The American Journal of Medical Sciences and Pharmaceutical Research
ISSN 2689-1026 Volume 08 - 2026

Plasma Homocysteine Dysregulation in Epilepsy: Antiepileptic Drug Exposure, B-Vitamin Metabolism, and Vascular Risk Across the Lifespan

[1] Dr. Alejandro Martinez Lopez
[1] Department of Neurology, University of Barcelona, Spain

Received: 25th Oct 2025 | Received Revised Version: 13th Nov 2025 | Accepted: 29th Nov 2025 | Published: 01th Jan 2026

Volume 08 Issue 01 2026 |

Abstract

Homocysteine has emerged over several decades as a biologically potent sulfur-containing amino acid whose accumulation in plasma reflects a convergence of nutritional status, genetic susceptibility, and pharmacological exposure, particularly in individuals receiving long-term antiepileptic drug therapy. Early clinical observations linking anticonvulsant use with alterations in folate and vitamin B12 metabolism gradually evolved into a more complex understanding of hyperhomocysteinemia as a multifactorial metabolic disturbance with implications extending far beyond epilepsy control alone. Drawing exclusively upon the existing body of literature referenced in this article, the present study develops an integrative, theory-driven analysis of homocysteine dysregulation in epileptic populations, situating antiepileptic drugs within broader biochemical, genetic, and vascular frameworks.

The abstract synthesis foregrounds three interlocking dimensions: first, the biochemical pathways governing homocysteine metabolism and the essential roles of vitamins B6, B12, and folate; second, the pharmacodynamic and pharmacokinetic mechanisms through which classic and newer antiepileptic drugs disrupt these pathways; and third, the clinical consequences of sustained hyperhomocysteinemia, particularly its association with vascular disease, thrombosis, and neurocognitive outcomes. By integrating early nutritional studies, molecular genetic investigations of methylenetetrahydrofolate reductase polymorphisms, and epidemiological analyses of vascular risk, the article positions epilepsy not merely as a neurological disorder but as a chronic systemic condition shaped by long-term metabolic perturbations.

Methodologically, the study employs an interpretive synthesis approach, systematically contextualizing findings from observational studies, mechanistic investigations, and clinical cohorts without recourse to new empirical data. This approach allows for a nuanced interpretation of convergent and divergent findings, highlighting both consensus and unresolved debates within the field. Particular emphasis is placed on pediatric and adult populations treated with enzyme-inducing antiepileptic drugs, whose vulnerability to B-vitamin depletion and homocysteine elevation underscores important clinical and ethical considerations.

The findings suggest that hyperhomocysteinemia in epilepsy represents a predictable yet frequently under-recognized consequence of chronic antiepileptic therapy, modulated by nutritional intake, genetic variation, and drug-specific metabolic effects. The discussion extends these findings into theoretical and clinical domains, arguing for a reconceptualization of epilepsy management that incorporates metabolic monitoring and preventative strategies against long-term vascular complications. In doing so, the article contributes a comprehensive, interdisciplinary perspective to ongoing scholarly discourse and delineates clear avenues for future research and clinical practice grounded firmly in the existing literature.

Keywords: Homocysteine metabolism; antiepileptic drugs; folate deficiency; vitamin B12; vascular risk; epilepsy; hyperhomocysteinemia

Cite This Article: Dr. Alejandro Martinez Lopez. (2026). Plasma Homocysteine Dysregulation in Epilepsy: Antiepileptic Drug Exposure, B-Vitamin Metabolism, and Vascular Risk Across the Lifespan. The American Journal of Medical Sciences and Pharmaceutical Research, 8(01), 1–6. Retrieved from https://theamericanjournals.com/index.php/tajmspr/article/view/7203

1. Introduction

The Epilepsy has long been conceptualized primarily as a disorder of abnormal neuronal excitability and recurrent seizures, with clinical management historically focused on achieving optimal seizure control through pharmacological intervention. However, as antiepileptic drug therapy has evolved from short-term symptomatic management to lifelong treatment in many patients, attention has increasingly shifted toward the systemic and metabolic consequences of chronic anticonvulsant exposure. Among these, disturbances in homocysteine metabolism have emerged as a particularly significant and theoretically rich area of inquiry, linking epilepsy treatment to broader concerns of nutritional deficiency, genetic vulnerability, and vascular disease (Ubbink et al., 1993; Schwaninger et al., 1999).

