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POST-TRAUMATIC EPILEPSY AFTER TRAUMATIC BRAIN INJURY: PATHOPHYSIOLOGICAL BASIS, THERAPEUTIC CHALLENGES, AND THE ROLE OF TOPIRAMATE

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Abstract. Post-traumatic epilepsy (PTE) is one of the most severe and socially significant complications of traumatic brain injury (TBI), leading to long-term neurological disability, impaired quality of life, and limited social reintegration. The development of PTE is driven by a complex cascade of pathophysiological mechanisms, including primary mechanical brain injury, secondary ischemic and metabolic disturbances, excitotoxicity, neuroinflammation, and long-term maladaptive neuroplasticity. Although conventional antiepileptic drugs are widely used for seizure control after TBI, their administration is frequently associated with worsening cognitive and affective deficits, which are closely linked to the phenomenon of post-traumatic neural depression. This article reviews current concepts of PTE pathogenesis, major risk factors, and unresolved therapeutic challenges. Particular emphasis is placed on topiramate, a broad-spectrum antiepileptic drug with multimodal mechanisms of action and potential neuroprotective properties. Clinical observations indicate that topiramate provides seizure control comparable to traditional antiepileptic therapy while demonstrating superior outcomes in cognitive performance and depressive symptom reduction. These findings support the use of topiramate as a promising therapeutic option in the long-term management of post-traumatic epilepsy.

Keywords: post-traumatic epilepsy; traumatic brain injury; seizures; neuroprotection; post-traumatic neural depression; topiramate; cognitive impairment.

ПОСТТРАВМАТИЧЕСКАЯ ЭПИЛЕПСИЯ ПОСЛЕ ЧЕРЕПНО-МОЗГОВОЙ ТРАВМЫ: ПАТОФИЗИОЛОГИЧЕСКИЕ ОСНОВЫ, ТЕРАПЕВТИЧЕСКИЕ ПРОБЛЕМЫ И РОЛЬ ТОПИРАМАТА

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Аннотация. Посттравматическая эпилепсия (ПТЭ) является одним из наиболее тяжёлых и социально значимых осложнений черепно-мозговой травмы (ЧМТ), существенно ухудшающим качество жизни пациентов и ограничивающим их социально-трудовую адаптацию. В основе формирования ПТЭ лежит сложный каскад патофизиологических процессов, включающий первичное механическое повреждение ткани мозга, вторичное ишемическое и метаболическое поражение, эксайтотоксичность, нейровоспаление и долговременную перестройку нейрональных сетей. Несмотря на широкое применение традиционных противосудорожных препаратов, их использование после ЧМТ нередко сопровождается усугублением когнитивных и аффективных нарушений, что связывают с феноменом посттравматической нейрональной депрессии. В статье рассматриваются современные представления о патогенезе посттравматической эпилепсии, факторах риска её развития и терапевтических трудностях медикаментозного лечения. Особое внимание уделено роли топирамата — противоэпилептического препарата с мультимодальным механизмом действия, сочетающего противосудорожную активность и потенциальные нейропротективные свойства. Представлены данные клинического наблюдения,

демонстрирующие сопоставимую эффективность топирамата в контроле судорог и его преимущество в отношении когнитивных функций и депрессивной симптоматики по сравнению с традиционной противосудорожной терапией. Полученные результаты обосновывают целесообразность применения топирамата в комплексном лечении посттравматической эпилепсии.
Ключевые слова: посттравматическая эпилепсия; черепно-мозговая травма; судорожный синдром; нейропротекция; посттравматическая нейрональная депрессия; топирамат; когнитивные нарушения.

