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Research Article

Efficacy and Safety of Zonisamide as Initial Monotherapy in Indian Patients with Epilepsy: A Subgroup Analysis of Prospective, Multicentre, Post-marketing Surveillance Study

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Abstract

Introduction: As very limited clinical data is available in Indian patients with Zonisamide initial monotherapy, a subgroup analysis of data from a prospective, post-marketing. A surveillance study was conducted to evaluate the efficacy and safety of Zonisamide as initial monotherapy in Indian adult patients.

Methods: A total of 655 patients were enrolled in a post-marketing surveillance study across 30 centers in India, out of which Zonisamide initial monotherapy was administered to 137 patients. This subgroup data were evaluated on the primary and secondary endpoints: median percentage reduction in seizure frequency and percentage responder rate and seizure-free patients over 24 weeks.

Results: Compared to baseline, the maximum percentage change in seizure frequency reduction was 90.98% at 24 weeks. The percentage of patients achieving overall responder rate and seizure freedom rate at 24 weeks was 84.67% and 59.12% respectively, whereas the percentage of patients achieving seizure freedom in focal impaired awareness (complex partial) and generalized motor (tonic-clonic) seizures was 64.10% and 66.67% respectively at 24 weeks. The most commonly reported adverse event was the loss of appetite in 13.87% of patients which was mild to moderate intensity, but 99.10% of patients had excellent tolerability to Zonisamide initial monotherapy.

Discussion: Because of the added clinical advantage in special patient populations, Zonisamide could be considered as a potential initial monotherapy drug for the treatment of focal onset and generalized seizures.

Keywords: Zonisamide; Monotherapy; Responder Rate; Focal Onset Seizures; Generalized Seizures

Introduction

Epilepsy is considered to be a serious neurological disorder in which almost 80% of people with epilepsy (PWE) are from low and middle-income countries viz: Southeast Asia, Latin America, and sub-Saharan Africa. Published evidence suggests that the incidence and prevalence of epilepsy in India is 38 - 60 person/lakh and 3 - 11.9/lakh population respectively [1].

Since the early 20th century, standard anti-epileptic drugs (AEDs) (Phenytoin, Phenobarbital, Primidone, Valproic Acid, Carbamazepine, and Ethosuximide) were commonly used as monotherapy and polytherapy too due to its firm belief that polytherapy was more effective than monotherapy in reducing seizure frequency and achieving seizure freedom in patients. A few years later due to abundant clinical evidence which was generated based on clinical trials, it was suggested that Zonisamide monotherapy is equally effective, less toxic, and more tolerable than polytherapy [2,3].

Despite more than 17 AEDs that are available for the last 35 years, yet seizure freedom is difficult to achieve in PWE. It would be inappropriate in such circumstances to suggest any particular AED which is completely effective, without any adverse effects, and efficacious for all patients. Many clinicians often prescribe the first generation AEDs in drug naïve patients because of their rich clinical experience and familiarity with the conventional AEDs, limited comparative studies with newer AEDs, and concern over the higher cost of newer AEDs.

But since the introduction of second-generation AEDs, there is an additional advantage of desirable safety profile and fewer adverse events and drug interactions than the predecessors along with its monotherapy use.

Since then controlling the seizures with better safety and tolerability remains the most crucial goal for epilepsy management. Considering these significant benefits, monotherapy is being preferred approach (as the chance of being seizure-free is highest with the first AED and it declines with the number of AED regimens) [4] in epilepsy management along with sequential appropriate polytherapy. Reported clinical evidence has shown better efficacy of an AED when given as monotherapy in drug naïve patients [5]. Monotherapy help to improve patient's compliance and avoids drug interactions with other AEDs [6].

Currently, there is an ever-increasing armamentarium of newer AED's as monotherapy, because of which selection of an appropriate monotherapy drug becomes challenging especially in special patient populations including pregnant women, childbearing age women, elderly, and those with co-morbid conditions (who are at increased risk for AED toxicity and drug interactions) [7-9].

