JPSIM Journal of Pakistan Society of Internal Medicine

Original Article

Treatment Outcomes of Topiramate and Levetiracetam for Generalized Tonic-Clonic Seizures Among Adults with Idiopathic Generalized Epilepsy

Faheem Saeed,[1] Zeeshan Rashid,[1] Mamoona Tanvir,[2] Zaib Zahid,[2] Muhammad Latif,[2] Muhammad Adnan[3]

[1]Sir Ganga Ram Hospital/Fatima Jinnah Medical University, Lahore, [2]Akhtar Saeed Medical College, Lahore, [3]Health Research Institute, National Institute of Health, Islamabad.

Abstract

Objective: To compare the safety and efficacy of Lrvetiracetam (LEV) versus Topiramate (TPM) as monotherapy for generalized Tonic-Clonic seizure (GTCS) alone in adults with idiopathic Generalized Epilepsy(IGE).

Methods: Out of 60 IGE patients with GTCS alone, 30 cases on oral topiramate (50 mg/day) were recruited in TPM group, and 30 cases taking oral levetiracetam (500 mg twice a day) in LEV group. Follow-up assessments, conducted for three months, aimed to evaluate reductions in seizure frequency and adverse events. Total 51 patients (25 in TPM group and 26 in LEV group) completed the study, and data subjected to final SPSS analysis.

Results: Mean age of 51 patients was 33.0 ± 13.0 years. Women proportion was little higher than men (54.9% vs. 44.1%). Two-third of them had >2 seizures at the time of enrollment. Baseline variables were similar among the two study groups (all p-values >0.05). At a 12-week follow-up visit, overall two-third of the total population became seizure-free. Seizure-free rate in TPM group was considerably greater than the LEV group (p-value 0.088). None of the patients in both groups reported headache, nausea, anxiety and vomiting. Incidence of adverse events in the TPM group was insignificantly higher than the LEV group (all p-values >0.05).

Conclusion: Topiramate was a more efficacious but less tolerated broad-spectrum anti-epileptic drug than levetiracetam for treating GTCS among adults with IGE.

Keywords: Epilepsy, Levetiracetam, Seizure, Topiramate.

How to cite this:

Saeed F, Rashid Z, Tanvir M, Zahid Z, Latif M, Adnan M. Treatment outcomes of topiramate and levetiracetam for generalized tonic-clonic seizures among adults with idiopathic generalized epilepsy. J Pak Soc Intern Med. 2025;6(2): 165-169

Corresponding Author: Muhammad Adnan **Email:** adnanpmrc@gmail.com

Received: 11.11.2024 **Revised:** 15-01-2025 **Accepted:** 25-04-2025

DOI: https://doi.org/10.70302/jpsim.v6i2.2531

Introduction

Idiopathic generalized epilepsy (IGE) constitutes a fifth of all epilepsy cases. A subtype characterized by generalized tonic-clonic seizures (GTCS) alone is more prevalent among four basic forms of IGE.[1] The frequency of adult onset IGE 14.3% was reported in Karachi,[2] and GTCS as the most prevalent seizure type observed in 57.9% epileptic patients of Khyber Pakhtunkhwa.[3] The patients with IGE and GTCS typically demonstrate severe muscle contractions and limb stiffness.[4] Over 20 AEDs are now being used in clinical settings. The selection of AEDs depends on seizure type, electroencephalogram (EEG) findings, epileptic syndrome, and drug stability.[5] Levetiracetam (LEV), a broad-spectrum antiepileptic drug (AED), effectively treats idiopathic generalized seizures with minimal adverse events and reasonable pharmacokinetics. However, concerns exist about behavioral side effects, including aggressiveness and emotional distress.[6] LEV benefits pregnant women and improves cognitive abilities. However, there is inadequate evidence supporting its cost-effectiveness.[7] Topiramate (TPM), another broad-spectrum AED, appears promising as an alternative

treatment for IGE. Although generally well-tolerated, common adverse effects of TPM include fatigue, weight loss and cognitive decline.[8] Some studies support use of LEV and TPM as the most effective therapy in partial and some generalized epilepsies.[9] However, evidence suggesting their efficacy for treating GTCS in adults with IGE) is still lacking. Therefore, we compare the safety and efficacy of LEV versus TPM as monotherapy for GTCS alone in adults with IGE.