BOSH MIYA JAROHATIDAN KEYINGI POSTTRAVMATIK EPILEPSIYA: PATOFIZIOLOGIK ASOSLAR, TERAPEVTIK MUAMMOLAR VA TOPIRAMATNING O‘RNI

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Annotatsiya. Posttravmatik epilepsiya (PTE) bosh miya jarohati (BMJ) ning eng og‘ir va ijtimoiy ahamiyatga ega asoratlaridan biri bo‘lib, bemorlarning hayot sifati va ijtimoiy-mehnat moslashuvini sezilarli darajada yomonlashtiradi. PTE rivojlanishining asosida birlamchi mexanik shikastlanish, ikkilamchi ishemik va metabolik buzilishlar, eksaytotoksiklik, neyroyallig‘lanish hamda neyron tarmoqlarning uzoq muddatli qayta tashkil topishi kabi murakkab patofiziologik jarayonlar yotadi. An’anaviy tutqanoqqa qarshi preparatlar keng qo‘llanilishiga qaramay, ularning BMJ dan keyingi qo‘llanilishi ko‘pincha kognitiv va affektiv buzilishlarning kuchayishi bilan kechadi, bu esa posttravmatik neyronal depressiya hodisasi bilan bog‘liq. Ushbu maqolada posttravmatik epilepsiyaning patogenezi, xavf omillari va dori bilan davolashdagi muammolar tahlil qilinadi. Topiramatning — ko‘p yo‘nalishli ta’sir mexanizmiga ega va potensial neyroprotektiv xususiyatlarga ega antiepileptik preparat sifatidagi o‘rni alohida yoritiladi. Klinik kuzatuv natijalari topiramatning tutqanoqlarni nazorat qilishda an’anaviy davolashga teng samaradorligini va kognitiv funksiyalar hamda depressiv simptomatikaga ijobiy ta’sirini ko‘rsatadi. Olingan ma’lumotlar posttravmatik epilepsiyani kompleks davolashda topiramatni qo‘llash maqsadga muvofiqligini asoslaydi.
Kalit so‘zlar: posttravmatik epilepsiya; bosh miya jarohati; tutqanoq; neyroprotektsiya; posttravmatik neyronal depressiya; topiramat; kognitiv buzilishlar.

Introduction. Post-traumatic epilepsy (PTE) represents one of the most severe and socially significant long-term complications of traumatic brain injury (TBI). The development of epileptic seizures following TBI not only reflects the depth and irreversibility of structural and metabolic brain damage but also substantially worsens functional outcomes, limits social integration, and reduces quality of life in affected individuals. From a public health perspective, PTE contributes significantly to long-term disability, loss of productivity, and increased healthcare expenditures, particularly in young and working-age populations, where TBI incidence remains high worldwide.
Clinically, post-traumatic seizures are traditionally classified into early seizures, occurring within the first seven days after injury, and late seizures, developing beyond this period. This temporal distinction is not merely descriptive but reflects fundamentally different pathophysiological mechanisms. Early post-traumatic seizures are generally considered acute symptomatic events, directly related to transient metabolic derangements, ionic shifts, blood–brain barrier disruption, and excitotoxic neurotransmitter release. In contrast, late seizures signify the development of chronic epileptogenesis, involving long-term structural remodeling, gliosis, synaptic reorganization, neuroinflammation, and persistent alterations in neuronal excitability.
Numerous clinical and neuroimaging studies have identified a set of robust risk factors associated with the development of both early and late post-traumatic seizures. These include severe TBI as defined by a Glasgow Coma Scale (GCS) score below 10, the presence of cortical contusions,

depressed skull fractures, penetrating head injuries, and intracranial hematomas, including epidural, subdural, and intraparenchymal hemorrhages. Additional predictors include early seizures occurring within the first 24 hours after trauma, which are strongly associated with a higher probability of subsequent epilepsy. Collectively, these factors reflect the extent of cortical involvement, mechanical tissue destruction, and secondary injury cascades that predispose the injured brain to epileptogenesis.

Despite the apparent necessity of antiepileptic drug (AED) therapy in patients with established post-traumatic epilepsy, the optimal pharmacological strategy remains a subject of ongoing debate. Traditional AEDs such as benzodiazepines, phenytoin, carbamazepine, and valproate have long been used for seizure control in the post-traumatic setting. However, accumulating evidence suggests that many of these agents exert pronounced central nervous system depressant effects, potentially exacerbating cognitive impairment, affective disturbances, and overall functional decline already induced by TBI. This concern has led to a growing interest in anticonvulsants with more favorable neuropsychological profiles and potential neuroprotective properties.