Zonisamide, a benzisoxazole derivative, is approved as an adjunctive and monotherapy in focal onset seizures in Indian adult patients, but multiple clinical evidence shows its acceptance as only adjunctive therapy in various forms of epilepsy and very few trials demonstrate its efficacy and safety in monotherapy. Zonisamide is considered to be the preferred AED because of its long half-life (63-69 hours) which allows once-daily dosing [10] and a broad spectrum of action which enhances adherence to therapy. Clinical evidence suggests that Zonisamide in focal onset seizures (FoS) has a good treatment potential as monotherapy with International League Against Epilepsy (ILAE) level A evidence [11] and clinically non-inferior to Carbamazepine. Most of these studies were conducted as initial monotherapy in newly diagnosed patients in the USA and Europe which included patients with focal onset seizures with or without focal to bilateral tonic-clonic seizures [12].

Reported evidence shows that two long term studies on Zonisamide monotherapy have distinctly demonstrated the retention rate in generalized and focal onset seizures for up to 6 years

which is comparable to Lamotrigine, Levetiracetam, and Topiramate [13] and safety and efficacy in newly diagnosed and AED resistant epilepsy for up to 180 months (15 years) [14]. However, there is limited clinical data on the use of Zonisamide monotherapy in Indian patients in different types of seizures. In this subgroup analysis study, the efficacy and safety of zonisamide initial monotherapy were evaluated.

Methods

This is a subgroup analysis of data from a post-marketing surveillance study (NCT01283256) [15] which was a prospective, multicentre, open-label, non-comparative, post-marketing surveillance study conducted across 30 centers in India. Total 655 patients with focal onset (focal aware, focal impaired awareness, and focal to bilateral tonic-clonic), generalized onset (generalized motor and non-motor seizures), or combined seizures, satisfied all the inclusion/exclusion criteria for enrolment in the study. At the start of therapy, Zonisamide was administered as initial monotherapy in 137 patients (20.92%) and add-on therapy in 518 patients (79.08%). A further subgroup analysis was conducted for patients who were only on Zonisamide initial monotherapy. Available data corresponding to certain specific and clinically relevant parameters was captured at regular time points (baseline, 4, 8, 12, 16, 20, and 24 weeks) from the patients who were on Zonisamide initial monotherapy. An evaluation was done based on two endpoints: Primary efficacy endpoint which was the median percentage reduction in seizure frequency over 24 weeks. The secondary efficacy end-points were percentage responder rate and seizure-free patients over 24 weeks. Zonisamide was administered as 100 mg tablets once daily before bedtime. Seizure activity was recorded by the subject or relative/caretaker in the patient diary provided, from day 1 through the end of the study. The dose was up- titrated by 100 mg every 2 weeks in each patient till the time it reached the maintenance dose. The maximum dose recommended and allowed was up to 600 mg, whereas the mean dose over 24 weeks was 164.67 mg. Data of patients who were having a seizure at baseline and those who were seizure-free after study completion were analyzed using paired t-test. Two populations were used for analysis i.e. intent to treat (ITT) population, corresponding to all included patients who met the eligibility criteria, and the per-protocol (PP) population, corresponding to all patients in the ITT population who completed the study. For all statistical tests, a P-value equal to 0.05 was considered significant. The Clinicians Global Assessment of Response to Therapy (CGART) was assessed by the clinician on a seven-point scale as compared to baseline rated as follows: 1= excellent response, 2= good response, 3= average response, 4= no response, 5= minimally poor response, 6= poor response, and 7= very poor response [16].

Adverse events, either spontaneously reported by the patients, or noted by the physician occurred during the study were recorded. Patient Global Assessment of Tolerability to Therapy (PGATT) was assessed by the patient on a four-point rating scale as follows: 1= excellent tolerability, 2= good tolerability, 3= average tolerability, and 4= poor tolerability [17].

The study was conducted under the ethical code of conduct laid out by the Declaration of Helsinki, Good Clinical Practice guidelines, and Indian Council of Medical Research guidelines. The protocol and statement of informed consent were approved by the Institutional Ethics Committee of each center. Details of the study population, efficacy assessments, safety and tolerability assessments, treatment, compliance, and ethical issues are explained in the post-marketing surveillance study [15].

Results

Baseline characteristics

Overall, 655 patients were randomized in post-marketing surveillance study [15], of whom 137 patients were administered Zonisamide initial monotherapy (ITT population). The demographic characteristics and clinical features of the study population are given in table 1. 112 patients completed the 24-week study period (PP population), whereas 25 discontinued the study (Table 2). Median seizure frequency at baseline was three seizures/month and the mean duration of epilepsy in patients was approximately 5 years.

