

(RESEARCH ARTICLE)



Exploring the factors influencing the usage of antiepileptic drugs in women with epilepsy

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Abstract

Background: Levetiracetam's relatively low teratogenic risk and minimal interactions with hormonal contraceptives have made it a preferred option in the management of women with epilepsy (WWE). This study aimed to analyze and evaluate the factors influencing antiepileptic drug (AED) usage in WWE.

Methods: The observational cross-sectional survey was conducted between April 2024 to May 2024, among neurologists from various regions across India, who are having special epilepsy clinics.

Results: A total of 253 neurologists participated in the survey. Approximately 47.04% of the neurologists reported that 20-40% of their patients were female in their clinical practice, while 45.06% reported that 40-60% of their patients were female. The majority of neurologists prefer levetiracetam for treating WWE across various groups: 87.75% for reproductive-age women with focal epilepsy, 84.98% for generalized epilepsy, and 73.91% for pediatric patients. It is also widely prescribed for elderly women (70.36%), pregnant women (86.56%), and breastfeeding women (85.38%). Additionally, 74.31% neurologists recommend it for male partners with epilepsy due to its high efficacy and tolerability. About 47.04% of neurologists preferred levetiracetam for treating WWE due to its advantage in lowering the risk of teratogenicity, followed by 26.48% who cited better seizure control. To reduce the teratogenic risk, 34.94% of neurologists consider alternative medications with lower teratogenic potential, while 34.94% consider folic acid supplementation.

Conclusion: The survey highlights a strong preference among neurologists for levetiracetam in treating WWE across various patient groups.

Keywords: Antiepileptic; Levetiracetam; Pregnancy; Teratogenicity; Women with epilepsy

1. Introduction

Epilepsy is a neurological condition characterized by either two or more unprovoked or reflex seizures occurring more than 24 hours apart, a single unprovoked or reflex seizure with a high risk of recurrence (at least 60%) within the next 10 years, or the diagnosis of an epilepsy syndrome [1]. Around 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally, with half of those affected being women [2]. Notably, about a sixth of women with epilepsy (WWE) reside in India, where an estimated 2.73 million WWE live, and 52% of them are within the reproductive age group (15-49 years) [3].

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While epilepsy affects both men and women, WWE face unique challenges due to the complex, multidirectional interactions between hormones, epilepsy, and antiepileptic drugs (AEDs). Studies have demonstrated that hormones, such as estrogen and progesterone, can influence seizure frequency, with estrogen exhibiting proconvulsant properties and progesterone demonstrating anticonvulsant effects [4,5]. Furthermore, several factors such as pregnancy, lactation, menopause, contraception, reproductive health, and the interaction of AEDs with contraceptives and other medications can significantly impact the effectiveness of treatment in WWE [6].

Pregnancy, in particular, poses additional risks for WWE, potentially leading to increased seizure frequency and complications from AED exposure, which may result in congenital malformations [7]. This risk of AED-induced teratogenicity is associated with both the number and dosage of AEDs used during pregnancy [8]. Older AEDs, such as barbiturates, phenytoin, carbamazepine, and valproate, are known for their teratogenic risks among women of childbearing age [9]. However, treatment patterns have shifted, with valproate use decreasing and being replaced by newer AEDs like lamotrigine and levetiracetam, particularly in women of childbearing age and during pregnancy. These drugs, when used in low doses as monotherapy, are associated with the lowest risk of major congenital malformations and are therefore recommended for WWE as a special population [10].

Levetiracetam, a second-generation AED, has gained popularity due to its broad-spectrum efficacy and favorable safety profile. Its mechanism of action involves the modulation of synaptic neurotransmitter release through binding to the synaptic vesicle protein 2A (SV2A), thereby inhibiting the release of neurotransmitters such as epinephrine, norepinephrine, and serotonin [11]. Its relatively low teratogenic risk and minimal drug interactions with hormonal contraceptives have made it a preferred choice for managing epilepsy in WWE. Despite this, there remains a lack of studies examining real-world practice patterns in India regarding the management of WWE during pregnancy. Therefore, the study aimed to analyze and evaluate the factors influencing the usage of AEDs in WWE and their overall management.