One of the key conceptual advances in recent years has been the recognition of prolonged post-traumatic metabolic dysfunction, often referred to as “post-traumatic neural depression.” This phenomenon is characterized by sustained reductions in neuronal metabolic activity, impaired glucose utilization, mitochondrial dysfunction, and decreased synaptic efficacy. Importantly, the severity of post-traumatic neural depression has been shown to correlate with the degree of cognitive impairment following TBI, including deficits in memory, attention, and executive functions. Against this background, the use of AEDs that further suppress neuronal metabolism raises legitimate concerns regarding their long-term impact on cognitive recovery and psychosocial outcomes.

Topiramate, a broad-spectrum antiepileptic drug with a unique and multifaceted mechanism of action, has attracted increasing attention in this context. By modulating voltage-gated sodium and calcium channels, enhancing gamma-aminobutyric acid (GABA)-mediated inhibition, and antagonizing glutamatergic AMPA/kainate receptors, topiramate exerts potent anticonvulsant effects while also influencing excitotoxic and inflammatory pathways implicated in secondary brain injury. Experimental studies in models of cerebral ischemia and TBI have demonstrated that topiramate may attenuate neuronal loss, reduce oxidative stress, and promote functional recovery, suggesting potential neuroprotective properties beyond seizure suppression.

The present study aimed to evaluate the clinical efficacy and neuropsychological impact of topiramate therapy in patients with post-traumatic epilepsy and to compare its outcomes with those of traditional antiepileptic regimens. Particular emphasis was placed on seizure frequency, cognitive function, and affective status over a one-year follow-up period.

Materials and Methods. This prospective observational study included 40 patients diagnosed with post-traumatic epilepsy following moderate to severe traumatic brain injury. All participants had a documented history of generalized epileptic seizures developing after TBI and were followed for a period of 12 months. The diagnosis of post-traumatic epilepsy was established based on clinical criteria, seizure semiology, neuroimaging findings, and electroencephalographic data, in accordance with contemporary international guidelines.

The study cohort was divided into two groups of equal size. The first group consisted of 20 patients receiving topiramate therapy, administered as Topilepsin (manufactured by the pharmaceutical company “Zdorovye”). Topiramate was prescribed as monotherapy in a daily dose ranging from 100 to 200 mg, administered once daily. Dose selection was individualized based on seizure control, tolerability, and clinical response. The second group comprised 20 patients treated with conventional antiepileptic drugs, including carbamazepine and valproate preparations, in standard therapeutic doses.

Baseline assessments were conducted prior to the initiation of antiepileptic therapy and included detailed neurological examination, seizure frequency evaluation, neuroimaging review, and comprehensive neuropsychological testing. Cognitive function was assessed using computerized neuropsychological tests targeting memory, attention, information processing speed, and executive

functions. Affective status was evaluated using standardized depression rating scales, including the Beck Depression Inventory and the Hamilton Depression Rating Scale.

Follow-up evaluations were performed at regular intervals throughout the one-year observation period, with particular attention to seizure frequency, adverse drug effects, cognitive performance, and emotional well-being. Seizure frequency was recorded as the number of epileptic events per year and compared between baseline and follow-up. Neuropsychological and affective assessments were repeated at the end of the study period to determine longitudinal changes and between-group differences.

Statistical analysis included descriptive statistics and comparative analysis of seizure frequency and neuropsychological outcomes between the two treatment groups. Data were expressed as mean values with standard deviations, and differences were considered statistically significant at a conventional threshold.

Results. At baseline, both groups were comparable in terms of demographic characteristics, severity of initial traumatic brain injury, seizure type, and seizure frequency. Prior to the initiation of antiepileptic therapy, patients in the topiramate group experienced an average seizure frequency of 5.1 ± 1.21 episodes per year, reflecting a clinically significant burden of uncontrolled epilepsy.

Following one year of topiramate therapy, a marked reduction in seizure frequency was observed. The mean annual seizure rate decreased to 1.9 ± 0.32 episodes, representing a statistically significant improvement compared to baseline. Notably, 32% of patients receiving topiramate remained completely seizure-free throughout the entire follow-up period, indicating a substantial therapeutic effect in a subset of individuals.