Efficacy

Seizure frequency reduction was statistically significant at each follow-up visit compared to baseline ($P < 0.0001$), with a maximum percentage change of -90.98% (-70.32 at week 4 to -90.98 at week 24) ($P < 0.0001$, Figure 1) and mean change in seizure frequency of

Table 1: Demographic and clinical features of study subgroup.

	Total population (N=137)
Age, mean ± SD (years)	33.19 ± 13.70
Sex, n (%)	
Male	85 (62.04%)
Female	52 (37.96%)
Past medical history, n (%)	
Epilepsy	5 (3.65%)
Psychiatric disorders	0
CVA	1 (0.73%)
Allergy	0
Valproate allergy	0
Hypertension	9 (6.57%)
CVD	2 (1.46%)
Diabetes	5 (3.65%)
Alcohol	2 (1.46%)
Smoking	3 (2.19%)
Hypercholesterolemia	1 (0.73%)
CHD	1 (0.73%)
Seizure type, n (%)	
Focal Aware (simple partial)	14 (10.22%)
Focal Impaired Awareness (complex partial)	39 (28.47%)
Focal to bilateral tonic-clonic (secondarily generalized)	28 (20.44%)
Generalized motor (tonic-clonic)	33 (24.09%)
Generalized motor (tonic)	8 (5.84%)
Generalized non-motor (atypical absence)	0
Mixed Seizures	15 (10.95%)
Duration of epilepsy (months), n (%)	
0 - 12	69 (50.36%)
12 - 24	16 (11.38%)
24 - 36	10 (7.30%)
36 - 48	6 (4.38%)
48 - 60	2 (1.46%)
> 60 months	34 (24.82%)
Seizure frequency	3 seizures/month
Seizure features, n (%)	
Pre-ictal phase	38 (27.74%)
Consciousness impaired	99 (72.26%)
Motor symptoms	90 (65.69%
Sensory Symptoms	30 (21.90%)
Autonomic symptoms	19 (13.87%)
Psychic symptoms	11 (8.03%)

Abbreviations: SD - standard deviation, CVD - cerebrovascular disorders, CVA - cerebrovascular accidents, N – total number of patients, intent to treat population; n – number of patients, % percentage of patients

Table 2: Data disposition of the study.

	No. of patients (n)
Total enrolled	137
Total discontinued/lost to FU	25
Adverse Events	1
Error in medication	3
Lost to follow up	12
Patients request	2
Screening failure	0
Pregnancy (SAE)	0
Other reasons (unspecified)	7
Total completed study	112
Intent-to-teat (ITT) population (safety analysis population)	137
Per-protocol (PP) population (efficacy analysis population)	112

Abbreviations: FU: Follow Up, SAE: Serious Adverse Events.

-2.80 at 24 weeks (-2.16 at week 4 to -2.80 at week 24). Mean seizure frequency at baseline was 3.07, whereas it was 0.28 at week 24.

In the ITT population, 88.28% of patients showed a significant reduction in seizure frequency at week 24, whereas 11.72% of the patients showed no statistically significant change. In the PP population, approximately 94.34% of the patients showed a statistically significant reduction in the seizure frequency and approximately

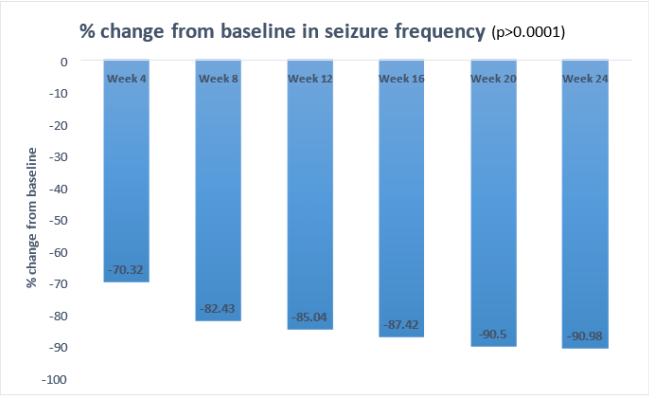

Figure 1: Percentage change from baseline in seizure frequency (ITT population).
Abbreviations: p value > 0.0001 statistically significant.

5.66% of the patients showed no significant change in seizure frequency at 24 weeks.

Compared to baseline, 84.67% of the patients achieved overall responder rate (defined as a percentage of patients whose seizure frequency decreased by ≥ 50% compared with baseline) and 79.56% of the patients achieved cumulative responder rate since baseline; whereas 89.05% of the patients achieved cumulative seizure freedom since baseline at 24 weeks with Zonisamide initial monotherapy (Figure 2).