2. Methods

The observational cross-sectional survey was conducted between April 2024 to May 2024 among 253 neurologists from various regions across India. A pre-designed, self-developed, questionnaire consisting of 15 closed-ended questions about the prescription and usage of AEDs in WWE was utilized to collect relevant information. The survey focused on several factors affecting the efficacy of AED usage in WWE and the overall management of epilepsy in this population, with particular emphasis on the use of Levetiracetam.

Neurologists were provided with a link via email to access the questionnaire. Upon agreement, neurologists proceeded to complete the digital questionnaire, contributing their clinical insights on AED's. Following the collection of all completed questionnaires, the data was reviewed and analyzed. Descriptive statistics were used to summarize the qualitative data by number (n) and percentage for each category in each question

3. Results

Table 1 Frequency of women patients encountered by neurologists and distribution of WWE in the reproductive age group (15 to 49 years)

Women patients (%)	Frequency* (N=253)	Distribution# (N=253)
20-40	119 (47.04)	109 (43.08)
40-60	114 (45.06)	108 (42.69)
60-80	16 (6.32)	32 (12.65)
>80	4 (1.58)	4 (1.58)

Data presented as n (%); * Frequency: This includes the number (%) of neurologists frequently encountering WWE in their clinical practice.; # Distribution: This includes the number (%) of neurologists encountering WWE falling within the reproductive age group (15 to 49 years); WWE: Women with epilepsy

A total of 253 neurologists participated in the survey. Of these, 36.36% were from the West Zone, followed by 29.25% from the South Zone, 13.44% from the East Zone, 12.65% from the Central Zone and 8.30% from the north zone. Approximately 47.04% of the neurologists reported that 20-40% of their patients were women in their clinical practice, while 45.06% reported that 40-60% of their patients were women (Table 1). Approximately 43.08% of neurologists

observed that 20-40% of their WWE in the reproductive age group (15-49 years) were affected, while 42.69% observed that 40-60% were affected (Table 1).

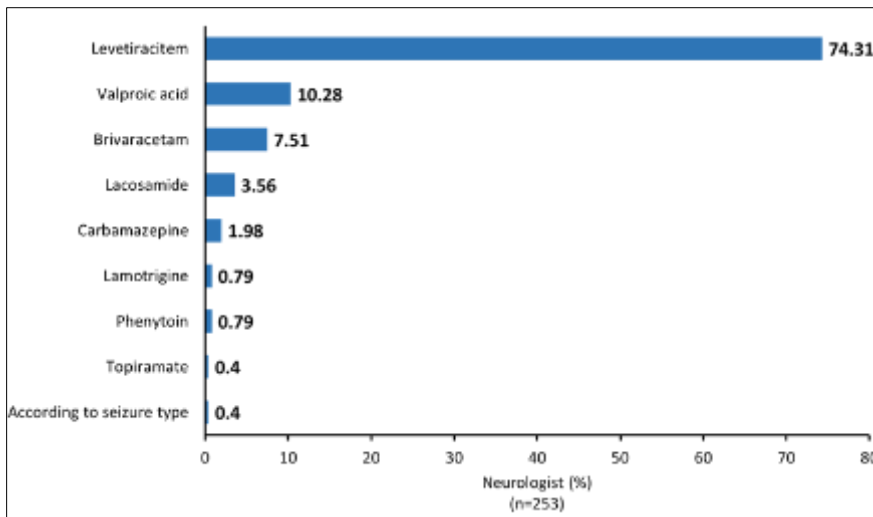
The majority of neurologists (87.75%) prescribed levetiracetam as the preferred AED for women patients of reproductive age with focal epilepsy, and 84.98% preferred it for generalized epilepsy. Levetiracetam was also the predominant choice among 73.91% of neurologists prescribing AEDs to pediatric female patients with epilepsy. Levetiracetam was the top AED prescribed by neurologists, with 70.36% recommending it for elderly women patients with focal or generalized epilepsy, 86.56% for women patients with epilepsy during pregnancy, and 85.38% for women epileptic patients who were breastfeeding (Table 2).