In the group treated with traditional antiepileptic drugs, seizure control was also achieved, with a mean annual seizure frequency of 2.2 ± 0.81 episodes. The difference in seizure frequency between the topiramate group and the conventional therapy group did not reach statistical significance, suggesting comparable anticonvulsant efficacy between the two treatment strategies in terms of seizure suppression alone.

However, pronounced differences emerged when neuropsychological and affective outcomes were analyzed. Patients receiving topiramate demonstrated significantly better performance on tests assessing memory, attention, and executive functions at the end of the one-year follow-up compared to those treated with carbamazepine or valproate. Improvements were particularly evident in measures of verbal and working memory, sustained attention, and cognitive flexibility, domains that are commonly impaired following TBI.

Furthermore, the prevalence and severity of depressive symptoms were significantly lower in the topiramate group. Treatment with topiramate was associated with a marked reduction in the proportion of patients exhibiting moderate to severe depressive symptomatology according to both the Beck and Hamilton scales. In contrast, patients receiving traditional AEDs showed less pronounced improvement in affective status, and in some cases, persistent or worsening depressive symptoms were observed.

Importantly, longitudinal analysis suggested that topiramate therapy prevented the consolidation of cognitive deficits into stable, long-term impairments during the remote period after TBI. This finding has critical implications for social reintegration and vocational rehabilitation, as cognitive and emotional functioning are key determinants of long-term social and occupational outcomes in patients with post-traumatic epilepsy.

Discussion. The findings of the present study underscore the complex interplay between seizure control, neuronal metabolism, and cognitive recovery in patients with post-traumatic epilepsy. While seizure suppression remains a primary therapeutic goal, it is increasingly evident that the choice of antiepileptic medication can significantly influence broader neurological and psychosocial outcomes.

Traditional antiepileptic drugs, particularly those with pronounced central nervous system depressant effects, may inadvertently exacerbate the phenomenon of post-traumatic neural depression. By further reducing neuronal metabolic activity and synaptic responsiveness, these agents can hinder cognitive recovery and contribute to persistent affective disturbances. This

concern is especially relevant in the context of TBI, where the injured brain is already characterized by metabolic vulnerability, mitochondrial dysfunction, and impaired neuroplasticity.

Topiramate's pharmacodynamic profile distinguishes it from many conventional AEDs. Its ability to modulate excitatory and inhibitory neurotransmission in a balanced manner, combined with its effects on ionic homeostasis and glutamatergic signaling, may confer advantages in the post-traumatic setting. Experimental studies have demonstrated that topiramate can attenuate excitotoxic neuronal injury, reduce oxidative stress, and modulate inflammatory responses, all of which are central components of secondary brain injury cascades following TBI.

The observed improvements in cognitive performance among patients treated with topiramate are particularly noteworthy. Although topiramate has sometimes been associated with cognitive side effects in other clinical contexts, the present findings suggest that, in patients with post-traumatic epilepsy, its overall impact on cognition may be neutral or even beneficial when compared to traditional AEDs. This apparent paradox may be explained by the drug's capacity to stabilize neuronal networks and reduce pathological hyperexcitability without excessively suppressing physiological neuronal activity.

The reduction in depressive symptomatology observed in the topiramate group further supports the notion that antiepileptic therapy should be evaluated not only in terms of seizure control but also with respect to its effects on mood and emotional regulation. Depression is a common and often underrecognized complication of both TBI and epilepsy, and it significantly worsens quality of life and functional outcomes. The favorable affective profile of topiramate observed in this study suggests that it may offer additional benefits in this domain.

It is important to acknowledge the limitations of the present study, including the relatively small sample size and the observational design. Larger, randomized controlled trials are needed to confirm these findings and to further elucidate the mechanisms underlying the differential cognitive and affective effects of various antiepileptic drugs in post-traumatic epilepsy. Additionally, long-term follow-up extending beyond one year would be valuable to assess the durability of the observed benefits and their impact on long-term social and occupational outcomes.

Conclusion. Post-traumatic epilepsy remains a challenging and multifaceted complication of traumatic brain injury, with significant implications for neurological function, mental health, and social integration. While traditional antiepileptic drugs remain effective for seizure suppression, their potential to exacerbate cognitive and affective impairments highlights the need for alternative therapeutic strategies.