Homocysteine occupies a central position in intermediary metabolism, acting as a junction point between methionine remethylation and transsulfuration pathways. Under physiological conditions, plasma homocysteine concentrations are tightly regulated through the coordinated action of folate-dependent remethylation, vitamin B12–dependent methionine synthase activity, and vitamin B6–dependent cystathionine β-synthase function (Mudd et al., 1985). Disruption at any point within this network can lead to homocysteine accumulation, a state termed hyperhomocysteinemia, which has been implicated in endothelial dysfunction, oxidative stress, and prothrombotic states (Boushey et al., 1995; Graham et al., 1997).

The historical roots of interest in homocysteine can be traced to rare inborn errors of metabolism, particularly homocystinuria due to cystathionine β-synthase deficiency, which provided early and compelling evidence of the vascular toxicity of markedly elevated homocysteine levels (Mudd et al., 1985). These observations laid the conceptual groundwork for later epidemiological studies demonstrating that even moderate elevations of homocysteine within the general population were associated with increased risks of cardiovascular and cerebrovascular disease (den Heijer et al., 1996; Graham et al., 1997). Within this expanding framework, epilepsy emerged as a clinically important context in which acquired hyperhomocysteinemia could be observed, studied, and potentially mitigated.

The association between anticonvulsant therapy and altered B-vitamin status was first documented in the mid-twentieth century, when clinicians noted reduced serum folate and vitamin B12 levels in patients receiving long-term anticonvulsants (Malpas et al., 1966). Subsequent studies refined these observations, demonstrating altered relationships between serum and red cell folate concentrations and suggesting impaired folate utilization rather than simple dietary deficiency (Preece et al., 1971). These early findings, while limited by the methodological standards of their time, established a foundational link between epilepsy pharmacotherapy and one-carbon metabolism that would later be reframed through the lens of homocysteine research.

By the early 1990s, advances in analytical techniques enabled more precise measurement of plasma total homocysteine, facilitating direct investigation of its relationship with vitamin status and drug exposure. Studies in non-epileptic populations demonstrated that deficiencies of vitamins B6, B12, and folate were independently associated with elevated homocysteine concentrations, providing a mechanistic explanation for earlier clinical observations (Ubbink et al., 1993). Importantly, these findings suggested that anticonvulsant-induced vitamin depletion could plausibly translate into clinically meaningful hyperhomocysteinemia, rather than remaining a biochemical curiosity.

Within epileptic populations, this hypothesis was soon borne out by empirical studies showing elevated plasma homocysteine levels in patients treated with various antiepileptic drugs, including phenytoin, carbamazepine, and valproate (Ono et al., 1997; Schwaninger et al., 1999). These findings were notable not only for establishing a consistent biochemical pattern but also for raising questions about drug-specific mechanisms, interindividual variability, and long-term clinical consequences. The recognition that antiepileptic drugs could act as independent predictors of plasma homocysteine levels further underscored the need to

consider epilepsy treatment within a systemic metabolic framework (Apeland et al., 2001).

The introduction of molecular genetics into this field added an additional layer of complexity. Polymorphisms in the methylenetetrahydrofolate reductase gene, particularly the 677C→T mutation, were shown to modulate homocysteine levels in both general and epileptic populations, with drug-treated patients exhibiting heightened susceptibility to hyperhomocysteinemia in the presence of this genetic variant (Yoo and Hong, 1999; Vilaseca et al., 2000). These findings challenged simplistic models of drug-induced vitamin deficiency and pointed toward gene–environment interactions as critical determinants of metabolic risk in epilepsy.

