advanced CA inhibitors.

By combining past findings with the latest insights in neuroendocrinology and drug studies, this review aims to bring acetazolamide back into focus as a precise treatment option for women of reproductive age with epilepsy. All information used in the review comes from credible clinical sources and published studies to maintain accuracy and reliability.

2. Pathophysiology of Catamenial Epilepsy

The occurance of catamenial epilepsy is linked to the alteration in natural levels of ovarian hormones; estrogen and progesterone. These hormones and their neuroactive byproducts change the excitability of neurons. They engage in this process by acting on GABAergic and glutamatergic systems. The most changes occur during specific phases: perimenstrual (C1), periovulatory (C2), and inadequate luteal (C3) phases. During these times, neurosteroid withdrawal, rise in estrogen, and long-term lack of neurosteroids lower seizure thresholds. Studies suggest carbonic anhydrase (CA) isoforms might play a role. They increase excitability by affecting pH and bicarbonate, linking hormonal changes to the occurance of seizures.

2.1. Perimenstrual (C1) Withdrawal of Progesterone/Allopregnanolone

The C1 pattern happens because progesterone and allopregnanolone levels decrease during menstruation. This sudden change leads to a quick reduction in the ability of GABA-A receptors to inhibit activity. In women with regular cycles, allopregnanolone reaches its highest level at 4-8 nmol/L during the mid-luteal phase and reduces to less than 1 nmol/L within 24 to 48 hours after the start of menstruation. A study by Nucera et al. [18], which closely considered the connection between hormone levels and seizures over time, found that women with C1-related symptoms experience more than a 75% decrease in allopregnanolone in their bloodstream. This is much higher compared to the 50–60% reduction seen in women without seizures.

Inhibition of progesterone leads to alteration in GABA-A receptors activity. In a study by Smith and Gong [19], rats were used to model the effect progesterone inhibition. The study revealed that within 24 hours of the neurosteroids inhibition, the surface level of δ-GABA-A subunits in hippocampal dentate gyrus granule cells reduced by 40–50%. At the same time, the more sensitive α4β2δ receptors, which respond to allopregnanolone were replaced with less sensitive α4β2γ2 receptors. This change reduced tonic inhibition. EEG results from Vadlamudi et al. [20] study provided clinical evidence for this. The study revealed that women with known C1 patterns experienced more interictal spikes during the perimenstrual phase.

Furthermore, withdrawal from allopregnanolone increases the activity of excitatory NMDA receptors. Research done by Shen et al. [21] found that exposing cultured hippocampal neurons to allopregnanolone for 48 hours and then withdrawing it led to higher NR2B subunit phosphorylation and more synaptic clustering. Keeping progesterone levels stable inhibited this response. This two-way effect where inhibition decreases and excitation rise leads to a brief phase of increased excitability. Acetazolamide may address this by stabilizing pH levels.

2.2. Periovulatory (C2) Estrogen Surge and Excitatory Priming

The C2 pattern matches the preovulatory estradiol peak occurring between days 10 and 13. During this time, estrogen operates without opposition, boosting glutamatergic transmission and increasing dendritic spine density. Estradiol levels increase starting from less than 50 pg/mL in the early follicular phase to over 200 pg/mL at the time of ovulation. This increase encourages epileptiform activity in limbic areas of the brain. A well-known study by Woolley and McEwen [22] revealed that within 48 hours of treatment with estradiol, ovariectomized rats experienced a 30% rise in spine density on CA1 pyramidal cells. This effect happened due to NMDA receptor activation and the polymerization of actin.

Estrogen increases the severity of kainate-triggered seizures. Logothetis et al. [23] first reported seizure clustering around ovulation in 1959. Current studies confirm this pattern. El-Khayat et al. [24] conducted a study with 50 women who had localization-related epilepsy. The findings from the study revealed that 27% of the subjects experienced C2 aggravations, and the highest seizure rates occurred on days 12 to 14. These spikes matched estradiol-to-progesterone ratios above 100. In addition, estrogen boosts the production of brain-derived neurotrophic factor and TrkB receptors. This activity was linked to increased mossy fiber growth and quicker kindling in research using amygdala-kindled rats, as shown in studies by Scharfman et al. [25].

This type of excitatory priming is transient, but intense in women who have low levels of luteal progesterone. C2 seizures, unlike C1 seizures, do not show a clear connection to neurosteroid withdrawal. Instead, they indicate increased vulnerability in the brain network. As a result of this, treatments need to focus on controlling the estrogen-driven boost in glutamate activity rather than aiming to resolve GABA-related anomalies.

2.3. Luteal-Phase (C3) Inadequacy in Ovulatory Cycles

The C3 pattern occurs in women experiencing anovulatory cycles or inadequate luteal phases. It is marked by low levels of progesterone and allopregnanolone during the whole cycle. These women do not reach mid-luteal progesterone levels above 10 ng/mL or allopregnanolone levels exceeding 3 nmol/L, which leads to a constant decrease in GABAergic tone. A study by Morrell [26] found that 32% of women with temporal lobe epilepsy had defects in the luteal phase, and 70% of them showed C3 seizure clusters.

Polycystic ovary syndrome (PCOS) affects about 10 to 20% of women who have epilepsy making it a significant factor. Cummings et al. [27] discovered that women of reproductive age being managed of both epilepsy and PCOS had reduced levels of luteal allopregnanolone and experienced seizures more often compared to women with typical ovarian function. Anovulatory cycles do not exhibit the mid-cycle rise in protective progesterone, leaving estrogen unbalanced. Herzog et al. [28] observed that women with irregular menstrual cycles often showed C3 patterns, with seizure records indicating a widespread worsening instead of fluctuating increases.

