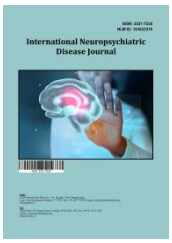

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Clinical Perspectives of Managing Epilepsy Across Different Patient Populations with a Focus on Brivaracetam: A Cross-sectional Study among Indian Physicians

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Authors' contributions

This work was carried out in collaboration between both authors. Both the authors contributed equally in managing literature search, designing the study, performed the statistical analysis, wrote the protocol and the first draft of the manuscript. Both the authors read and approved the final manuscript.

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ABSTRACT

Objective: To evaluate clinicians' preferences, prescribing patterns, and clinical experiences with brivaracetam compared to other antiepileptic drugs, particularly levetiracetam, in the management of epilepsy across different patient populations.
Methodology: This cross-sectional study used a 24-item multi-response questionnaire to gather expert opinion across different Indian settings regarding their perspectives on epilepsy and

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brivaracetam. Data analysis employed descriptive statistics, with results reported as frequencies and percentages.

Results: The survey included 360 participants. Clinicians showed a strong preference for brivaracetam as the first-line antiepileptic drug in patients with newly diagnosed epilepsy, with 72% favoring it for younger patients and 74% for elderly. This preference was particularly notable for managing partial-onset seizures, as cited by 71% of clinicians. Additionally, 65% reported that partial-onset seizures were the primary reason for switching to brivaracetam from other antiepileptics. Behavioral and psychiatric adverse effects were cited by 60% of clinicians as the main reasons for transitioning from levetiracetam to brivaracetam. Moreover, 47% reported that 10-20% of patients experiencing behavioral changes on levetiracetam were switched to brivaracetam, with 49% noting improved efficacy and behavioral outcomes in 20-30% of these cases. The minimal psychiatric and behavioral side effects of brivaracetam were noted as its main advantage by 41% of clinicians in managing partial-onset seizures. Furthermore, 70% of clinicians preferred brivaracetam for treatment-resistant epilepsy, and approximately half of them preferred it for pediatric partial seizures.

Conclusion: This study highlighted brivaracetam as a preferred antiepileptic drug in clinical practice, especially for managing partial-onset seizures. It serves as an effective alternative for patients experiencing adverse effects with levetiracetam.

Keywords: Epilepsy; brivaracetam; levetiracetam; partial-onset seizures; behavioral changes.

1. INTRODUCTION

Epilepsy contributes substantially to the global disease burden, impacting approximately 50 million individuals worldwide. The estimated prevalence of active epilepsy ranges from 4 to 10 per 1,000 individuals in the general population. Each year, around 5 million individuals are newly diagnosed with epilepsy globally. In high-income countries, the incidence rate is estimated at 49 per 100,000 people, while in low- and middle-income countries, this figure can reach as high as 139 per 100,000 [1]. Approximately one-sixth of the global epilepsy population resides in India, with an estimated 10–12 million individuals affected. A substantial portion of these individuals do not receive adequate treatment, resulting in a significant treatment gap [2]. Epilepsy, with its chronic nature, places a considerable burden on both individuals and society [3]. The growing burden of epilepsy in India, driven by sociodemographic and epidemiological shifts, underscores the need for the public health community to prioritize this largely preventable and manageable condition within healthcare delivery [4].

Antiepileptic medications (AEMs) remain the cornerstone of epilepsy treatment. Despite the growing array of available drugs over the past two decades, approximately one-third of individuals with epilepsy still experience seizures despite receiving appropriate therapy. Brivaracetam, an AEM, is characterized by its high and selective affinity for the synaptic vesicle protein 2A (SV2A). It is currently approved by the European Medicines Agency for use as adjunctive therapy in patients over the age of 2 years with partial onset seizures, with or without secondary generalization. Additionally, the Food and Drug Administration has approved Brivaracetam for both monotherapy and adjunctive therapy in the treatment of partial-onset seizures in patients aged 1 month and older [5,6].

Brivaracetam demonstrates greater binding affinity and selectivity for the SV2A compared to levetiracetam and exhibits approximately 15 to 30 times higher affinity for SV2A than LEV and demonstrates superior inhibition of vesicle release. Its mechanism of action is more selective than that of levetiracetam, as it does not interact with other targets. In contrast, levetiracetam also influences the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamatergic postsynaptic receptor and presynaptic calcium channels. Additionally, brivaracetam shows broad-spectrum antiseizure activity in animal models of epilepsy, possesses a favorable pharmacokinetic profile, has minimal clinically significant drug-drug interactions, and penetrates the brain rapidly [7].