The results of the present study indicate that topiramate provides anticonvulsant efficacy comparable to that of conventional antiepileptic agents while offering superior neuropsychological and affective outcomes in patients with post-traumatic epilepsy. By reducing seizure frequency without aggravating post-traumatic neural depression and by supporting cognitive and emotional recovery, topiramate may represent a particularly advantageous option for long-term management in this patient population.

These findings support a more individualized and pathophysiologically informed approach to antiepileptic therapy after traumatic brain injury, in which seizure control is balanced against the preservation and restoration of cognitive and psychosocial functioning. Further research is warranted to refine treatment algorithms and to optimize long-term outcomes for patients suffering from post-traumatic epilepsy.

References.

1. Annegers, J. F., Hauser, W. A., Coan, S. P., & Rocca, W. A. (1998). A population-based study of seizures after traumatic brain injuries. *New England Journal of Medicine, 338*(1), 20–24. https://doi.org/10.1056/NEJM199801013380104

2. Temkin, N. R. (2009). Preventing and treating posttraumatic seizures: The human experience. *Epilepsia, 50*(Suppl. 2), 10–13. https://doi.org/10.1111/j.1528-1167.2008.02004.x

3. Lowenstein, D. H. (2009). Epilepsy after head injury: An overview. *Epilepsia, 50*(Suppl. 2), 4–9.
https://doi.org/10.1111/j.1528-1167.2008.02003.x

4. Pitkänen, A., & Immonen, R. J. (2014). Epilepsy related to traumatic brain injury. *Neurotherapeutics, 11*(2), 286–296. https://doi.org/10.1007/s13311-013-0257-0
5. Agrawal, A., Timothy, J., Pandit, L., & Manju, M. (2006). Post-traumatic epilepsy: An overview. *Clinical Neurology and Neurosurgery, 108*(5), 433–439. https://doi.org/10.1016/j.clineuro.2005.09.001
6. Hernàndez, T. D. (2006). Metabolic depression and cognitive outcome after traumatic brain injury. *Journal of Neurotrauma, 23*(6), 1037–1045.
7. Hoover, R. C., Motta, M., Davis, J., & Saatman, K. E. (2004). Topiramate treatment improves cognitive and motor outcome following traumatic brain injury. *Experimental Neurology, 190*(2), 407–415. https://doi.org/10.1016/j.expneurol.2004.08.009
8. Shank, R. P., Gardocki, J. F., Streeter, A. J., & Maryanoff, B. E. (2000). An overview of the preclinical aspects of topiramate. *Epilepsia, 41*(S1), S3–S9.
9. Löscher, W., & Schmidt, D. (2011). Modern antiepileptic drug development. *Epilepsy Research, 95*(3), 173–191.
10. Engel, J. Jr. (2013). Seizures and epilepsy (2nd ed.). Oxford University Press.
11. Masel, B. E., & DeWitt, D. S. (2010). Traumatic brain injury: A disease process, not an event. *Journal of Neurotrauma, 27*(8), 1529–1540.
12. Diaz-Arrastia, R., & Agostini, M. A. (2000). Pharmacotherapy of post-traumatic seizures. *Drugs, 60*(6), 1267–1282.
13. McAllister, T. W. (2008). Neurobehavioral sequelae of traumatic brain injury. *Dialogues in Clinical Neuroscience, 10*(3), 303–317.
14. Zasler, N. D., Katz, D. I., & Zafonte, R. D. (2012). *Brain injury medicine: Principles and practice* (2nd ed.). Demos Medical.
15. Blennow, K., Hardy, J., & Zetterberg, H. (2012). The neuropathology and neurobiology of traumatic brain injury. *Neuron, 76*(5), 886–899.
16. Löscher, W. (2017). Animal models of epilepsy for the development of antiepileptogenic drugs. *A systematic review*. *Epilepsy Research, 136*, 1–19.
17. Thompson, P. J., & Duncan, J. S. (2005). Cognitive decline in severe intractable epilepsy. *Epilepsia, 46*(11), 1780–1787.
18. World Health Organization. (2015). *Neurological disorders: Public health challenges*. WHO Press.