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Original Research Article

Expert Opinion on the Prescription Practice of Levetiracetam for Different Types of Epilepsy in Indian Clinical Settings

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Abstract: Despite some studies assessing antiepileptic drug usage patterns in single-centre settings, there was a lack of consensus regarding usage patterns, drug choices for various seizure types, and the sociodemographic and clinical factors that influence treatment decisions in India. So, this current survey-based study was intended to gather expert opinions regarding the clinical use of anti-epileptic drugs with a special focus on levetiracetam for the management of epilepsy in Indian settings. A questionnaire-based cross-sectional study involving 25 questions collected perspectives of experts across India regarding the prescription practice of anti-epileptic drugs for epilepsy management. It was noted that majority of the responders (85.93% of 192 experts) stated levetiracetam as a preferred therapeutic option for patients with newly diagnosed epilepsy. Levetiracetam 1000 mg/day was the frequently recommended dosage for such patients in clinical practice (66%). Approximately 76% of the experts suggested that patients receiving the drug might experience behavioural changes. About 49% and 82% of responders recommended levetiracetam for treating resistant epilepsy and pregnant epilepsy respectively. Nearly 62% of the clinicians recommended levetiracetam for paediatric patients with partial seizures over other antiepileptic drugs. Levetiracetam and brivaracetam were both rated as beneficial for treating epileptic patients by 50% of clinicians. Levetiracetam was rated as being more effective than brivaracetam by 28% of clinicians, while brivaracetam was rated as being more effective by 14% of clinicians. Hence, this consensus among clinician's highlights levetiracetam as the preferred antiepileptic medication for the management of patients with recently diagnosed epilepsy. This recommendation extends patients with refractory epilepsy, pregnant subjects with epilepsy, and young children experiencing partial seizures, where the majority of the clinicians endorse levetiracetam over alternative antiepileptic medications. Both levetiracetam and brivaracetam offer comparable treatment benefits for patients with epilepsy.

Keywords: Epilepsy, Seizures, Antiepileptic drugs, Levetiracetam, Brivaracetam, Expert opinion.

INTRODUCTION

Epilepsy affects approximately 50 million individuals worldwide, making it one of the most prevalent neurological conditions globally. Nealy 80% of the patients with epilepsy reside in low- and middle-income nations. Estimates suggested that 70% of epilepsy patients could avoid seizures if it was adequately identified and treated [1].

Despite significant treatment advances, around 75% of patients in low- and middle-income countries, are unable to access care due to the lack of effective antiepileptic medications and increased treatment costs [2-5]. The mainstay of epilepsy treatment was monotherapy, but combination therapy was recommended for patients with unmanageable or resistant epilepsy [6, 7]. Levetiracetam was a commonly prescribed antiepileptic medication in clinical practice. Since its authorization in the early 2000s, its usage has steadily increased and has become a preferred choice for epilepsy management [8]. This could be attributed to ease of administration, effectiveness, broad spectrum of action, minimal risk of idiosyncratic/life-threatening events and congenital malformations, and limited pharmacologic interactions [9, 10]. Additionally, the evidence suggested that levetiracetam has a considerably

wider therapeutic window, more convenient dosing, and fewer side effects than other anti-epileptic drugs [11]. Apart from having positive pharmacological benefits, levetiracetam also has favourable pharmacoeconomic consequences [12].

Several clinical studies have shown that levetiracetam was safe and effective for epileptic childbearing patients and was the most effective medication in reducing seizure frequency [13, 14]. Despite some studies assessing antiepileptic drug usage patterns in single-center settings, there was a dearth of consensus regarding usage patterns, drug choices for various seizure types, and the sociodemographic and clinical factors that influence treatment decisions in India. The present study aims to gather expert opinions regarding the prescribing practice of various epileptic drugs, with a special focus on levetiracetam, across different patient populations in Indian clinical settings.