From a theoretical standpoint, the convergence of anticonvulsant pharmacology, nutritional biochemistry, and vascular epidemiology invites a reconceptualization of epilepsy as a condition whose management necessarily extends beyond seizure suppression. Hyperhomocysteinemia, in this view, functions as a biomarker and mediator of broader systemic effects, linking chronic drug exposure to long-term vascular and neurocognitive outcomes (Katsiki et al., 2014; Al Mutairi, 2020). This perspective aligns with growing recognition of epilepsy as a disorder associated with increased cardiovascular morbidity and mortality, particularly in older patients and those with prolonged treatment histories (Mintzer et al., 2018).

Despite substantial progress, significant gaps remain within the literature. While numerous studies have documented elevated homocysteine levels in drug-treated epileptic patients, there is ongoing debate regarding the relative contributions of specific antiepileptic drugs, nutritional status, genetic polymorphisms, and disease-related factors. Moreover, the clinical significance of moderate hyperhomocysteinemia in epilepsy, particularly in pediatric populations, continues to be contested, with some authors emphasizing vascular risk and others highlighting neurodevelopmental and cognitive implications (Verrotti et al., 2000; Besag and Vasey, 2021).

The present article seeks to address these gaps by providing a comprehensive, theoretically grounded synthesis of the existing literature on homocysteine metabolism in epilepsy. Rather than summarizing findings in a cursory manner, the analysis elaborates the biochemical, historical, and clinical contexts in which these studies were conducted, critically examining points of convergence and divergence. By situating antiepileptic drug–induced hyperhomocysteinemia within a broader framework of metabolic and vascular risk, the article aims to advance scholarly understanding and inform more holistic approaches to epilepsy management (Zaric et al., 2019).

2. Methodology

The methodological approach adopted in this study is grounded in qualitative interpretive synthesis, a strategy particularly suited to fields characterized by heterogeneous study designs, evolving theoretical frameworks, and complex biological interactions. Given that the objective of the present work is not to generate new empirical data but to develop an integrative and publication-ready scholarly analysis based strictly on the provided references, the methodology prioritizes depth of interpretation, contextualization, and critical reasoning over quantitative aggregation (Boushey et al., 1995).

The primary corpus of literature was defined a priori by the reference list supplied as input data, encompassing foundational biochemical studies, clinical investigations in epileptic populations, genetic analyses, and narrative reviews addressing vascular and metabolic risk. By restricting the analysis exclusively to these sources, the methodology ensures conceptual coherence and fidelity to established evidence while avoiding the introduction of extraneous or potentially conflicting data (Ubbink et al., 1993). Each reference was treated as a primary text, with its theoretical assumptions, methodological limitations, and interpretive claims examined in relation to the broader body of work.

A central methodological principle guiding the analysis is the recognition that homocysteine research spans multiple epistemological domains, including molecular biology, clinical medicine, and epidemiology. As such, findings derived from different methodological traditions cannot be directly compared without careful attention to context and scope. For example, insights from rare genetic disorders such as homocystinuria provide mechanistic clarity but cannot be straightforwardly extrapolated to drug-induced hyperhomocysteinemia in epilepsy, which typically involves more modest elevations of homocysteine

(Mudd et al., 1985). The methodology therefore emphasizes theoretical triangulation, whereby evidence from disparate sources is integrated to illuminate underlying mechanisms and clinical implications.

Within the epileptic population, particular attention was paid to studies examining the effects of specific antiepileptic drugs on vitamin status and homocysteine levels. These studies vary considerably in design, including cross-sectional analyses, longitudinal observations, and pediatric versus adult cohorts (Ono et al., 1997; Apeland et al., 2001). Rather than privileging any single design, the methodological approach treats this diversity as analytically productive, enabling exploration of drug-specific effects, age-related vulnerabilities, and duration-dependent outcomes.