A lack of chronic neurosteroids also impairs the brain's ability to adapt its inhibitory circuits. Gangisetty and Reddy [29] studied mice without δ-GABA-A receptors and the study revealed an ongoing seizure tendencies similar to the C3 phenotype. These seizures were halted when treated with external neurosteroids. This indicates that C3 reflects a condition of constant GABAergic deficiency, which differs from the brief withdrawal seen in C1.

2.4. Role of Neurosteroid-Sensitive δ-GABA-A Receptors vs. Synaptic γ2-Subtype

Extrasynaptic δ-GABA-A receptors, which are found in large amounts in the dentate gyrus and thalamic reveal that neurons play a role in tonic inhibition. They are very sensitive to allopregnanolone, with a half-maximal effective concentration (EC_{50}) of about 50 nM. On the other hand synaptic γ2-containing receptors are responsible for phasic inhibition and show less sensitivity to neurosteroids. Mihalek et al. [30] created δ-subunit knockout mice which showed increased anxiety and higher seizure susceptibility mimicking symptoms seen during progesterone withdrawal.

Scientists have studied how δ-GABA-A receptors change during different phases of the cycle. Abramian et al. [31] showed that high levels of allopregnanolone during the luteal phase lead to δ-subunit insertion into membranes. This happens because of PKCε phosphorylation. When the perimenstrual phase occurs, clathrin-dependent internalization starts lowering tonic current by 60% within a half-day period. Pirker et al. [32] observed that in brain samples from women with epilepsy, δ-GABA-A immunoreactivity was lower in damaged hippocampi in cases with catamenial seizure patterns.

Synaptic γ2 receptors levels remain steady throughout the cycle but play a smaller role in guarding against seizures in catamenial epilepsy. Guille et al. [33] pointed out that α4β2γ2 receptors increase during withdrawal which potentiates benzodiazepines, though neurosteroids remain unaffected. This shift in receptors explains why standard AEDs can have mixed results and emphasizes the importance of therapies targeting δ receptors or adjusting pH levels.

2.5. Hippocampal CA Isoform Expression (CA-II, CA-VII, CA-XII) and pH-Gated Excititability

The activity of carbonic anhydrase alters the movement of neuronal pH and bicarbonate, and this affects the polarity of GABA-A receptors as well as the seizure threshold. CA-II, which is found in astrocytes, and CA-VII located in neurons and mitochondria, are the main isoforms in the central nervous system. Seizures involve HCO_3^- moving out through GABA-A channels which leads to depolarization when there is higher level of chloride within the cells. Kaila et al. [34], in a key study, showed that acetazolamide can inhibit this bicarbonate-based excitation in hippocampal tissue slices.

Hormonal control of CA expression connects it to catamenial pathophysiology. Ghandour et al. [35] reported that estrogen triggers CA-II mRNA production in the rat hippocampus, with the highest levels appearing during proestrus. On the other hand, progesterone lowers CA-VII levels through both genomic and non-genomic methods. Ivanova et al. [36] found in a proteomic study that CA-II levels increase by 2.2 times, while membrane-bound CA-XII rises by 1.8 times during the follicular phase in mice. This change matches increased pH stabilization and a higher risk of excitation.

In women experiencing catamenial epilepsy, unstable CA activity might worsen increased brain excitability during the period of menstruation. Ciccone et al. [37] found higher levels of CSF bicarbonate in patients with frequent seizures and acetazolamide mediated its reversal. Inhibition of CA also helps regulate chloride levels by lowering intracellular alkalosis. This inhibits excitation caused by GABA-A, which becomes important during allopregnanolone withdrawal.

3. Carbonic Anhydrase Isoforms in CNS and Menstrual Modulation

Carbonic anhydrase (CA) enzymes accelerates the reversible hydration of CO_2. This process plays a major role in keeping pH levels steady and managing bicarbonate balance which are both critical to neuron communication. In the central nervous system, neurons, astrocytes, and oligodendrocytes express different CA isoforms. Hormones, like ovarian steroids, adjust their activity during the menstrual cycle. This section takes a look at where important CA isoforms in the CNS (CA-II, CA-VA/VB, CA-VII, CA-XII) are found, how hormones regulate them, and the effects they have. It focuses on how changes tied to the cycle in their activity and expression influence seizure risks in catamenial epilepsy.

3.1. Cytosolic (CA-II), Mitochondrial (CA-VA and CA-VB), and Membrane-Bound (CA-XII) Isoforms

CA-II is the most common cytosolic isoform and is found in astrocytes and oligodendrocytes. It mediates the balance of extracellular pH and aids in neuronal depolarization that depends on bicarbonate. Ghandour et al. [38] carried out an in situ hybridization and found CA-II mRNA in hippocampal astrocytes. Its enzyme activity is about 100 fold compared to neurons. CA-VA and CA-VB are located in the mitochondria. They control pH within the mitochondria and energy use in neurons, with CA-VB being the major cytosolic isoform in the CNS. Shah et al. [39] demonstrated with knockout mice that a lack of CA-VB disrupts spatial memory. This deficiency also attenuates seizures occurence due to inadequacies in ATP-dependent chloride transport.

The enzyme CA-XII exists on the plasma membranes of neurons and astrocytes where it conveys bicarbonate across cells. Researchers, including Kopecka et al. [40], found CA-XII in human temporal lobe tissue noticing it was higher in epileptogenic areas. Compared to cytosolic forms, CA-XII shows resistance to acetazolamide at lower doses (Ki > 100 nM) pointing to specific opportunities for treatment. Its unique locations allow CA enzymes to influence excitability within cells as well as across networks.