METHODOLOGY

We carried out a cross sectional, multiple-response questionnaire based survey among clinicians specialized in treating epilepsy patients in the major Indian cities from June 2022 to December 2022.

Questionnaire

The questionnaire booklet titled LEAP (Levetiracetam Efficacy and Tolerability Profile) study was sent to the physicians who were interested to participate. The LEAP study questionnaire included 25 items primarily focused on diagnosing epilepsy, clinical traits of epilepsy patients, and potential therapies. The study was conducted after receiving approval from Bangalore Ethics, an Independent Ethics Committee which is recognized by the Indian Regulatory Authority, Drug Controller General of India.

Participants

An invitation was sent to leading clinicians in managing epilepsy in the month of March 2022 for participation in this Indian survey. 192 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Physicians were asked to complete the questionnaire without discussing with peers. A written informed consent was obtained from each clinician's prior initiation of the study.

Statistical Analysis

Descriptive statistics were used. Categorical variables were represented by percentages. The frequency and percentage distribution were used to present each variable's distribution. Excel 2013 (16.0.13901.20400) was used to generate pie and bar charts.

RESULTS

The study included 192 physicians, with the majority (86%) recommending levetiracetam for patients with newly diagnosed epilepsy (Table 1).

Table 1: Response on the drug preference for treating newly diagnosed epilepsy

Preference of drug for patients with newly diagnosed epilepsy	Response rate (n=192)
Levetiracetam	165 (85.93%)
Carbamazepine	0
Brivaracetam	14 (7.29%)
Sodium valproate	9 (4.68%)
Oxcarbazepine	1 (0.52%)
Depending upon the type of epilepsy	1 (0.52%)
Not attempted	2 (1.04%)

According to 70% of the respondents, generalized tonic-clonic seizures were the most common form of epilepsy, followed by partial seizures, myoclonic seizures, and focal seizures in the secondary generation. Further, Irritability and mood swings were the most common adverse effects (41%) observed when using levetiracetam for treating epilepsy.

Approximately 36% of the clinicians reported co-prescribing pyridoxine with levetiracetam to <10% of cognitive deficit epilepsy patients. However, 33% of respondents reported that 10-20% of patients were co-prescribed pyridoxine with levetiracetam. About 38% of the responders stated that pyridoxine was beneficial, as it was safe and effective, inexpensive, and easily available for treating levetiracetam-induced behavioural side effects. A dosage of 50 mg/day of pyridoxine was recommended for treating levetiracetam-induced behavioural side effects by 37% of the responders. Pyridoxine supplementation was reported to be effective when taken for >2 weeks, as indicated by 42% of the respondents.

Approximately 49% of the respondents recommended levetiracetam for patients with resistant epilepsy (Figure 1). The drug was also preferred by 82% of the respondents for pregnant epileptic patients (Figure 2) and by 62% of respondents for paediatric patients with partial seizures over lamotrigine, brivaracetam, sodium valproate, oxcarbazepine, lamotrigine, and other medications (Table 2).