Table 2 Prescribing pattern of AEDs in WWE (N=253)

Women patients group	Levetiracetam	Brivaracetam	Lamotrigine	Lacosamide	Valproic Acid	Topiramate	Carbamazepine	Phenytoin
<i>Reproductive age (15 to 49 years)</i>								
Focal epilepsy	222(87.75)	6 (2.37)	10 (3.95)	10 (3.95)	1 (0.40)	2 (0.79)	1 (0.40)	1 (0.40)
Generalized epilepsy	215 (84.98)	13 (5.14)	11 (4.35)	4 (1.58)	5 (1.98)	2 (0.79)	1 (0.40)	2 (0.79)
<i>Pediatric</i>								
Focal/generalized epilepsy	187 (73.91)	11 (4.35)	10 (3.95)	11 (4.35)	20 (7.91)	1 (0.40)	12 (4.74)	1 (0.40)
<i>Elderly (> 50 years)</i>								
Focal/generalized epilepsy	178 (70.36)	26 (10.28)	7 (2.77)	19 (7.51)	16 (6.32)	0	6 (2.37)	1 (0.40)
<i>Special Population</i>								
Pregnancy	219 (86.56)	3 (1.19)	16 (6.33)	7 (2.77)	2 (0.79)	1 (0.40)	3 (1.19)	2 (0.79)
Breastfeeding	216 (85.38)	7 (2.77)	7 (2.77)	9 (3.56)	6 (2.37)	0	5 (1.98)	2 (0.79)

Data presented as n (%); AED, antiepileptic drugs; WWE, women with epilepsy

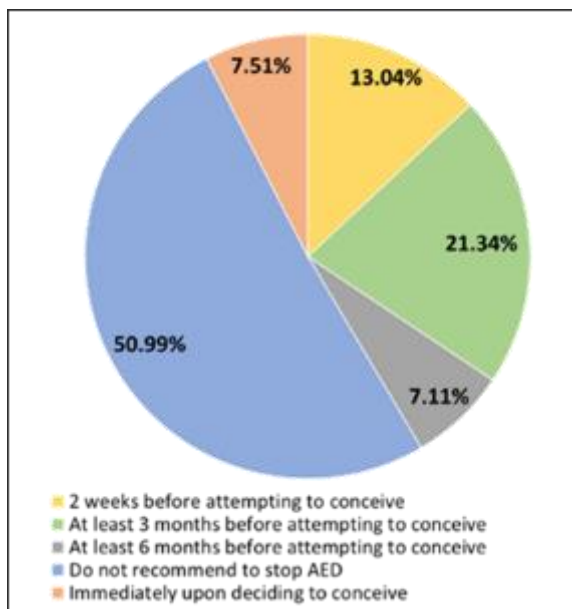
Due to its high efficacy and tolerability, 74.31% of neurologists predominantly recommended levetiracetam for male partners with epilepsy (Figure 1).



AED, antiepileptic drugs

Figure 1 Preferred AED for male partners suffering from epilepsy

The majority of neurologists (50.99%) did not recommend discontinuation of AEDs in male partners. Among those who recommended stopping AEDs, 21.34% of neurologists advised discontinuing the medication at least 3 months before attempting to conceive, while 13.04% suggested stopping it 2 weeks prior to conception (Figure 2).



AED, antiepileptic drugs

Figure 2 Timing for discontinuing of AEDs in male partners to enhance fertility (N=253)

Approximately 47.83% of neurologists managed breakthrough seizures in WWE by increasing the dosage of levetiracetam, while 43.48% chose to maintain add-on therapy with the appropriate AED (Figure 3).