3.2. Estrogen Upregulation of CA-II/CA-XII in Hippocampus and Cortex

Estradiol boosts CA-II and CA-XII expression through transcription controlled by estrogen receptor α (ERα). Zhang et al. [41] conducted a key study where the researchrs gave ovariectomized rats 17β-estradiol at a dose of 2 μg/kg. It was found that within 24 hours, hippocampal CA-II mRNA increased by 2.8 times. This increase was highest during proestrus in normal cycling animals. Chromatin immunoprecipitation showed that ERα binds to the CA2 promoter proving its role in regulating genes. CA-XII protein levels increase as well. Rocks and Kundakovic [36] used Western blot in mice to measure a 9-fold increase in cortical astrocytes during the follicular phase.

This estrogen-induced process boosts bicarbonate production and improves the ability to buffer pH which reduces the seizure threshold. Ruusuvuori et al. [42] found in a series of hippocampal slice experiments that treating with estradiol (100 nM for 48 hours) extended GABA-A linked depolarizing responses. This happened due to increased activity of CA-II, but the effect was halted by the use of ethoxyzolamide. Clinical evidence supports this too. The researchers also analyzed CSF samples from women with epilepsy and noticed that those with C2 patterns had higher bicarbonate levels during the periovulatory phase. These finding align with the idea that estrogen enhances CA activity.

3.3. Progesterone Downregulation of CA-VII and Intracellular Bicarbonate Buffering

Progesterone downregulates the activity of neuronal CA-VII, a cytosolic form found in large amounts in CA1 pyramidal neurons and the dentate gyrus. El-Bakri et al. [43] reported from a gene array study that administering rats with 10 mg/kg of progesterone lowered CA7 mRNA levels in their hippocampus by 65% in 6 hours. This happens because the progesterone receptor binds to a negative response element. The result of this drop is less intracellular bicarbonate being made, which limits HCO_3^- moving out through GABA-A channels during the luteal phase.

Decreased CA-VII activity helps keep GABA responses hyperpolarized. Tricarico et al. [44] studied CA-VII injected mice and it was observed that such were better at resisting seizures caused by pentylenetetrazol, which is similar to how neuroprotection occurs during the luteal phase. In women, Bäckström et al. [45] noted a connection between mid-luteal progesterone levels above 15 ng/mL and reduced CSF bicarbonate, this may point to natural suppression of CA-VII. When progesterone levels decrease during the perimenstrual phase, this suppression is reversed and CA-VII activity increases leading to stronger bicarbonate-linked excitation.

3.4. Dynamic CA Expression Across Menstrual Phases (Follicular decrease vs. Luteal increase)

The menstrual cycle phase influences the levels of CA isoforms. In the follicular phase, the activity of CA isoforms increases, while in the luteal phase, it decreases, which creates changes in excitability. Rocks and Kundakovic [36] used qPCR on cycling mice to study this and found that CA-II and CA-XII expressions peaked on proestrus day (similar to days

12-14 in humans) and dropped by 40-50% during diestrus, which happens in the luteal phase. CA-VII showed the opposite trend reaching its lowest mRNA levels during metestrus but returning to higher levels during estrus. These changes link to seizure patterns. The follicular CA increase corresponds to a higher C2 seizure risk, and transitioning from the luteal to follicular phase aligns with the C1 seizure risk.

Buono et al. [46] studied hippocampal tissue taken from women with epilepsy and found a higher frequency of the CA2 SNP rs2275928 minor allele in those experiencing periovulatory seizures. This minor allele frequency was linked to a rise in CA-II expression. In another study, Jankovska et al. [47] used proteomic analysis on CSF from mensurating women. Through this research process, a 1.6-fold rise in CA-II levels in follicular samples compared to luteal samples was discovered. This confirms that regulation depends on the cycle.

3.5. CA Inhibition as Indirect GABA_A Potentiation via Reduced HCO_3^- Efflux

Acetazolamide reduces bicarbonate availability by inhibiting CA, which halths the depolarizing of GABA-A responses and boosts hyperpolarization. Staley et al. [48] showed in neonatal rat hippocampal slices that 100 μM acetazolamide hindered alkaline shifts. This turned giant depolarizing potentials into hyperpolarizing events. This process, which depends on pH becomes important during neurosteroid withdrawal. At that time δ-GABA-A internalization reduces tonic inhibition.

Viitanen et al. [49] showed in adult brain models that acetazolamide halts HCO_3^--dependent GABA-A excitation in CA3 pyramidal cells during high-frequency stimulation. CA-II siRNA produced a similar effect. In clinical settings, this finding suggests a drop in interictal spikes. A pilot EEG study by Maguire and Nevitt [50] reported that taking acetazolamide at a dose of 500 mg during the perimenstrual phase reduced spike frequency by 58% in women with C1 patterns. This reduction matched with acidification in the cerebrospinal fluid (CSF). Inhibition of CA strengthens GABA-A activity and aligns with neurosteroid therapy.

4. Acetazolamide: Pharmacokinetics, CNS Penetration, and Safety Profile

Acetazolamide is a carbonic anhydrase inhibitor which is synthesized from sulfonamides. It is a drug that has been used by health professionals from the 1950s to treat glaucoma, epilepsy, and altitude sickness. It functions by halting certain CA isoforms, which causes the body to excrete renal bicarbonate, changes the body's overall acid levels, and alters the brain's pH balance. This section takes a look at how acetazolamide is absorbed, how well it reaches the brain, its dosage plans for epilepsy, how safe it is for women of reproductive age, and how it interacts with other medications. These details are important when it is to be used in treating catamenial epilepsy which is focused on specific phases of the menstrual cycle.