The survey is intended to evaluate clinicians' real-world experiences and preferences regarding brivaracetam use across different patient populations, focusing on its efficacy, tolerability, and specific advantages compared to other AEMs, particularly levetiracetam.

Understanding these prescribing patterns and clinical outcomes can provide valuable insights for optimizing epilepsy management strategies and improving patient care.

2. MATERIALS AND METHODS

We carried out a cross-sectional study involving clinicians with expertise in managing epilepsy in the major Indian cities from June 2023 to December 2023. The study was conducted after getting approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

2.1 Questionnaire

The questionnaire booklet named BEST (Brivaracetam in Epilepsy Management - Clinicians Perspective Study) was sent to the clinicians who were interested in participating in this study. The BEST study questionnaire included 24-item questions designed to assess clinicians' practices and preferences in epilepsy management, with a particular focus on AEM selection and experiences with brivaracetam. The questionnaire was structured to cover multiple domains of epilepsy management, including clinical practice patterns, AEM preferences, prescribing patterns, and specific experiences with brivaracetam and levetiracetam.

2.2 Participants

A simple random sampling method was utilized in this study. An invitation was sent to leading clinicians in treating epilepsy in March 2023 for participation in this Indian survey. About 360 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provided necessary data. Participants were asked to complete the questionnaire without discussing it with their peers. A written informed consent was obtained from each physician before initiation of the study.

2.3 Statistical Methods

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to clearly illustrate their distribution. The frequency and corresponding percentage of each variable were used for representation. Pie and bar charts were created using Microsoft Excel 2013 (version 2409, build 16.0.18025.20030) to visualize the distribution of categorical variables.

3. RESULTS

Nearly 37% of clinicians reported managing 21–30 epilepsy cases per month. Most clinicians (60%) identified partial seizures as the most observed form of epilepsy. Approximately 36% of clinicians indicated managing between 11 and 20 cases of partial-onset seizures per month. Around 40% of experts reported that 21–30% of their patient population consists of individuals with epilepsy. More than half of the clinicians (52%) indicated that 21–30% of partial-onset seizure patients in their clinical practice did not respond to older antiepileptic medications. Majority of the clinicians (55%) noted the flavor of antiepileptic syrup is a very important factor for pediatric patients.

Nearly half of the clinicians (48%) preferred social media-based mass education as their primary method for educating patients with epilepsy. Half of the surveyed clinicians (50%) identified lack of patient education as the primary factor associated with medication non-adherence in epilepsy patients. A significant number of experts (72%) reported a preference for brivaracetam as the preferred AEMs for young patients, whereas 74% of the clinicians preferred it in elderly patients with newly diagnosed epilepsy (Table 1). Majority of the clinicians (71%) reported preferring brivaracetam over other AEMs primarily for partial onset seizures, and 65% of clinicians indicated partial onset seizures as the primary reason for the switching from other antiepileptics to brivaracetam (Table 2)

More than half of the respondents (52%) reported that 10-20% of their patients experienced behavioral changes with levetiracetam, and 44% reported that behavioral changes associated with levetiracetam were common across all age groups. Majority of the experts (42%) reported prescribing brivaracetam predominantly to the 18-45 years age group. Nearly 61% reported prescribing brivaracetam at a daily dose of 100 mg/day in their clinical practice.

Approximately 60% of the respondents reported that the primary reason for discontinuing levetiracetam and switching to brivaracetam was both behavioral and psychiatric adverse effects (Fig. 1). Majority of the clinicians reported that 10-20% of patients in their practice experienced

behavioral changes with levetiracetam were shifted to brivaracetam (47%), while 49% noted that 20-30% of patients switched to brivaracetam showed improvement in efficacy and behavioral changes (Table 3).