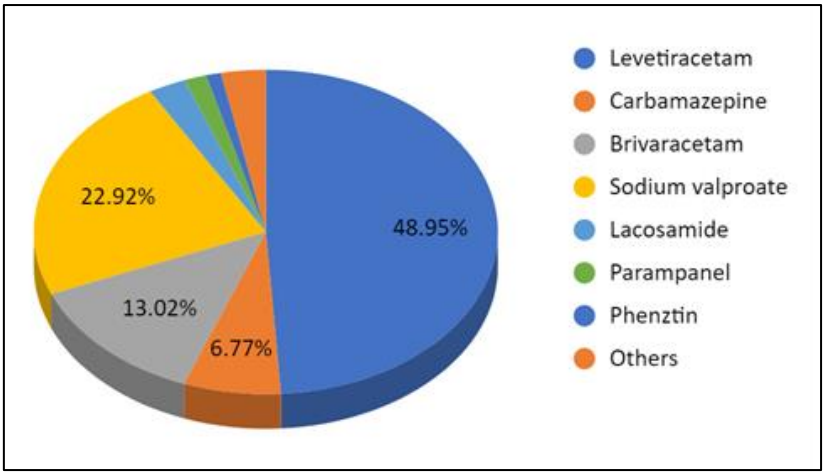

Figure 1: Response to the preferred drug for patients with resistant epilepsy

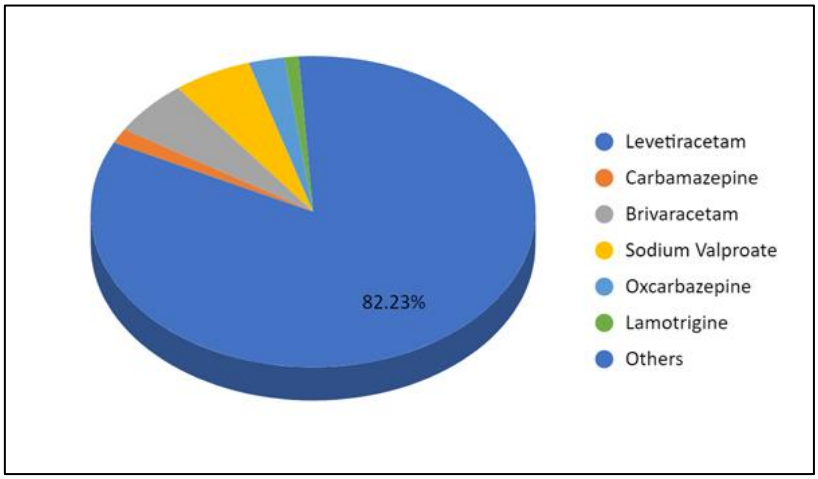

Figure 2: Response on the preferred antiepileptic drug for treating pregnant epileptic patients

Table 2: Response on the preferred antiepileptic drug for treating partial seizure among paediatric subjects

Preference of antiepileptic drug for the treatment of partial seizure among paediatric subjects	Response rate (n=192)
Levetiracetam	61.97%
Lamotrigine	3.64%
Brivaracetam	7.81%
Sodium valproate	10.41%
Oxcarbazepine	15.10%
Others	1.04%

About 72% of respondents reported reduced behavioural disturbance when using brivaracetam over levetiracetam. In addition, reduced side effects of depression and conversion from oral to intravenous preparations were the other advantages noted for brivaracetam over levetiracetam. A notable proportion of clinicians (50.52%) reported that both levetiracetam and brivaracetam were equally effective for treating epilepsy (Table 3).

Table 3: Response on the effectiveness of brivaracetam over levetiracetam

Efficacy of brivaracetam vs. levetiracetam	Response rate (n=192)
Levetiracetam is more efficacious	53 (27.60%)
Brivaracetam is more efficacious	27 (14.06%)
Both are equal in efficacy	97 (50.52%)
Not used	2 (1.04%)
Require more experience and data	1 (0.52%)
Others	12 (6.25%)

DISCUSSION

The majority of the current study participants preferred levetiracetam as the drug of choice for newly diagnosed epilepsy. A study by Karlov *et al*., comprising 107 patients with newly diagnosed epilepsy (42 patients with focal epilepsy, and 65 with idiopathic generalized epilepsy), noted that levetiracetam significantly decreased epileptiform activity index (EAI) post one month of therapy, and the decrease was persistent throughout the follow-up period [15]. Jacob *et al*., studied 37 patients with newly diagnosed partial-onset seizures. They found that 62.96% of patients achieved seizure control at 6 months with a levetiracetam dosage of 20 mg/kg/day, while 25.92% and 7.40% achieved control with dosages of 30 mg/kg/day and 40 mg/kg/day, respectively [16]. In line with current study findings, Alsaadi *et al*., reported the effectiveness and tolerability of levetiracetam therapy in newly diagnosed patients with epilepsy [17]. Levetiracetam was the recommended first-line treatment for newly diagnosed epilepsy, including both focal and generalized seizures with tonic-clonic seizures [18].