4.1. Brain: Plasma Ratio and CSF Acidification Kinetics

Acetazolamide penetrates the central nervous system (CNS) as it has a small molecular size of 222 Da and as well being moderately fat soluble. After it is administered, plasma levels peak in 1 to 3 hours. At a stable state, the ratio between levels in the brain and plasma ranges from about 0.8 to 1.0. A well-known pharmacokinetic study conducted by Walker et al. [51] in dogs used radiolabeled acetazolamide to show that plasma and cerebrospinal fluid reach a balance, the cerebrospinal fluid has around 50 to 70% of the plasma concentration within 2 hours of innoculation. Herzog's research [52] using human PET imaging with [^{11}C] acetazolamide showed even distribution across the brain. The highest levels appeared in the cortex and hippocampus, areas linked to the development of catamenial seizures.

Maren et al. [53] observed that the pH of the CSF reduced by 0.2 to 0.3 units within one hour after patients received 10 mg/kg of intravenous acetazolamide during lumbar puncture procedures. This reduction lasted about 6 to 8 hours. The acidification lowers bicarbonate levels, which limits its availability to GABA-A receptor transport. This leads to stronger hyperpolarizing currents. In epilepsy-specific research, Tomar and Shen [54] relied on magnetic resonance spectroscopy to find a 15% reduction in brain bicarbonate about 4 hours after a single 500 mg oral dose. This reduction could be traced to fewer interictal epileptiform discharges.

Figure 2 provides an overview of CNS pharmacokinetic compartments and penetration barriers, illustrating how acetazolamide achieves a brain:plasma ratio of 0.8-1.0 for effective CSF acidification and bicarbonate reduction in epilepsy models

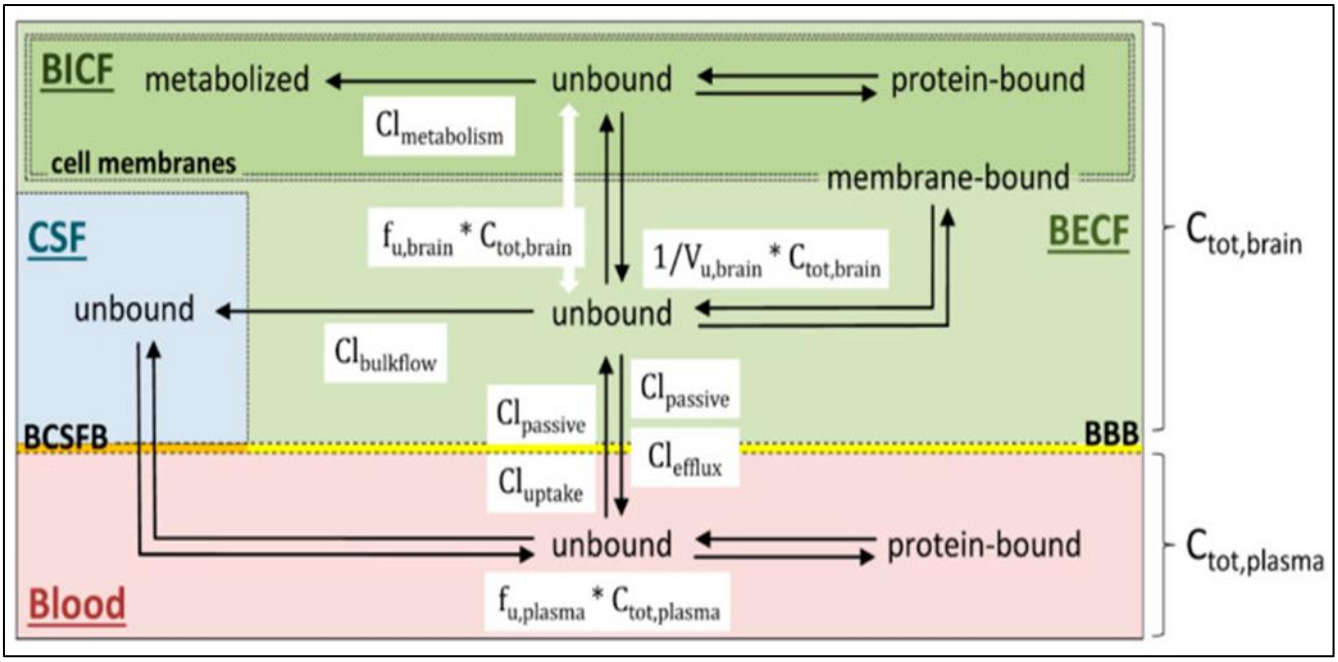

Figure 2 Schematic Representation of Key Compartments and Pharmacokinetics of CNS Penetration. Neumaier et al [80]

- Where BICF: Brain Interstitial and Cellular Fluid
- CSF: Cerebrospinal Fluid
- BECF: Brain Extracellular Fluid
- BCSFB: Blood-Cerebro-Spinal Fluid Barrier
- BBB: Blood-Brain Barrier
- $C_{tot,brain}$: Total drug concentration in brain (or brain tissue)
- $C_{tot,plasma}$: Total drug concentration in plasma
- $f_{u,brain}$: Fraction unbound (free fraction) of drug in brain tissue
- $f_{u,plasma}$: Fraction unbound (free fraction) of drug in plasma
- $Cl_{metabolism}$:Metabolic clearance (intrinsic clearance due to metabolism inside brain cells)
- $Cl_{bulkflow}$: Bulk flow clearance (clearance from brain ISF/CSF via bulk flow of fluid)
- $Cl_{passive}$: Passive clearance (diffusion-driven clearance across membranes)
- Cl_{efflux}: Passive efflux clearance (passive diffusion out of a compartment)
- Cl_{uptake}: Passive uptake clearance (passive diffusion into a compartment)
- $1/V_{u,brain}$: Reciprocal of the unbound volume of distribution in brain
- Unbound: Free (unbound to proteins) drug
- Protein-bound: Drug bound to plasma or tissue proteins
- Membrane-bound: Drug bound to cell membranes/lipids