Methods

The research study sought permission from the Ethics Review Committee of the hospital. All volunteer patients provided written informed consent. The prospective observational study was conducted at the hospital, over a six-month period. Inclusion criteria were known cases of IGE with >2 GTCS, aged 18 to 60 years, and of any gender. Exclusion criteria encompassed patients with a history of mental illness, hepatic, renal, or hematologic disease; patients who experienced pseudo seizures in the previous year; patients taking other AEDs; and pregnant women. IGE patients with GTCS fulfilled the following three conditions: (1) experiencing ≥2 GTCS within a six-month period, (2) presenting generalized spike wave discharge on electroencephalography at frequencies greater than 2.5 Hz, without cognitive impairment even during hyperventilation, and (3) having no other seizure types (e.g., myoclonic, absences, phantom absences, or focal).

Out of 60 IGE patients with GTCS alone, 30 cases were recruited in TPM group, and another 30 cases in LEV group. In TPM group, patients received oral topiramate 50 mg/day as initial dose, which was gradually increased to an effective dose ranging from 200-400 mg/day, divided into two doses. In LEV group, patients received oral levetiracetam 500 mg twice a day as initial dose, which could be further increased to a maximum of 1500 mg twice a day based on individual patient response and tolerability.

Follow-up assessments, conducted for three months, aimed to evaluate reductions in seizure frequency and adverse events. Data collection utilized a purposively designed structured proforma, capturing information such as age, gender, seizure count, seizure duration, BMI, and adverse events. Seizure control was assessed based on the percentage reduction in seizure frequency: 100% reduction was deemed seizure-free. Total 51 patients (25 in TPM group and 26 in LEV group) completed the study, and their data were subjected to final analysis.

Statistical Package for Social Sciences (SPSS) version 26.0 was used for data entry and analysis. Age, BMI, number, and duration of seizures were reported as Mean±SD. Gender distribution, seizure control, and adverse events were presented as n(%). Chi-square test was employed to compare seizure control rate and adverse event incidence between the TPM and LEV groups. A p-value ≤ 0.05 considered as significant.

Results

The mean age of 51 adults with IGE and GTCS was 33.0 ± 13.0 years (range 18 – 60 years). The participation of women was little higher than men (54.9% vs. 44.1%). Two-third of them had >2 seizures at the time of enrollment. Baseline variables were similar among the two study groups (all p-values >0.05), see Table 1.

Table 1: *Baseline characteristics of study population*

		Total (N=51)	TPM group (N=25)	LEV group (N=26)	p-value
Gender	**Men**	23 (45.1%)	12 (48.0%)	11 (42.3%)	0.899
	Women	28 (54.9%)	13 (52.0%)	15 (57.7%)	
Age (years)		33.0 ± 13.0	32.5 ± 14.0	33.5 ± 12.2	0.8
	≤35	31 (60.8%)	15 (60.0%)	16 (61.5%)	1
	>35	20 (39.2%)	10 (40.0%)	10 (38.5%)	
Body mass index (Kg/m^2)		23.7 ± 3.3	23.6 ± 3.5	23.8 ± 3.0	0.879
	<25	29 (56.9%)	14 (56.0%)	15 (57.7%)	1
	≥25	22 (43.1%)	11 (44.0%)	11 (42.3%)	
Number of seizures		3.1 ± 1.1	3.2 ± 1.1	3.1 ± 1.2	0.798
	2	18 (35.3%)	07 (28.0%)	11 (42.3%)	0.438
	>2	33 (64.7%)	18 (72.0%)	15 (57.7%)	
Duration of seizure		1.8 ± 0.7	2.0 ± 0.7	1.7 ± 0.7	0.12

Table 2: *Seizure-free rate at 12-week follow-up visit*

		Total (N=51)	TPM group (N=25)	LEV group (N=26)	p-value
Number of seizures	**0**	34 (66.7%)	20 (80.0%)	14 (53.8%)	0.088
	2-Jan	11 (21.6%)	03 (12.0%)	08 (30.8%)	
	>2	06 (11.8%)	02 (8.0%)	04 (15.4%)	
Second drug requirement	**No**	38 (%)	17 (68.0%)	21 (80.8%)	0.469
	Yes	13 (%)	08 (32.0%)	05 (19.2%)	

When compared for numbers of seizures reported at 2-, 4- and 8-week follow-up visits, an improvement was observed. Yet, none of the patients in both groups could become seizure-free. At a 12-week follow-up visit, overall two-third of the total population became seizure-free. When compared between the two groups, seizure-free rate in the TPM group was considerably greater than the LEV group (p-value 0.088). The requirement for second AED was also greater in the TPM group, but the difference was not significant (p-value 0.469), see Table 2.