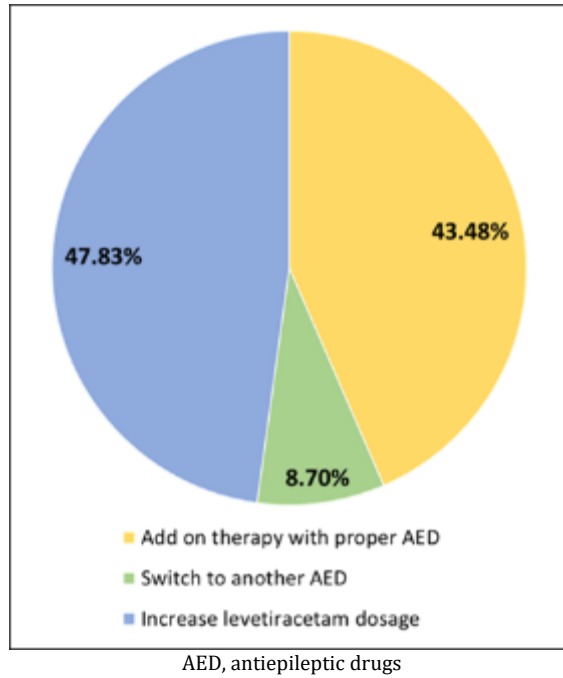


Figure 3 Management strategies for breakthrough seizures in women on levetiracetam monotherapy (n = 253)

For the management of WWE who intend to conceive while on levetiracetam, 56.13% of neurologists recommended continuing levetiracetam therapy throughout pregnancy, 29.64% suggested adjusting the dosage during pregnancy, 7.51% recommended switching to a different AED before conception, and only 6.72% recommended tapering and discontinuing levetiracetam prior to conception (Figure 4).

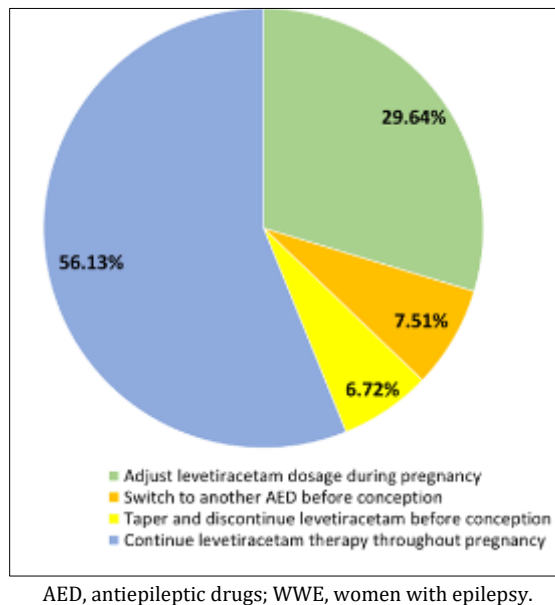
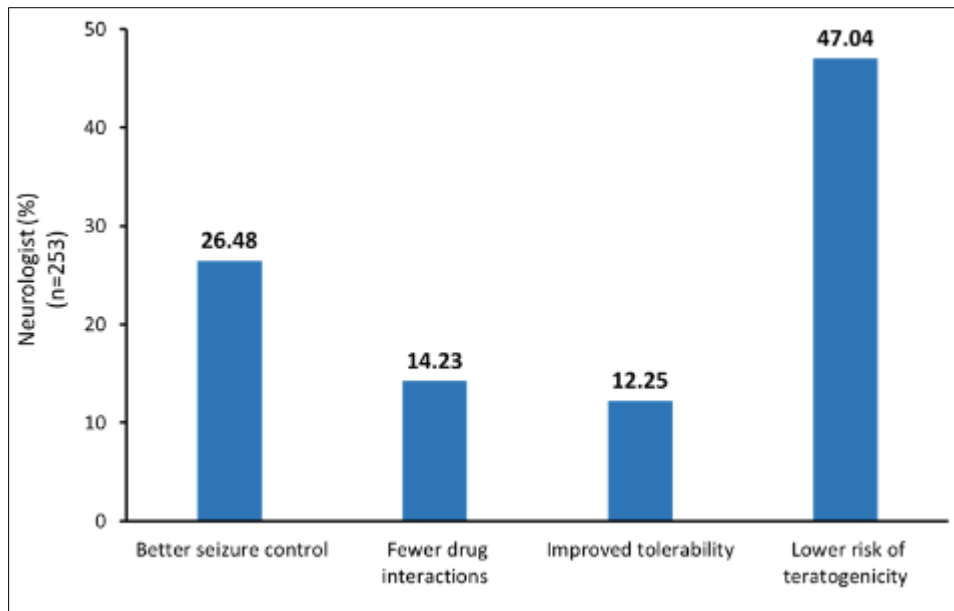


Figure 4 Management of WWE planning pregnancy on levetiracetam (N=253)