Approximately 41% of the clinicians reported that the primary advantage of brivaracetam in partial onset seizure patients was its minimal psychiatric and behavioral adverse effects (Fig. 2). The majority (43%) of the clinicians reported that 30-50 patients with partial onset seizure noted in their clinical practice were on brivaracetam (Fig. 3).A significant proportion of clinicians (70%) preferred brivaracetam for patients with resistant epilepsy, while in pediatric patients with partial seizures, brivaracetam remained the most preferred choice, with approximately half of the clinicians (51.11%) selecting it as their primary AEDs (Table 4). Majority of clinicians reported that 21-30% of individuals were seizure-free with brivaracetam compared to levetiracetam, with 43% selecting this proportion (Fig. 4).

Table 1. Distribution of response to preferred drug for young and elderly patients with newly diagnosed epilepsy

Preferred drug	Response rate (n = 360)	
	Young patients	Elderly patients
Brivaracetam	262 (72.78%)	268 (74.44%)
Levetiracetam	63 (17.5%)	77 (21.39%)
Carbamazepine	11 (3.06%)	7 (1.94%)
Sodium valproate	22 (6.11%)	7 (1.94%)
Not attempted	2 (0.56%)	1 (0.28%)

Table 2. Distribution of response to indications for preferring brivaracetam over other antiepileptic drugs

Indication	Response rate (n = 360)	
	Indications for preferring brivaracetam	Cases for shifting to brivaracetam
Generalized tonic-clonic seizure	93 (25.83%)	110 (30.56%)
Partial onset seizure	255 (70.83%)	234 (65%)
Myoclonic seizure	9 (2.5%)	14 (3.89%)
All of the above	3 (0.83%)	2 (0.56%)

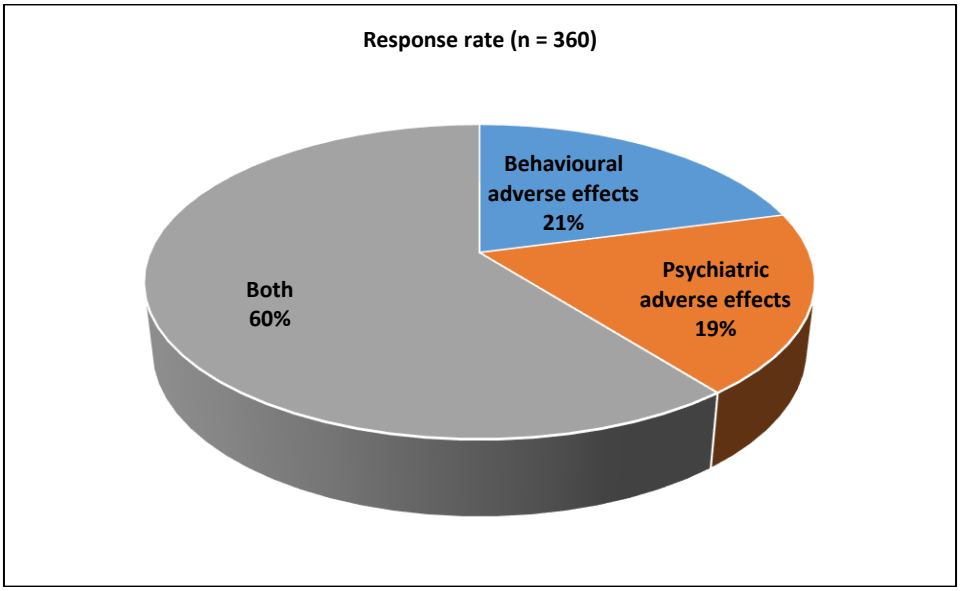

Fig. 1. Distribution of response to reasons for discontinuation of levetiracetam and switching to brivaracetam in clinical settings

Table 3. Proportion of patients shifted to brivaracetam due to behavioral changes and improvement in efficacy and behavioral changes

Percentage range	Response rate (n = 360)	
	Patients shifted to brivaracetam	
	Due to behavioral changes with levetiracetam	Showing improvement in efficacy and behavioral changes
<10%	51 (14.17%)	31 (8.61%)
10-20%	170 (47.22%)	154 (42.78%)
20-30%	139 (38.61%)	175 (48.61%)