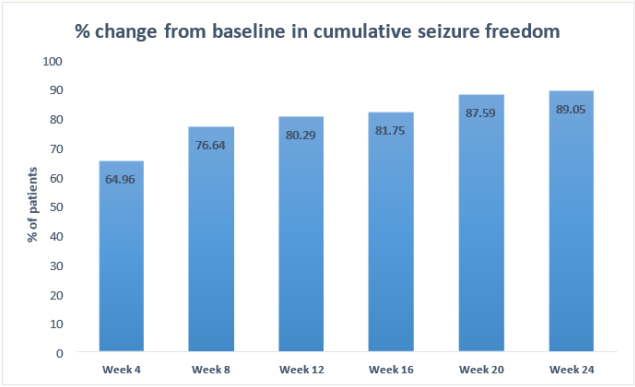

Figure 2: Percentage change from baseline in cumulative seizure freedom (ITT population).

The majority of the patients had focal impaired awareness seizures (n = 39) and generalized motor (tonic-clonic) (n = 33) followed by focal to bilateral tonic-clonic (n = 28) of which 64.10%, 66.67%, and 50% of patients achieved seizure freedom respectively at the end of 24 weeks. Overall seizure freedom was achieved by 59.12% of patients at 24 weeks (Table 3).

Table 3: Seizure freedom at 24 weeks in different seizure types (ITT population)

Seizure Type	Patients (n)	% of patients
Focal Aware	07/14	50.00
Focal Impaired Awareness	25/39	64.10
Focal to bilateral tonic-clonic	14/28	50.00
Generalized motor (tonic-clonic)	22/33	66.67
Generalized motor (tonic)	02/08	25.00
Mixed seizures	11/15	73.33
Total	81/137	59.12

At 24 weeks, the investigator-assessed CGART was "good to excellent" in 99.09% of patients receiving Zonisamide therapy (Figure 3).

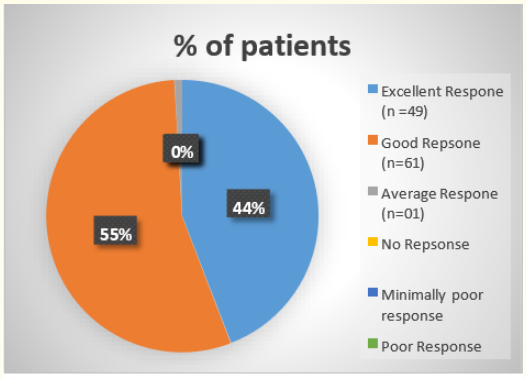

Figure 3: Clinicians Global Assessment of Response to Therapy (CGART) at week 24, (PP population, N-111.
Abbreviations: %: Percentage of Patients; n: Number of Patients; N: Total Number of Patients.

Safety and tolerability

A total of 33 patients (24.09%) reported adverse events in the ITT population (Table 4). The most common reported adverse event was a loss of appetite (13.87%). Other adverse events which were reported are weight loss in 6 patients (4.38%), dizziness in 3 patients (2.19%), and sedation in 2 patients (1.46%). Rash (0.73%), viral fever (0.73%) and aggressive behaviour and sleep disturbance (0.73%) were reported in one patient each. The majority of these events were of mild-to-moderate intensity. No reports of death, disability, clinically relevant metabolic acidosis or oligohydrosis, the incidence of kidney stone. No hospitalization was required for any of the adverse events. One patient (0.73%) discontinued therapy due to adverse events. The tolerability of Zonisamide assessed by patients on a four-point PGATT scale was "good" to "excellent" in 99.10% of the patients at 24 weeks (Figure 4).

Table 4: Adverse events (AEs) reported during the study n=137, (ITT population).

Serial No.	Adverse Events	n (%)
1	Loss of appetite	19 (13.87%)
2	Weight Loss	06 (4.38%)
3	Dizziness	03 (2.19%)
4	Sedation	02 (1.46%)
5	Rash	01 (0.73%)
6	Viral Fever	01 (0.73%)
7	Aggressive behaviour and sleep disturbance	01 (0.73%)
	Total patients with AE	33 (24.09%)

Abbreviations: n: Number of Patients;%: Percentage of Patients.