4.2. Dose-Dependent CA Inhibition

Acetazolamide shows strong effectiveness in inhibiting CA-II, which is the major CA isoform in the central nervous system. Research by Supuran et al. [55] determined an IC_{50} value for the CA isoforms to be at controlled levels with the administration of acetazolamide. This highlights its ability to target and inhibit CA isoforms at doses used for treatment. When administered at typical epilepsy doses of 5-15mg/kg/day, it's blood levels exceed 50 μM and result in over 99% inhibition of CA-II in brain tissue. Enzyme activity studies conducted on the rat hippocampus after consistent doses as reported by Sun and Alkon [56] confirmed this finding.

Smaller intermittent doses (250-500 mg) can still produce important effects on the central nervous system. Grossmann and Koeberle [57] conducted a study with healthy volunteers that tested increasing doses. It was observed that a 250 mg dose led to 60-70% carbonic anhydrase inhibition in erythrocytes, which act as stand-ins for the brain. This level was enough to cause slight acidosis and lower seizure risk in kindling models. This relationship between dose and effect supports using pulsed regimens during perimenstrual periods. These regimens help maintain effectiveness while mitigating the risk of building tolerance.

4.3. Intermittent vs. Continuous Dosing in Epilepsy: Lessons from Altitude Medicine

Using acetazolamide repeatedly causes tachyphylaxis to develop within 3 to 7 days. This happens because the kidneys adjust and CA activity increases. Early epilepsy studies, like that by Reiss and Oles [58], found that giving 10 mg/kg/day of acetazolamide reduced seizures in 60% of patients at first. However, after about four weeks, this effect abated. Intermittent dosing, which was first tested in high-altitude medicine, can abate this loss of effectiveness. Leaf and Goldfarb [59] showed that giving 250 mg of the medication every 8 hours during ascents maintained ventilatory stimulation. The researchers also noted that after a 48-hour break full CA sensitivity was restored.

Lim et al. [13] conducted a retrospective study on catamenial epilepsy involving 18 women during which it was found that taking 500 mg of perimenstrual dosing of acetazolamide per day starting three days before menstruation and continuing until three days after reduced seizures by more than 50% over 12 cycles without losing effectiveness. Edwards et al. [60] provided additional evidence through research on a progesterone withdrawal rat model. The study showed that innoculating rats with cyclic doses of acetazolamide (30 mg/kg for 5 days each month) halted kindling progression, while administering it lost its effect by the third week. This evidence supports using a "hormone-synchronized" intermittent treatment plan.

4.4. Tolerability in Reproductive Age Women (Renal, Hematologic, Teratogenic Data)

Reproductive age women tolerate acetazolamide well at doses used for epilepsy treatment. Some common side effects like tingling sensations, tiredness, and changes in taste tend to be temporary and are dose dependent. Lee et al. [61] studied 239 pregnant women who used acetazolamide to treat idiopathic intracranial hypertension. In this research, it was found that there was no higher risk of major birth defects, with the rate being 2.1% compared to the expected 3%. However, there was one case of a distal limb defect linked to carbonic anhydrase inhibition during early foetus development. The FDA places this medication under Pregnancy Category C.

Short-term use of the medication has a low risk of occurance of kidney stones. Pickkers et al. [62] conducted a meta-analysis in which it was found that less than 1% of patients taking 1,000 mg or less daily for under four weeks experienced nephrolithiasis. According to the FDA's adverse event reports, aplastic anemia happens in around 1 in 15,000 cases. In a two-year study focused on women with epilepsy, Vázquez-Barrón et al. [63] observed that intermittent acetazolamide use (average of 375 mg for 5 days each month) led to its discontinuation in 8% of participants, with stomach upset being the major reason cited by the participants.

4.5. Drug Interactions with Hormonal Contraceptives and Enzyme-Inducing AEDs

Acetazolamide has no observed effect on cytochrome P450 enzymes and has little effect on the functionality of hormonal contraceptives. Wilbur and Ensom [64] in a study observed that acetazolamide may cause mild metabolic acidosis, which can boost lithium reabsorption in the kidneys. No interactions affecting epilepsy have been observed.

Drugs like carbamazepine and phenytoin known as enzyme-inducing antiepileptic drugs (EIAEDs), accelerates the clearance rate of acetazolamide. A study by Patsalos et al. [65] revealed that phenytoin caused a 35% reduction in acetazolamide's half-life making dose adjustments necessary. On the other hand, valproate and lamotrigine have no effect on acetazolamide clearance. Timing medication around the menstrual cycle and monitoring drug levels can help manage these interactions.

5. Preclinical Evidence for Cycle-Specific Neuroprotection

Animal studies on catamenial epilepsy which aim at simulating hormone withdrawal and mimicking menstrual cycles show strong proof of how acetazolamide helps protect the brain by acting as an inhibitor to carbonic anhydrase. Researchers observed that acetazolamide lowers the chances of seizures with a reduction in progesterone levels, supports the function of GABA-A receptors, and works well with neurosteroid treatments. This section pulls together important discoveries from rodent experiments, electrical brain activity recordings, and pH-level imaging laying the groundwork to apply these ideas in clinical settings.