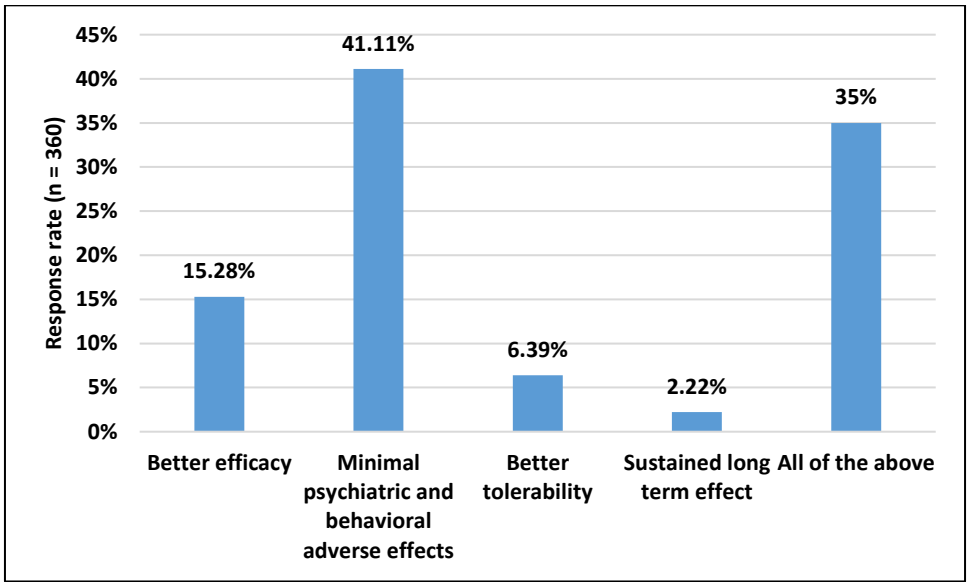

Fig. 2. Distribution of response to perceived advantages of brivaracetam in partial onset seizure patients

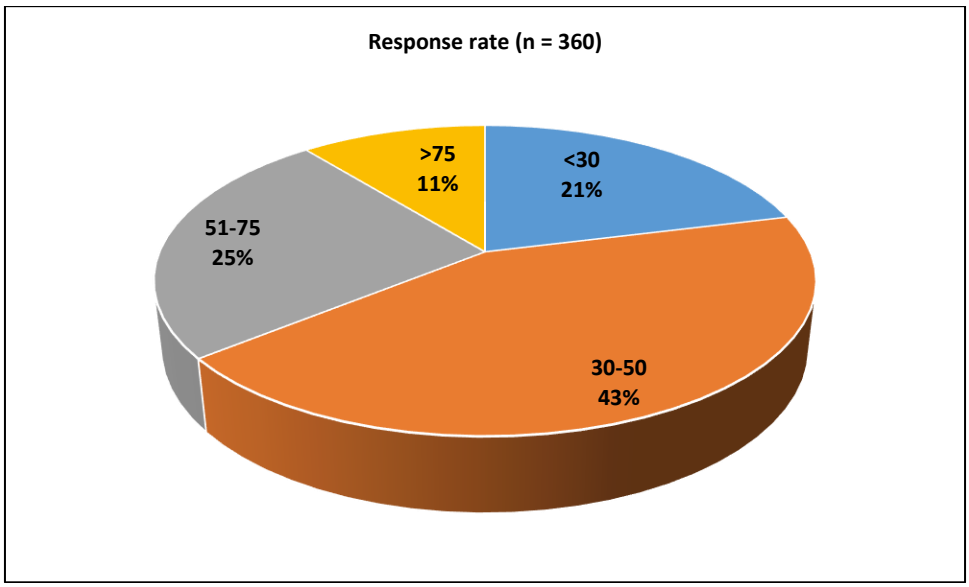

Fig. 3. Distribution of response regarding the number of patients with partial-onset seizures on brivaracetam in clinical practice

Table 4. Distribution of response regarding the preferred drug for patients with resistant epilepsy and partial seizures among the pediatric age group

Drug	Response rate (n = 360)	
	Resistant epilepsy (%)	Pediatric partial seizures (%)
Brivaracetam	253 (70.28)	184 (51.11)
Levetiracetam	49 (13.61)	70 (19.44)
Sodium valproate	33 (9.17)	50 (13.89)
Carbamazepine	20 (5.56)	-
Oxcarbazepine	-	47 (13.06)
Lamotrigine	-	9 (2.50)
No preference	5 (1.39)	-