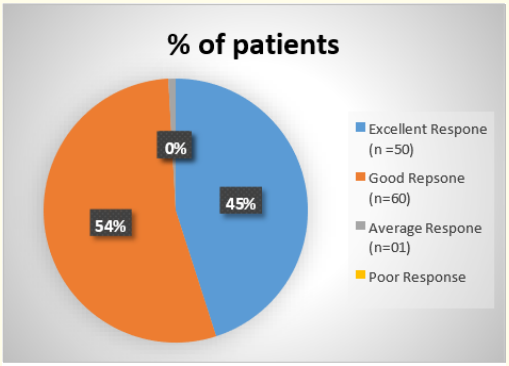

Figure 4: Patients Global Assessment of Tolerability to Therapy (PGATT) at week 24 (ITT population, N- 111).
Abbreviations: %: Percentage of Patients; n: Number of Patients; N: Total Number of Patients.

Discussion

In India, Zonisamide has been approved as monotherapy and adjunctive therapy in patients with primary generalized seizures and focal onset seizures. Zonisamide is approved and recommended by the updated International League against Epilepsy recommendation (ILAE) monotherapy guidance as it has level A evidence of efficacy/effectiveness as initial monotherapy for the treatment of adults with focal onset [11]**.** Currently only a few AEDs have level A evidence such as Carbamazepine, Levetiracetam, and Phenytoin.

The therapeutic outcomes of epileptic patients majorly depend on the first drug. Brodie., *et al*. showed in two studies that patients respond well when treated with monotherapy, approximately 47% of patients achieved seizure freedom with the first AED than the second AED as monotherapy [18]. In the second study which was a hospital-based observational study, it was evident that as many as 49.5% of patients were seizure-free with the first drug than the second drug (36.7% of the patients) [4]. But not all monotherapy drugs may be effective in a certain group of patients such as Phenytoin or Carbamazepine in the elderly [4,19], (risk of adverse effects such as osteoporosis) or valproate in women of childbearing age [7]. AEDs such as Carbamazepine, Phenytoin, Phenobarbital, Oxcarbazepine, and high dose Topiramate which are enzyme inducers may lead to therapeutic failure of other drugs in comorbid patients [20].

In the main trial, post-marketing surveillance study (NCT01283256) [15], it was observed that compared to baseline seizure frequency reduction was statistically significant with a reduction of 91.5% at week 24 ($P < 0.0001$), whereas responder rate was 78.06% and approximately 41.22% of the patients achieved seizure freedom at 24 weeks of Zonisamide therapy (initial monotherapy and add on). In the ITT population, the percentage of patients who showed some significant reduction in seizure frequency was 93%, whereas, In the PP population, approximately 95% of the patients showed a statistical reduction in the seizure frequency. In contrast to the main trial, in this subgroup analysis of Zonisamide initial monotherapy patients, the primary efficacy endpoint was statistically significant compared to baseline ($P < 0.0001$), with 90.98% patients achieving seizure frequency reduction, whereas responder rate was 84.67% and patients who achieved cumulative and overall seizure freedom was 89.05% and 59.12% respectively at 24 weeks. Overall responder rate and seizure freedom was found

Table 5: Overall Responder rate and Seizure freedom of Zonisamide from post marketing surveillance study (NCT01283256) and subgroup data at 24 weeks.

Patients	Monotherapy and Add on (655 patients)	Only Initial Monotherapy (137 patients)
Overall Responder Rate (%)	78.06%	84.67%
Overall Seizure Freedom (%)	41.22%	59.12%

Abbreviations: %: Percentage of Patients.

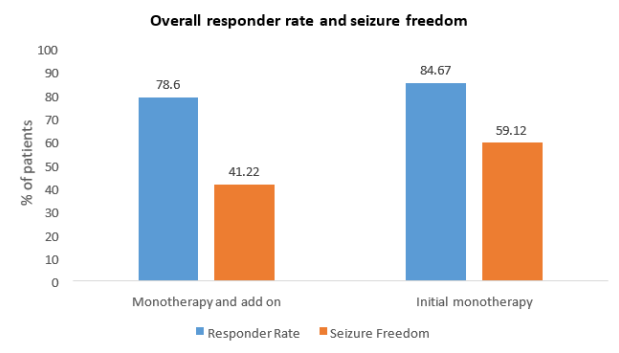

Figure 5: Overall Responder rate and Seizure freedom of Zonisamide from post marketing surveillance study (NCT01283256) and subgroup data at 24 weeks.