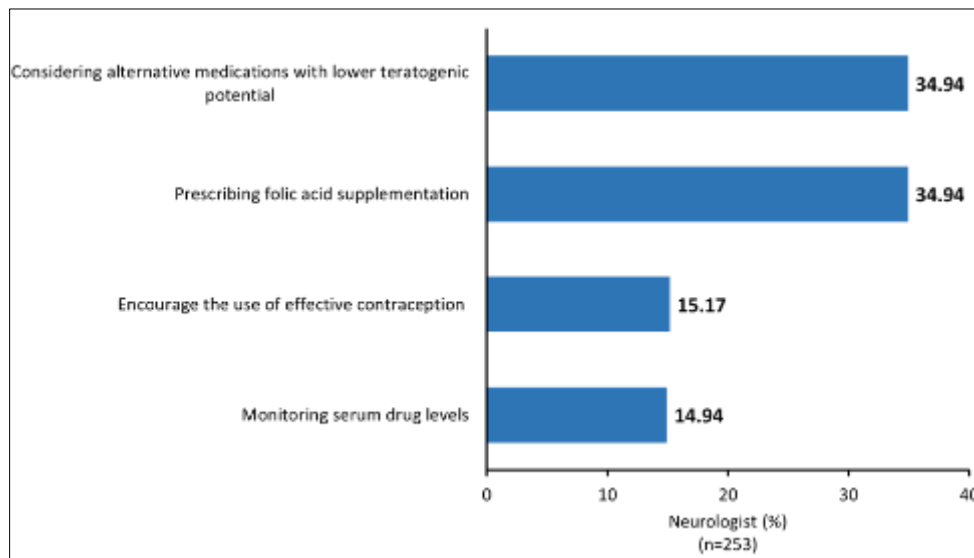
About 47.04% of neurologists preferred levetiracetam for treating WWE due to its advantage in lowering the risk of teratogenicity, followed by 26.48% who cited better seizure control, 14.23% who believed it offered minimal drug-drug interactions, and 12.25% who considered its improved tolerability as a key benefit (Figure 5).



WWE, women with epilepsy.

Figure 5 Advantages of prescribing levetiracetam for WWE

To reduce the teratogenic risk, 34.94% of neurologists consider alternative medications with lower teratogenic potential, while 34.94% consider folic acid supplementation. Additionally, 15.17% of neurologists encourage the use of effective contraception, and 14.94% focus on monitoring serum drug levels (Figure 6).



WWE, women with epilepsy.

Figure 6 Strategies to mitigate teratogenic risks in WWE of reproductive age (N=253)

Behavioral changes are the most frequent side effect reported by 34.11% of neurologists, followed by irritability (25.85%), dizziness (21.40%), and fatigue (12.29%).

4. Discussion

Levetiracetam a preferred option for managing epilepsy in WWE due to relatively low teratogenic risk and minimal interactions with hormonal contraceptives. However, there is a significant gap in research on real-world practice patterns in India regarding the management of WWE during pregnancy. The present study aimed to analyze and evaluate the factors influencing the usage of AEDs in WWE and their overall management. The principal observations of this study were: a) Levetiracetam emerges as the preferred antiepileptic AED among neurologists for women of

reproductive age. b) The preference for levetiracetam can be attributed to several key advantages, including low teratogenic risk, better seizure control, minimal drug-drug interactions, and greater tolerability. c) The most frequently reported side effect of levetiracetam was behavioral changes, followed by irritability, dizziness, and fatigue.

In current study, levetiracetam was emerging as a preferred AED among women of reproductive age, as evidenced by multiple studies. A Canadian perspective study highlighted that lamotrigine and levetiracetam were the most frequently selected AEDs for both focal and generalized epilepsy during pregnancy. Furthermore, the majority of practitioners (85.9%) conducted therapeutic drug monitoring during pregnancy, and nearly all (96.2%) counseled WWE on the benefits of switching from valproic acid to less teratogenic alternatives [12]. In Germany, a longitudinal analysis showed that lamotrigine prescriptions remained stable, while the use of carbamazepine and valproate significantly decreased among women of reproductive age. Meanwhile, levetiracetam monotherapy prescriptions surged from 6.6% to 30.4%, whereas lamotrigine prescriptions held steady [13]. A Polish study analyzing trends from 2015 to 2019 revealed a similar shift toward prescribing less teratogenic AED for WWE, with a notable rise in the use of newer AEDs such as lamotrigine, levetiracetam, and topiramate [14].