The current participants recommended levetiracetam therapy over other medications in patients with resistant epilepsy, pregnancy, and paediatric patients with partial seizures. A phase III randomized controlled trial by Manreza *et al.*, reported that levetiracetam was a safe and effective antiseizure medication for patients with refractory focal epilepsy. The recommended doses are 1,000-3,000 mg/day or 60 mg/kg/day (paediatric) [19]. Several other studies have established that adults with refractory focal seizures respond well to add-on treatment with levetiracetam at dosages of 1,000-3,000 mg/day [20-22]. In a study involving 65 children with refractory epilepsy, levetiracetam add-on therapy showed rapid and significant effectiveness with fewer side effects. Chen *et al*., suggested levetiracetam as an ideal choice for treating paediatric refractory epilepsy [23]. Viteva *et al*., noted that in patients with drug-resistant epilepsy, levetiracetam treatment was linked to low and persistent improvement in seizure severity, good and persistent improvement in seizure frequency, and good safety and tolerability [24].

Certain studies have shown that women who use traditional antiepileptic drugs during pregnancy have a higher risk of foetal abnormalities (4%-9% compared to 1%-2% risk in the general population). However, a study by Bansal *et al*., which included 99 pregnant women with epilepsy (WWE), found no foetal malformations in WWE exposed to levetiracetam [25]. Similar results were observed in several other studies, where the risk of major congenital malformations (MCMs) was zero or minimal (0.7%) in WWE on levetiracetam [26-28]. An Indian study by Sharma *et al.*, has also corroborated the safety of levetiracetam monotherapy in epileptic women of reproductive age [13]. Levetiracetam was an effective therapeutic option for acute seizures in both children and newborns due to its linear kinetics, limited protein binding, lack of hepatic metabolism, and favourable response in status epilepticus and recurrent seizures [29]. Studies by Wheless *et al*., and Zhao *et al*., have also validated the efficacy, safety, and tolerability of levetiracetam in paediatric epilepsy [30, 31].

The majority of participants reported that both levetiracetam and brivaracetam have comparable effectiveness in treating epileptic patients. A meta-analysis of randomized controlled studies by Zhang *et al*., comprising 1876 patients using levetiracetam and brivaracetam, found that LEV may be more effective than brivaracetam while having a reduced risk of dizziness [32]. Contrarily, Beaty *et al*., reported that due to decreased or equivalent rates of ICU admission, intubation, and 30-day seizure-related readmission, intravenous (IV) brivaracetam may offer an option to IV levetiracetam for the treatment of seizures in the hospital environment [33].

The study provided valuable insights into clinicians' perspectives on treating epilepsy in Indian settings. One of the major strengths of the study was the use of a well-crafted and validated questionnaire to gather expert opinions based on evidence-based practices. The study findings can help make informed decisions regarding the best treatment options, thereby enhancing patient outcomes in managing epilepsy. However, it was essential to acknowledge the study's limitations. Relying on expert judgments increases the risk of bias, as each person's perspectives and preferences may have influenced the conclusions. Hence, it was crucial to interpret the results with these limitations and conduct further research to validate the findings.

CONCLUSION

Clinicians widely recommend levetiracetam as the top choice for treating patients with recently diagnosed epilepsy. This endorsement also applies to those with refractory epilepsy, pregnant individuals with epilepsy, and young children with partial seizures, with the majority of clinicians preferring levetiracetam over other antiepileptic medications. Both levetiracetam and brivaracetam provide similar treatment benefits for epilepsy patients.

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DECLARATIONS

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Conflict of Interest: None declared

Ethical Approval: This study was approved by the Independent Ethics Committee.

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