Genetic studies investigating methylenetetrahydrofolate reductase polymorphisms were analyzed using a similar interpretive lens. The methodology recognizes that genetic associations are inherently probabilistic and context-dependent, particularly when interacting with environmental factors such as drug exposure and nutritional intake (Yoo and Hong, 1999). Consequently, genetic findings were not interpreted as deterministic explanations but as modulators of risk within a multifactorial system.

An explicit limitation of this methodological approach lies in its reliance on descriptive and interpretive reasoning rather than statistical meta-analysis. However, this limitation is also a deliberate methodological choice, reflecting the constraints of the source material and the objectives of the study. By focusing on theoretical elaboration and critical discussion, the methodology allows for a more nuanced exploration of mechanisms and implications that might be obscured in purely quantitative syntheses (Zaric et al., 2019).

Throughout the analysis, methodological reflexivity was maintained by acknowledging the historical context in which studies were conducted, including changes in antiepileptic drug prescribing practices, analytical techniques for measuring homocysteine, and evolving definitions of vascular risk. This reflexive stance is essential for interpreting older studies alongside more recent investigations without imposing anachronistic standards (Malpas et al., 1966).

3. Results

The synthesis of findings across the referenced literature reveals a consistent pattern of elevated plasma homocysteine concentrations among individuals receiving long-term antiepileptic drug therapy, although the magnitude and clinical significance of this elevation vary according to multiple interacting factors (Schwaninger et al., 1999). Early studies demonstrated that epileptic patients treated with anticonvulsants exhibited higher homocysteine levels than non-treated controls, even after accounting for age and baseline nutritional status (Ono et al., 1997). These results provided the first direct biochemical evidence linking antiepileptic drugs to hyperhomocysteinemia.

Subsequent investigations expanded upon these findings by examining the role of specific vitamins involved in homocysteine metabolism. Reduced plasma concentrations of folate and vitamin B12 were frequently observed in treated patients, supporting the hypothesis that anticonvulsant-induced vitamin depletion contributes to homocysteine accumulation (Ubbink et al., 1993). Importantly, these deficiencies were not uniformly distributed, suggesting that individual susceptibility plays a critical role in determining metabolic outcomes.

Vitamin B6 status emerged as an additional determinant of homocysteine levels, particularly in the context of transsulfuration pathway impairment. Studies demonstrated that even subnormal vitamin B6 status could significantly disrupt homocysteine metabolism, leading to measurable elevations in plasma concentrations (Ubbink et al., 1996). In epileptic populations, this finding is especially relevant given the enzyme-inducing properties of several antiepileptic drugs, which may accelerate vitamin B6 degradation or interfere with its biological activity.

Genetic analyses further clarified the heterogeneity observed in clinical studies. The presence of the 677C→T mutation in the methylenetetrahydrofolate reductase gene was consistently associated with higher homocysteine levels in epileptic patients receiving anticonvulsants, indicating a gene–drug interaction effect (Yoo and Hong, 1999; Vilaseca et al., 2000). These findings suggest that genetic screening could potentially identify patients at elevated risk for metabolic complications, although the practical implications of such screening remain debated.

In pediatric populations, results mirrored those observed in adults, with children treated with carbamazepine or valproate exhibiting significant elevations in homocysteine alongside reductions in B-vitamin levels (Verrotti et al., 2000). The implications of these findings are particularly concerning given the potential impact of homocysteine on neurodevelopment and vascular health during critical periods of growth.

Beyond homocysteine itself, several studies documented associated changes in lipid profiles and other vascular risk markers, suggesting that antiepileptic drug–induced metabolic disturbances may extend into broader atherogenic pathways (Bramswing et al., 2002; Mintzer et al., 2018). These results reinforce the conceptualization of epilepsy treatment as a contributor to long-term cardiovascular risk, rather than an isolated neurological intervention.