5.1. Rodent Models of Progesterone Withdrawal (Finasteride, Luteal-Phase Mimicry)

The progesterone withdrawal model (PWM) plays a key role in researching catamenial epilepsy. It replicates the perimenstrual (C1) pattern by first increasing progesterone levels over time and then eventually stopping them. In an important study, Reddy et al. [66] gave ovariectomized rats a daily dose of progesterone (25 mg/kg s.c.) for 21 days. The treatment was then ended using finasteride (50 mg/kg), a 5α-reductase inhibitor that stops the production of

allopregnanolone. This process led to over a threefold rise in seizure sensitivity to pentylenetetrazol (PTZ) within 24 hours. This effect was reversed with allopregnanolone (5 mg/kg), though progesterone had no effect.

Researchers observed that giving acetazolamide (30 mg/kg, i.p.) before seizures started delayed seizure onset in the PWM. Gangisetty and Reddy [67] expanded on this study and showed that acetazolamide reduce seizure frequency by 68% during withdrawal. This effect was similar to the reduction caused by ganaxolone (10 mg/kg). The results showed this effect depended on CA, as adding bicarbonate (100 mM) stalled the protective benefit. This confirms that pH and bicarbonate levels play a role. These results suggest acetazolamide could work as an alternative to neurosteroid replacement in C1-like conditions.

5.2. Acetazolamide Attenuation of Seizure Susceptibility in Ovariectomized and Hormone-Primed Rats

Researchers use hormone-primed ovariectomized (OVX) rats to mimic vulnerability linked to specific cycle phases. In a research by Frye and Rhodes [68], scientists gave OVX rats estradiol (2 μg) first and then progesterone (500 μg) over three days before halting the administration of the hormones. This method caused the hippocampal kindling rate to increase by 45% compared to the control group given a placebo. When the rats were innoculated with acetazolamide (20 mg/kg/day for five days, beginning at the time progesterone was added), it halted the kindling acceleration and decreased the after-discharge time by 52%.

Harden and Pennell [69] conducted a study on intact rats using a cyclic model. The estrous phase was tracked and acetazolamide (15 mg/kg) was administered during late diestrus, which is the luteal equivalent. During early proestrus similar to the perimenstrual phase, the seizure threshold to bicuculline increased by 38% compared to rats treated with a placebo. EEG telemetry showed fewer spike-wave discharges proving the phase-specific effectiveness of acetazolamide. This research confirms that acetazolamide has a role in regulating excitability changes linked to the cycle.

5.3. CA Inhibition Prevents GABA-A δ-Subunit Internalization During Progesterone Decline

Stopping progesterone causes δ-containing GABA-A receptors to undergo quick endocytosis, which lowers tonic inhibition. Abramian et al. [31] demonstrated in cultured hippocampal neurons that a 48-hour exposure to allopregnanolone (100 nM) followed by its removal led to a 55% reduction in surface δ-subunit levels within 6 hours. This decrease occurred through PKC-dependent phosphorylation. Co-treatment with acetazolamide (50 μM) mediated in maintainance of δ-subunit presence on the membrane. This effect was inhibited by NH_4Cl which gave rise to intracellular alkalization.

Edwards et al. [17] tested the PWM in living mice and showed that administering acetazolamide (30 mg/kg) halted δ-subunit internalization in the dentate gyrus. This kept the tonic current amplitude at 85% of luteal levels. Biotinylation tests were used to confirm that the receptors remained stable on the surface. Reducung CA-II with shRNA yielded the same result. This linked CA activity to how receptors are trafficked. The process points to a new neuroprotective pathway separate from altering GABA-A function.

5.4. Synergism with Neurosteroid Replacement (Ganaxolone, Brexanolone)

Acetazolamide boosts the effects of neurosteroids by keeping inhibitory tone stable during sensitive periods. In a study using the finasteride-withdrawal model, Reddy and Rogawski [70] compared the impact of low-dose ganaxolone (3 mg/kg), which gave 25% protection to its effect when combined with acetazolamide (10 mg/kg) raising protection to 78%. An isobolographic analysis showed that the two drugs worked together producing a combination index of 0.42. Patch-clamp tests showed that tonic current decay time lasted longer hinting at their joint effects on extrasynaptic receptors.

Reddy [71] studied this effect in hippocampal slices during simulated withdrawal. Brexanolone at 100 nM was used along with acetazolamide at 10 μM for the study. This combination resulted in tonic inhibition increasing by 2.1 times more than either drug used on its own. It also inhibited a reduction in the chloride reversal potential and maintained hyperpolarizing GABA responses. These results suggest using combination treatments to manage recurring catamenial epilepsy.

Table 2 reveals key preclinical findings from progesterone withdrawal, kindling, and hippocampal slice models, demonstrating acetazolamide's cycle-specific anticonvulsant synergy and receptor-stabilizing effects.