Incidence of adverse events was not significantly different between the two groups at 2-week (p-value 0.492) and 4-week follow-up visit (p-value 0.469). However, the difference was statistically significant at 8-week follow-up visit (p-value 0.002). As shown in Figure I, incidence of adverse events declined with time in both groups.

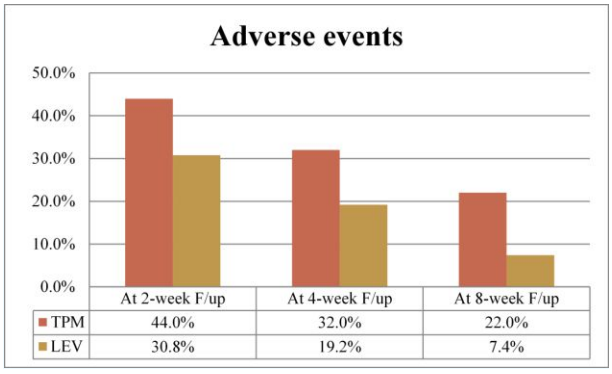

Figure I: *Incidence of adverse events at 2-, 4- and 8-week follow-up visits*

At a 12-week follow-up visit, none of the patients in both groups reported headache, nausea, anxiety and vomiting. Figure II shows that the proportions of adverse events in the TPM group were insignificantly greater than the LEV group (all p-values >0.05).

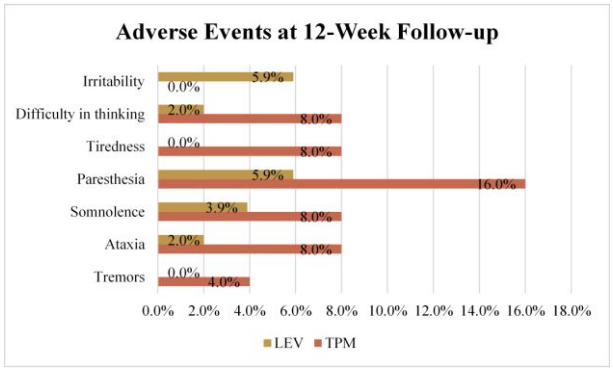

Figure II: *Incidence of adverse events at 12-week follow-up visit*

Discussion

Seizures are manageable for most IGE patients, but others require lifelong medication. Choosing AEDs for IGE patients might be tricky due to the requirement to avoid long-term medication side effects while maintaining adequate seizure control.[10] As a result, we evaluated and compared the safety and efficacy of LEV versus TPM as monotherapy for GTCS alone in adults with IGE. In the current study, the TPM group had a greater seizure-free rate than the LEV group, albeit the difference was not statistically significant. This could be owing to the small sample size and short follow-up period. Nonetheless, these findings are consistent with other studies. Jeon et al. conducted a meta-analysis of 47 studies to assess the efficacy of ten AEDs recommended for monotherapy, including LEV and TPM. It was discovered that the seizure-free and adverse event rates did not differ significantly among the AEDs under investigation.[11] Similarly, Bootsma et al. found that seizure-free rates ranged from 11.6% to 20.0% for TPM and 11.1% to 14.3% for LEV. During follow-up, no substantial differences between the two AEDs could be identified at 6M (p-value 0.468), 12M (p-value 0.653) and 18M (p-value 0.244).[12] However, in a meta-analysis, Wang et al. found that LEV was associated with a higher percentage of seizure free (OR=1.9, 1.2-2.9) and a lower risk of at least one adverse event (OR=0.5, 0.4-0.7) than TPM.[13]

While TPM is only FDA approved drug for primary generalized seizures, research suggests that LEV could also be a beneficial broad-spectrum AED.[14] TPM-related side effects were primarily central nervous system-related symptoms, such as somnolence, dizziness and psychomotor slowness.[15] On the other side, LEV-associated side effects frequently reported in combined analyses of the regulatory trials were headache, asthenia, somnolence and dizziness.[16] Bootsma et al. also reported that activating mood disorders and tiredness were the most prevailing adverse events for LEV. While, mental slowing, dysphasia and weight loss were the major side effects for TPM.[13] According to Chappell et al., LEV and TPM were the most effective AEDs for treating primary generalized epilepsy and the least effective for symptomatic generalized epilepsy. However, TPM was the least well-tolerated.[17] Similarly, in the current study, the TPM group had a higher proportion of adverse events than the LEV group at the 2-week and 4-week follow-up visits, however the difference was not substantial. However, the difference between the two groups was statistically significant at the 8-week follow-up. It was also observed that the incidence of adverse events in both groups decreased over time.