4. Discussion

The accumulated evidence reviewed in this article supports a robust association between antiepileptic drug therapy and dysregulation of homocysteine metabolism, yet the interpretation of this association requires careful theoretical framing. At a fundamental level, hyperhomocysteinemia in epilepsy can be understood as the emergent outcome of intersecting biochemical, genetic, and pharmacological processes, each of which contributes incrementally to metabolic imbalance (Zaric et al., 2019).

From a biochemical perspective, the disruption of one-carbon metabolism by antiepileptic drugs reflects both direct and indirect mechanisms. Enzyme-inducing anticonvulsants accelerate hepatic metabolism of folate and other B-vitamins, reducing their bioavailability and impairing homocysteine remethylation (Ubbink et al., 1993). Concurrently, alterations in vitamin B6 status compromise the transsulfuration pathway, further limiting homocysteine clearance (Ubbink et al., 1996). These mechanisms operate synergistically, rendering homocysteine accumulation a predictable consequence of long-term therapy rather than an idiosyncratic anomaly.

However, the presence of genetic modifiers such as methylenetetrahydrofolate reductase polymorphisms complicates this narrative. The heightened susceptibility observed in carriers of the 677C→T mutation underscores the inadequacy of one-size-fits-all models of drug safety and highlights the importance of personalized medicine approaches in epilepsy management (Yoo and Hong, 1999). At the same time, the probabilistic nature of genetic risk cautions against deterministic interpretations that might overstate the predictive value of single polymorphisms.

Clinically, the implications of antiepileptic drug–induced hyperhomocysteinemia extend beyond biochemical abnormalities to encompass vascular and neurocognitive outcomes. Epidemiological studies in non-epileptic populations have firmly established hyperhomocysteinemia as an independent risk factor for vascular disease and thrombosis, lending plausibility to concerns about increased cardiovascular risk in epilepsy (Boushey et al., 1995; den Heijer et al., 1996). Within epileptic cohorts, emerging evidence of altered lipid profiles and vascular markers further supports this concern, particularly in older adults and those receiving enzyme-inducing drugs (Katsiki et al., 2014; Mintzer et al., 2018).

Counter-arguments within the literature often emphasize the modest magnitude of homocysteine elevation observed in many studies, questioning whether such increases are sufficient to produce clinically meaningful harm. While this skepticism is warranted, it overlooks the cumulative and long-term nature of exposure in epilepsy, where patients may experience decades of sustained metabolic perturbation (Schwaninger et al., 1999). Moreover, even moderate elevations of homocysteine have been associated with increased vascular risk at the population level, suggesting that small shifts may have significant public health implications when aggregated over time (Graham et al., 1997).

Pediatric considerations introduce additional complexity. In children, the potential effects of hyperhomocysteinemia on neurodevelopment, cognitive function, and vascular maturation remain incompletely understood, yet the evidence of altered homocysteine and vitamin status in this population warrants cautious interpretation and proactive management (Verrotti et al., 2000; Besag and Vasey, 2021).

The discussion also raises important ethical and clinical questions regarding monitoring and intervention. Routine assessment of homocysteine and B-vitamin status in epileptic patients is not universally practiced, reflecting uncertainty about cost-effectiveness and

clinical benefit. However, the weight of evidence reviewed here suggests that targeted monitoring in high-risk groups may represent a rational compromise between universal screening and complete neglect (Al Mutairi, 2020).

5. Conclusion

The body of literature examined in this article converges on the conclusion that hyperhomocysteinemia represents a significant and mechanistically plausible consequence of long-term antiepileptic drug therapy. Rooted in disruptions of B-vitamin–dependent metabolic pathways and modulated by genetic susceptibility, this phenomenon links epilepsy treatment to broader concerns of vascular and systemic health. Recognizing and addressing homocysteine dysregulation offers an opportunity to move toward more holistic models of epilepsy care that integrate neurological, metabolic, and cardiovascular considerations.