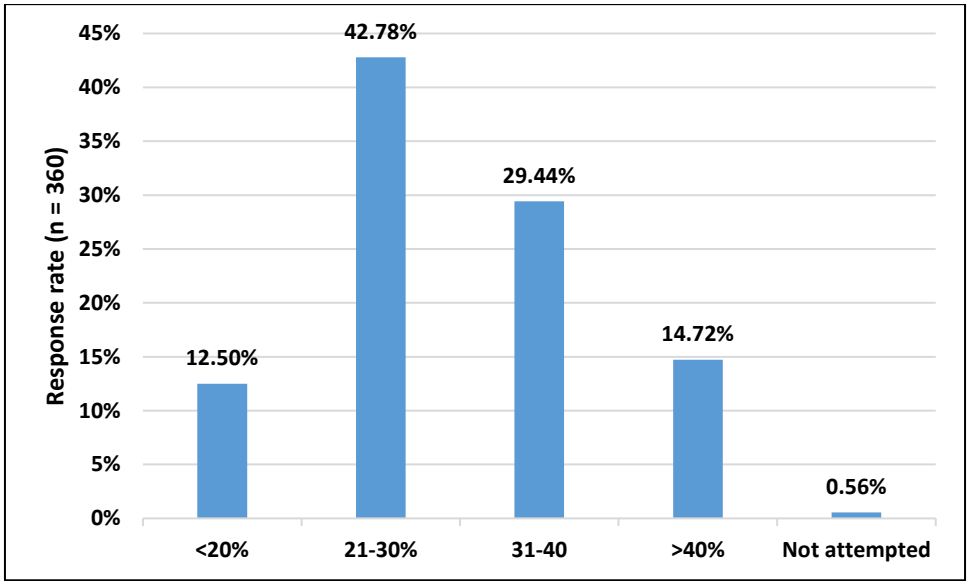

Fig. 4. Distribution of response to reported seizure-free rates with brivaracetam compared to levetiracetam in clinical practice

4. DISCUSSION

The selection of AEM remains a critical challenge in epilepsy management, particularly when considering efficacy, tolerability, and patient-specific factors. This survey provides important insights into real-world clinical preferences and experiences with brivaracetam across diverse patient populations in epilepsy care. The study findings offer valuable perspectives on positioning of brivaracetam in current clinical practice and its comparative advantages over other AEMs, particularly levetiracetam.

The survey results demonstrated a strong clinician preference for brivaracetam across multiple patient populations and clinical scenarios. The notably high preference rates for brivaracetam in both young (72%) and elderly patients (74%) with newly diagnosed epilepsy suggest that clinicians perceive it as a versatile AEM with a favorable safety profile across age groups. The BRIVAracetam add-on First Italian netwoRk Study (BRIVAFIRST) demonstrated that adjunctive brivaracetam was effective, well-tolerated, and presented no new or unexpected safety concerns when used to treat older patients (≥65 years of age) with epilepsy with uncontrolled focal seizures in clinical practice [7]. In a study by Stefanatou et al. comprising 156 patients aged 16 and older with various types of epilepsy, 36% achieved complete seizure control at their first follow-up, and an additional 36% experienced a significant reduction in seizure frequency. Adverse events were observed in 17% of patients, though none were life-threatening. These findings suggested that brivaracetam was a practical, safe, and effective option for seizure management in a diverse epilepsy population [8].

Majority of the survey respondents preferred brivaracetam over other antiepileptics for partial onset seizures, with most citing partial onset seizures as the main reason for switching from other medications. A phase III randomized controlled trial involving 400 patients with uncontrolled partial epilepsy found that adding brivaracetam at a daily dose of 50 mg significantly reduced seizure frequency compared to placebo [9]. Ben-Menachem et al. pooled data from three phase III trials and demonstrated the efficacy, safety, and tolerability of adjunctive brivaracetam in a large cohort of adult patients with partial-onset seizures. All three brivaracetam doses (50, 100, and 200 mg/day) were found to be effective, showing clear numerical separation from placebo across multiple endpoints, including seizure freedom [10]. Multiple other studies have also reported the effectiveness and good tolerability of brivaracetam treatment for partial-onset seizures [11-15].