Conclusion

Topiramate was a more efficacious but less tolerated broad-spectrum anti-epileptic drug than levetiracetam for treating GTCS among adults with IGE in our setting. Thus, topiramate can be used as a safe and effective drug for adult onset generalized epilepsy. However, well-designed clinical trials are recommended for evidence.

Limitations: The limitations of study include observational design of study, relatively smaller sample size, shorter duration of follow-up and consecutive enrollment of patients. These shortcomings may decrease the generalizability of results.

Acknowledgement: We are thankful to all those patients who voluntarily participated in the study.

Ethical Approval: The IRB/EC approved this study via letter no 73/ERB dated 14-06-2024.

Conflict of Interest: *None*

Funding Source: *None*

Authors' Contribution

FS, ZR: Conception

MT, MA: Design of the work

ZZ, ML: Data acquisition, analysis, or interpretation

ZR, MT, ZZ, ML: Draft the work

FS, MA: Review critically for important intellectual content

All authors approve the version to be published

All authors agree to be accountable for all aspects of the work

References

1. Devinsky O, Elder C, Sivathamboo S, Scheffer IE, Koepp MJ. Idiopathic generalized epilepsy: misunderstandings, challenges, and opportunities. Neurology. 2024; 102(3): e208076.
2. Shahbaz NN, Hassan Y, Abdullah M. Adult onset idiopathic generalized epilepsy: A hospital-based study. Pak J Med Sci. 2011; 27(2): 256-60.
3. Ullah S, Ali N, Khan A, Ali S, Nazish HR. The epidemiological characteristics of epilepsy in the province of Khyber Pakhtunkhwa, Pakistan. Front Neurol. 2018; 9: 845.
4. Elmali AD, Auvin S, Bast T, Rubboli G, Koutroumanidis M. How to diagnose and classify idiopathic (genetic) generalized epilepsies. Epileptic Disord. 2020; 22(4): 399-420.
5. Kim H, Kim DW, Lee ST, Byun JI, Seo JG, No YJ, et al. Antiepileptic drug selection according to seizure type in adult patients with epilepsy. J Clin Neurol. 2020; 16(4): 547-55.
6. Kumar A, Maini K, Kadian R. Levetiracetam. [Updated 2023 Dec 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024; Available from: https://www.ncbi.nlm.nih.-gov/books/NBK499890/.
7. Yi ZM, Wen C, Cai T, Xu L, Zhong XL, Zhan SY, et al. Levetiracetam for epilepsy: an evidence map of efficacy, safety and economic profiles. Neuropsychiatr Dis Treat. 2018; 15: 1-19.
8. Fariba KA, Saadabadi A. Topiramate. [Updated 2024 Jun 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024; Available from: https://www.ncbi.nlm.nih.gov/books/NBK554530/.
9. Sarhan EM, Walker MC, Selai C. Evidence for efficacy of combination of antiepileptic drugs in treatment of epilepsy. J Neurol Res. 2016; 5(6): 267-76.
10. Rathore C, Patel KY, Satishchandra P. Current concepts in the management of idiopathic generalized epilepsies. Ann Indian Acad Neurol. 2022; 25(1): 35-42.

11. Jeon J, Oh J, Yu KS. A meta-analysis: efficacy and safety of anti-epileptic drugs prescribed in Korea as monotherapy and adjunctive treatment for patients with focal epilepsy. Transl Clin Pharmacol. 2021; 29(1): 6-20.
12. Bootsma HP, Ricker L, Diepman L, Gehring J, Hulsman J, Lambrechts D, et al. Long-term effects of levetiracetam and topiramate in clinical practice: A head-to-head comparison. Seizure. 2008; 17(1): 19-26.
13. Wang H, Wang H, Liu Y, Zhao J, Niu X, Zhu L, et al. Efficacy and safety of five broad-spectrum antiseizure medications for adjunctive treatment of refractory epilepsy: a systematic review and network meta-analysis. CNS Drugs. 2023;37(10):883-913.
14. Bergey GK. Evidence-based treatment of idiopathic generalized epilepsies with new antiepileptic drugs. Epilepsia. 2005; 46(9): 161-8.
15. Fariba KA, Saadabadi A. Topiramate. [Updated 2024 Jun 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025; Available from: https://www.ncbi.nlm.nih.gov/books/NBK554530/.
16. Privitera M. Efficacy of levetiracetam: a review of three pivotal clinical trials. Epilepsia. 2001; 42(4): 31-5.
17. Chappell B, Crawford P. An audit of lamotrigine, levetiracetam and topiramate usage for epilepsy in a district general hospital. Seizure. 2005; 14(6): 422-8.