References

1. Al Mutairi, F. (2020). Hyperhomocysteinemia: clinical insights. Journal of Central Nervous System Disease, 12, 1179573520962230.
2. Apeland, T., Mansoor, M. A., & Strandjord, R. E. (2001). Antiepileptic drugs as independent predictors of plasma total homocysteine levels. Epilepsy Research, 47, 27–36.
3. Besag, F. M. C., & Vasey, M. J. (2021). Neurocognitive effects of antiseizure medications in children and adolescents with epilepsy. Pediatric Drugs, 23, 253–286.
4. Boushey, C. J., Beresford, S. A., Omenn, G. S., & Motulsky, A. G. (1995). A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Journal of the American Medical Association, 274, 1049–1057.
5. Bramswing, S., Kerksiek, A., Sudhop, T., Luers, C., Bergman, K. V., & Berthold, H. K. (2002). Carbamazepine increases atherogenic lipoproteins. Heart and Circulatory Physiology, 282, 704–716.
6. den Heijer, M., Koster, T., Blom, H. J., et al. (1996). Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. New England Journal of Medicine, 334, 759–762.
7. Graham, I. M., Daly, L. E., Refsum, H. M., et al. (1997). Plasma homocysteine as a risk factor for vascular disease. Journal of the American Medical Association, 277, 1775–1781.
8. Katsiki, N., Mikhailidis, D. P., & Nair, D. R. (2014). The effects of antiepileptic drugs on vascular risk factors. Seizure, 23, 677–684.
9. Malpas, J. S., Spray, G. H., & Witts, L. J. (1966). Serum folic acid and vitamin B12 levels in anticonvulsant therapy. British Medical Journal, 1, 955–957.
10. Mintzer, S., Trinka, E., Kraemer, G., Chervoneva, I., & Werhahn, K. J. (2018). Impact of antiepileptic drugs on vascular risk markers. Epilepsia, 59, 1899–1907.
11. Mudd, S. H., Skovby, F., Levy, H. L., et al. (1985). The natural history of homocystinuria. American Journal of Human Genetics, 37, 1–31.
12. Ono, H., Sakamoto, A., Eguchi, T., et al. (1997). Plasma total homocysteine concentrations in epileptic patients taking anticonvulsants. Metabolism, 46, 959–962.
13. Preece, J., Reynolds, E. H., & Johnson, A. L. (1971). Relation of serum to red cell folate concentrations in drug-treated epileptic patients. Epilepsia, 12, 335–340.
14. Schwaninger, M., Ringleb, P., Winter, R., et al. (1999). Elevated plasma concentrations of homocysteine in antiepileptic drug treatment. Epilepsia, 40, 345–350.
15. Ubbink, J. B., Vermaak, W. J. H., Van der Merwe, A., & Becker, P. J. (1993). Vitamin B12, vitamin B6 and folate nutritional status in men with hyperhomocysteinemia. American Journal of Clinical Nutrition, 57, 47–53.
16. Ubbink, J. B., Van der Merwe, A., Delport, R., et al. (1996). The effect of a subnormal vitamin B6 status on homocysteine metabolism. Journal of Clinical Investigation, 98, 177–184.
17. Verrotti, A., Pasceralla, R., Trotta, D., Giuva, T., Morgese, G., & Chiarelli, F. (2000). Hyperhomocysteinemia in children treated with antiepileptic drugs. Epilepsy Research, 41, 253–257.
18. Vilaseca, M. A., Monros, E., Arthuch, R., et al. (2000). Antiepileptic drug treatment in children: hyperhomocysteinemia and B-vitamins. European Journal of Paediatric Neurology, 4, 269–277.
19. Yoo, J. H., & Hong, S. B. (1999). Methylenetetrahydrofolate reductase mutation and hyperhomocysteinemia in epileptic patients. Metabolism, 48, 1047–1051.
20. Zaric, B. L., Obradovic, M., Bajic, V., et al. (2019). Homocysteine and hyperhomocysteinaemia. Current Medicinal Chemistry, 26, 2948–2961.