In the present survey, a significant proportion of clinicians identified behavioral and psychiatric adverse effects as the primary reasons for discontinuing levetiracetam and transitioning patients to brivaracetam, considering it the drug's primary advantage in treating partial-onset seizures. Notably, clinicians reported that 10-20% of their patients who experienced behavioral changes with levetiracetam were transitioned to brivaracetam, and among those switched, majority of clinicians observed improvements in both seizure control and behavioral symptoms. A study by Yates et al. in patients aged 16 and older with nonpsychotic behavioral adverse events on levetiracetam showed promising outcomes after switching to brivaracetam. Among 29 patients enrolled, 93% experienced clinically meaningful reductions in behavioral adverse events and a decrease in maximum behavioral adverse event intensity, while quality of life scores improved significantly by the end of 12 weeks [16]. Brivaracetam appears to be a safe and well-tolerated treatment option for children and adolescents with focal epilepsy. An immediate switch from levetiracetam to brivaracetam at a 10:1 ratio was feasible, with fewer psychobehavioral adverse events observed compared to levetiracetam. These findings support brivaracetam as a viable alternative, particularly for patients experiencing levetiracetam-induced adverse events [17].

Most current survey clinicians observed that a notable proportion of individuals between 21% and 30% achieved seizure freedom with brivaracetam compared to levetiracetam. A systematic review by Steinhoff et al. investigated the incidence of irritability, anger, and aggression associated with brivaracetam and other ASMs. The weighted mean incidence reported for irritability, anger, and aggression with brivaracetam were 5.6%, 3.3%, and 2.5%, respectively. These findings indicated relatively low overall incidences of these behavioral adverse events. Importantly, there was several real-world evidence suggesting that switching from levetiracetam to brivaracetam led to improvements in behavioral side effects. Furthermore, brivaracetam was demonstrated to be safer than levetiracetam, with lower incidences of irritability and aggression compared to both levetiracetam and perampanel. The rates of discontinuation due to irritability and aggression were also lower with brivaracetam than with levetiracetam, perampanel, and topiramate [18]. Hirsch et al. indicated that patients previously treated with levetiracetam experienced improved tolerability and efficacy after switching to brivaracetam. Among the 102 patients analyzed, 22% became seizure-free, and 33% achieved at least a 50% reduction in seizure frequency. Patients who switched directly from LEV to BRV often benefited from higher doses of brivaracetam, suggesting prior seizure control was limited by LEV dosage. Notably, 57% of those switching due to psychiatric side effects reported improved tolerability with brivaracetam [19].

The survey also highlighted brivaracetam as a primary choice for treatment-resistant epilepsy and pediatric partial seizures, with many clinicians indicating it as their preferred ASM in these contexts. Russo et al. demonstrated the efficacy and tolerability of brivaracetam as an add-on therapy in pediatric patients with severe drug-resistant epilepsy, particularly among those with later onset of seizures (>12 months), shorter disease duration (≤6 years), and lower baseline seizure frequency [20]. A systematic review and meta-analysis by Lattanzi et al. reported that brivaracetam demonstrated efficacy as an add-on therapy in reducing seizure frequency in adults with drug-resistant partial epilepsy and showed a favorable safety profile [21]. McGuire et al. found that brivaracetam is an effective treatment for refractory focal epilepsy in children over the age of 4 years [22]. Brivaracetam was an effective add-on treatment for both focal and generalized seizures in children, with minimal

side effects, even in that refractory to levetiracetam [23].

The study provides valuable insights into real-world use and perception of brivaracetam, reinforcing its position as a favorable AEM for epilepsy, particularly among patients with partial-onset seizures or those previously treated with levetiracetam. The findings contribute to understanding the role of brivaracetam in enhancing patient outcomes by minimizing behavioral and psychiatric adverse effects, supporting its use as a primary AEM in specific patient populations. The key strengths of the survey are the use of a carefully designed and validated questionnaire to gather expert data and a larger sample size. However, this study has certain limitations, including its reliance on clinician-reported preferences and observations, which may introduce bias. Additionally, the study lacks randomization and control, restricting the ability to draw definitive conclusions about brivaracetam's efficacy and tolerability compared to other AEMs.

5. CONCLUSION

The survey underscores the role of brivaracetam as a preferred AEM in clinical practice, particularly for managing partial-onset seizures and as a switch option for patients experiencing adverse effects on levetiracetam. The findings demonstrate that clinicians widely recognize brivaracetam for its effectiveness, tolerability, and favorable behavioral side-effect profile, suggesting it is a practical and versatile choice across age groups and clinical scenarios.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

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COMPETING INTERESTS

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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