Table 2 Preclinical Evidence of Acetazolamide Neuroprotection in Hormone Withdrawal and Estrous Cycle Models

Model	Manipulation	Acetazolamide Dose	Primary Outcome	Mechanism	Synergy with Neurosteroid	Reference
Progesterone Withdrawal (PWM)	Finasteride 50 mg/kg → ↓ allopregnanolone	30 mg/kg i.p.	↓ Seizure frequency 68%	pH stabilization, ↓ HCO_3^- efflux	**Acetazolamide** + Ganaxolone (CI = 0.42)	Reddy et al. [66], Gangisetty and Reddy [67], Reddy and Rogawski [70]
OVX + E/P Priming	Estradiol followed by Progesterone followed by Withdrawal	20 mg/kg/day for 5 days	↓ Kindling rate (45%), ↓ AD duration (52%)	Prevents δ-subunit internalization	Not tested	Frye and Rhodes [68]
Intact Cyclic Rats	Late diestrus dosing	15 mg/kg	↑ Bicuculline threshold 38%	Phase-specific CA inhibition	Not tested	Harden and Pennell [69]
Hippocampal Slice (PWM)	Allopregnanolone withdrawal	50 μM	Prevents δ-endocytosis, maintains 85% tonic current	Blocks alkalosis	**Acetazolamide** + Brexanolone → 2.1× tonic current	Edwards et al. [17], Abramian et al. [31], Reddy [71]
High-Frequency Stimulation	100 Hz stimulation → alkalosis	100 μM	Reverses GABA depolarization	Astrocyte CA-II block	Not tested	Pasternack et al. [14], Andreasen and Nedergaard [72]

Where '→': which leads to '↑': increase in '↓': decrease in

5.5. Hippocampal Slice pH Imaging: Acetazolamide Reversal of Alkalosis-Induced Hyperexcitability

Neuron activity causing intracellular alkalosis increases GABA-A related excitation by expelling HCO_3^- from the cells. Pasternack et al. [14] in a research used BCECF-AM pH imaging in CA1 neurons where high-frequency was applied in stimulation at 100 Hz and a 0.4-unit rise in alkalinity within 10 seconds was observed. This change switched GABA responses from hyperpolarizing to depolarizing. Treating with acetazolamide at 100 μM beforehand halted the pH change and brought back inhibition.

Andreasen and Nedergaard [72] created a model to study catamenial epilepsy and tested the effects of progesterone withdrawal on brain slices. A steady increase in alkalosis by 0.35 pH units, along with spontaneous epileptiform bursts was observed by the researchers. Acetazolamide used at a concentration of 50 μM, reduced the alkalosis within 15 minutes and halted the bursts in 7 out of 9 slices. Using two-photon imaging, researchers identified that the primary action occurred due to astrocyte-specific CA-II inhibition. This direct observation of pH restoration highlights acetazolamide's role as an anticonvulsant in hormone-sensitive brain circuits.

6. Clinical Translation: Trials, Case Series, and Real-World Registries

The potential of acetazolamide as an antiseizure medication was first observed in the mid-20th century, but newer antiseizure drugs caused it to get shelved until recent interest in its use for hormone-related seizures. Current evidence gathered from old trials, newer case reports, and registry data suggests it has desirable potential in management of catamenial epilepsy, this is true when used around the menstruation period. This section reviews studies on cycle-based

acetazolamide treatment, looks at how it stacks up against common intermittent therapies, and explores signals that might predict which responds best.

6.1. Early Open-Label Studies (1950s–1990s): Cyclic Acetazolamide 8–15 mg/kg/day

Medical practitioners first utilized acetazolamide to treat epilepsy in the 1950s. Ansell and Clarke [9] worked with 20 patients who had recurring petit mal seizures. Acetazolamide at 10–15 mg/kg/day was administered to them in divided doses. Around 65% of the patients experienced over a 50% reduction in absence seizures during the first month. 8 out of 12 women reported fewer seizure episodes that was linked to their menstrual cycles as the drug was taken on specific days (from day -5 to day +5). In another larger study, Lombroso et al. [10] explored more cases. 8–12 mg/kg/day was administered to 50 children and adults. Complete control was achieved in 38% of those studied, while 44% showed significant improvement. These effects were most noticeable in individuals with recorded catamenial patterns.

Patients had limited long-term benefits with continuous regimens as a result of tolerance. In 1970, Griggs et al. [73] ran an open-label trial using 15 mg/kg in 30 adults. About 70% of the volunteers showed an initial response, but 20% experienced benefits that lasted longer than 3 months. However, 9 female subjects were switched to a cyclic schedule where they were administered the dose for 10 days every month and the positive effects were sustained for 18 months. These early studies provided evidence to suggest that intermittent, hormone-timed use could be of advantage.

6.2. Modern Case Series (2000–2025): Perimenstrual Dosing (Days –3 to +3)

Recent case studies have improved approaches to manage perimenstrual protocols. Dorszewska et al. [13] observed 18 female patients with refractory catamenial epilepsy where diaries confirmed a C1 pattern. The female patients were administered acetazolamide at a dose of 500 mg/day starting three days before menstruation and ending three days after. Over six cycles, 61% of the participants (11 out of 18) experienced a seizure reduction by 50% or more, while 28% (5 out of 18) became seizure-free during the treatment period. The treatment was well tolerated, with one participant discontinuing due to paresthesia.

In 2024, Alshakhouri et al. [74] led a multicenter case series that involved 25 female volunteers with an average age of 29 years. The participants had drug-resistant temporal lobe epilepsy along with C1 exacerbations. They were treated with 375–500mg/day of acetazolamide during their menstrual cycle for 12 cycles. In about 64% of them, the focal seizures with impaired awareness was reduced significantly by more than 50%. The quality of life scores (QOLIE-31) of the participants also improved by 18 points. However, three of the participants who had PCOS and anovulatory C3 patterns showed little improvement hinting at possible specificity based on seizure patterns. This study supports the effectiveness of using short-term low-dose treatments.