A study on five patients with catamenial seizures showed a positive response to intermittent levetiracetam therapy, with 67% responding to 0.5g twice daily and 33% requiring 0.75g twice daily. This supports its effectiveness in managing catamenial seizures [15]. Another study found levetiracetam to have similar efficacy and safety as valproic acid in treating genetic generalized tonic-clonic seizures and juvenile myoclonic epilepsy, making it a suitable alternative, especially for women of reproductive age [16].

Levetiracetam has emerged as a preferred AED due to several key advantages over other AEDs. It offers lower teratogenic risk, better seizure control, and improved tolerability, making it particularly favorable for women of childbearing age and during pregnancy [17,18]. Levetiracetam pharmacokinetics are favorable, showing complete bioavailability, no hepatic metabolism, and minimal interaction with other drugs, unlike first-generation AEDs. It does not require routine therapeutic drug monitoring and has less impact on cognitive functioning [19-21]. These properties may make levetiracetam more suitable for use in child bearing years and during pregnancy. In line with current study, exposed pregnancies, confirms a low risk for major congenital malformations (MCM) with levetiracetam monotherapy use in pregnancy [22]. Studies demonstrated that levetiracetam carries a lower risk of major congenital malformations in infants born to WWE compared to other AEDs. One prospective cohort from the EURAP registry confirmed that MCM risks with levetiracetam, lamotrigine, and oxcarbazepine were comparable to those in unexposed pregnancies [23]. A pooled analysis of 26 studies found that MCM rates were lowest with levetiracetam, followed by lamotrigine and carbamazepine, with phenobarbital and valproate having higher risks [24]. One study was designed to evaluate the influence of levetiracetam on the pharmacokinetics of oral contraceptives pills (OCPs). Levetiracetam did not affect the pharmacokinetics or efficacy of OCPs. In a study of healthy women taking OCPs, levetiracetam did not interfere with the levels of ethinyl estradiol and levonorgestrel, nor did it alter contraceptive effectiveness based on progesterone and luteinizing hormone levels. This made levetiracetam a safer option for women of reproductive age [25].

Behavioral changes were the most frequently reported side effect, followed by irritability, dizziness, and fatigue. Levetiracetam was highly regarded for its favorable safety profile and ease of use as an AED. Its minimal protein binding and limited metabolism by the hepatic cytochrome P450 system made it convenient, reducing the likelihood of drug interactions and the need for extensive monitoring that was often required with other AEDs. These symptoms were generally manageable but could lead to discontinuation if they persisted beyond the initial titration phase [26, 27]. Though the drug was relatively well tolerated, neuropsychiatric side effects could emerge beyond the initial titration period and were often the most common reason for drug discontinuation. The exact mechanism by which levetiracetam caused neuropsychiatric side effects remained unclear. Nevertheless, studies suggested that the relationship between the medication and these symptoms was not dose-dependent. This implied that while the severity of side effects did not necessarily increase with dosage, they could still occur at various levels of treatment [27].

Limitations

Responses were based on neurologists' perceptions and practices, susceptible to self-reporting errors or subjective interpretations.

5. Conclusion

The survey outcomes shed light on the prescribing trends, challenges, and strategies that neurologists use when managing WWE. The survey highlights a strong preference among neurologists for levetiracetam in treating WWE across various patient groups. This preference was due to its favorable safety profile and effectiveness in treating both

focal and generalized epilepsy. Levetiracetam's lower risk of teratogenicity, compared to older AEDs like valproic acid, carbamazepine, and phenytoin, makes it particularly attractive for women planning to become pregnant. When selecting AEDs for WWE, it's essential for clinicians to consider the potential for teratogenicity, or the risk of causing fetal malformations. Hence, it is evident that neurologists consider multiple criteria when selecting AEDs for WWE, with safety being a key factor.

Compliance with ethical standards

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Disclosure of conflict of interest

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