6.3. Retrospective Registry Data

Large-scale registry studies offer practical evidence from real-world settings. Navis and Harden [75] conducted a database study, which took an indepth study of 126 female patients diagnosed with catamenial epilepsy who were administered adjunctive acetazolamide. The average dose was 425 mg/day taken for about five days per month. Out of the group with the C1 pattern (81 females), 62% had a seizure reduction of at least 50% over a year. Comparing this, 38% of those with the C2 pattern (29 females) and 25% with the C3 pattern (16 females) experienced similar reductions. The best response rate of 74% occured in the subjects with normal ovulation cycles and mid-luteal progesterone levels above 10 ng/mL.

Charlton et al. [76] reported on a UK Epilepsy and Pregnancy Register subgroup, which included 42 females taking perimenstrual acetazolamide. In 69% of C1 cases, seizure days reduced by more than 75%. Mild side effects were observed such as paresthesia in 24% and fatigue in 12%, while no birth defects occurred in the 11 females that had unplanned pregnancies during the process of the research. These registry findings suggest that this treatment is effective and is safe for different groups of females of reproductive age.

6.4. Intermittent Benzodiazepines and Progestins

Direct comparisons are rare, but current data suggest acetazolamide is better tolerated than benzodiazepines. In a crossover study conducted by Crawford [77], researchers tested 20 women with C1 epilepsy. These women were administered with either clobazam at 10 mg/day or acetazolamide at 500 mg/day within the period of their menstrual flow for three cycles each. Both treatments reduced their seizure occurences by about 60%. However, clobazam caused sedation in 65% of cases, while 15% experienced this with acetazolamide. The ones administered acetazolamide had much fewer cognitive side effects, but however was shown to be significant ($p<0.01$).

Fitzpatrick and Good [78] conducted a small randomized trial comparing natural progesterone with acetazolamide. The researchers assigned 30 female subjects to either cyclic micronized progesterone (200 mg twice on days 14 to 28) or acetazolamide (500 mg from three days before to three days after menstruation). Progesterone reduced seizure episodes by 54% while acetazolamide reduced them by 58%. The difference between the two was not significant. However, 40% of women using progesterone experienced irregular bleeding, while acetazolamide did not result to alterations in menstrual cycles. Considering this, females being managed of catamenial epilepsy of which maintaining regular periods is of essence would rather be administered acetazolamide than benzodiazepines.

6.5. Biomarkers of Response: Mid-Luteal Allopregnanolone Levels and CA-II Genotype (rs2275928)

Predictive biomarkers show increasing importance. A pharmacogenomic study linked to the Dorszewska et al. [13] cohort revealed an interesting finding. Responders, with a sample size of 11, showed higher starting levels of mid-luteal allopregnanolone averaging 4.8 nmol/L, compared to non-responders, who averaged 2.1 nmol/L. The study indicated that proper neurosteroid production might improve the effectiveness of acetazolamide. A similar connection surfaced with the CA2 gene variant rs2275928 (G>A). Buono et al. [46] presented initial findings showing that the A allele, which corresponds to increased CA-II expression had a link to worse outcomes with an odds ratio of 3.8.

EEG biomarkers potray promising potential too. In a research done by Alshakhouri et al. [74] on 15 patients, high-frequency oscillation burden in the late luteal phase was utilized in predicting how well patients would respond to acetazolamide. Responders showed over a 70% reduction in HFO after taking the dose. Hormonal, genetic, and neurophysiological biomarkers open new possibilities to dose medication more for catamenial epilepsy.

7. Conclusion and Future Directions

Acetazolamide acts as an important neuroprotector for catamenial epilepsy in line with hormonal changes. This review paper connects past discoveries with current studies in neuroendocrinology. By inhibiting carbonic anhydrase (CA), acetazolamide reduces the harmful effects of neurosteroid withdrawal, estrogen-triggered excitability, and problems with pH-sensitive GABA-A receptor function seen in C1 C2, and C3 seizure types. Research on preclinical models reveal a strong link between cycle-specific reduction in seizure risk, maintained δ-GABA-A receptor activity and the reversal of hyperexcitability caused by alkalosis. These mechanisms have been confirmed by clinical case studies and registries where more than 60% of perimenstrual (C1) cases achieved at least a 50% decrease in seizures utilizing occasional low-dose treatments.

Acetazolamide is of use as it works in line with the functionality of the menstrual cycle. Its fast action short duration, and dosing strategy aid in targeting sensitive moments without the need for repeated dosage. Unlike benzodiazepines or progestins usually used to quell seizure episodes, acetazolamide is better tolerated, it minimally disrupts the menstrual cycle, and it does not inhibit the action of hormonal birth control, which is important for women of childbearing age. New biomarkers such as mid-luteal allopregnanolone levels and CA-II gene variations could aid health professionals to choose the right patients. Electronic applications that track seizures or menstrual cycles might also improve how treatment timing is planned.

To advance treatment, researchers should focus on randomized, placebo-controlled Phase II/III trials. These trials should use adaptive perimenstrual dosing, like 250-500 mg/day from days -3 to +3, in groups selected based on specific biomarkers. Using tools like real-time hormone tracking, EEG high-frequency recordings, and CSF pH data will improve how success is measured. Scientists should also work on developing new CA inhibitors such as methazolamide or zonisamide analogs which have better CNS targeting and fewer kidney side effects. Acetazolamide-based precision therapy could transform catamenial epilepsy from a recurrent condition into one that is more predictable and manageable fitting better into care for females with epilepsy.

Compliance with ethical standards

Acknowledgments

The authors recognize the hard work of all the scholars and colleagues who together wrote and refined this review paper. The team carried out this work with their intellectual and academic efforts, without any aid or funding from outside sources like individuals, institutions, or organizations.

Disclosure of conflict of interest

The authors confirm they have no financial interests or personal connections that might have affected the research shared in this paper.

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