to be better with initial monotherapy than adjunctive therapy (Table 5, Figure 5). Tosches., *et al*. [21] demonstrated the long-term effects of Zonisamide as monotherapy or adjunctive therapy on 90 patients (n = 45 monotherapy, n = 45 adjunctives). In this study, seizure freedom was achieved by 28% and 14% of patients who were on monotherapy and adjunctive therapy, respectively. Lu yang., *et al*. [22] demonstrated the efficacy and safety of adjunctive Zonisamide in focal onset seizure patients in 104 patients for 16 weeks, which showed a significant responder rate of approximately 55% in these patients.

Also, it was evident from this subgroup analysis that seizure freedom and responder rate of Zonisamide initial monotherapy was better than with individual concomitant therapy (Table 6, Figure 6). Because of this useful clinical advantage, Zonisamide could be considered as an initial monotherapy drug.

Table 6: Responder rate and seizure freedom of Zonisamide initial monotherapy and individual concomitant therapy 15 at 24 weeks.

	ZNS + CBZ	ZNS + VAL	ZNS + PHY	ZNS + LEV	ZNS initial monotherapy
Responder rate (%)	69.64%	89.51%	67.01%	79.35%	84.67%
Seizure Freedom (%)	30.4%	33.64%	44.9%	35.9%	59.12%

Abbreviations: %: Percentage of Patients; ZNS: Zonisamide; VAL: Valproate; PHY: Phenytoin; LEV: Levetiracetam.

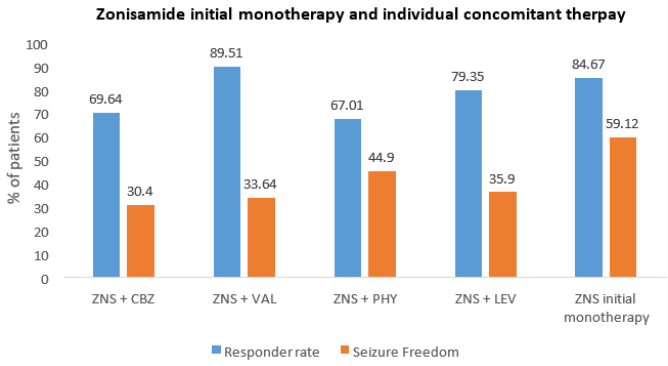

Figure 6: Overall responder rate and seizure freedom of Zonisamide initial monotherapy and individual concomitant therapy [15] at 24 weeks.
Abbreviations: %: Percentage of Patients; ZNS: Zonisamide; VAL: Valproate; PHY: Phenytoin; LEV: Levetiracetam.

The other studies which were conducted for 24 weeks according to current study criteria were the Levetiracetam versus controlled-release Carbamazepine [23] and Zonisamide versus controlled-release Carbamazepine trial [24].

In the first study [23], a phase III multicentre, double-blind, non-inferiority, parallel-group trial, Brodie., *et al*. compared efficacy and safety of Levetiracetam (500 mg twice daily, n = 288)

and controlled - release Carbamazepine (200 mg twice daily, n = 291) monotherapy for 26-52 weeks in adults with newly diagnosed focal onset epilepsy. The study showed that 73% of patients were free of seizures at 26 weeks in the Levetiracetam group, as compared to 72.8% of patients in the Carbamazepine group. In the second study [24], a Phase III multicentre randomized-controlled trial, Baulac., *et al*. compared efficacy and safety of Zonisamide 300 mg/day and Carbamazepine 600 mg/day monotherapy for 26-78 weeks in adults with newly diagnosed focal onset epilepsy. The study showed that 79.4% of the patients were free of seizures at 26 weeks in the Zonisamide group, as compared to 83.7% of the patients in the Carbamazepine group. Based on the reported findings from these two Phase III studies and our subgroup analysis data it is clear that Zonisamide offers comparable efficacy to Levetiracetam and Carbamazepine but better tolerability in patients with epilepsy.

The overall efficacy with Zonisamide treatment assessed by the clinician on a seven-point CGART scale was "good" to "excellent" in 99.09% of the patients, whereas the tolerability of Zonisamide assessed by patients on a four-point PGATT scale was "good" to "excellent" in 99.10% of the patients at week 24.

With regards to safety and tolerability, this study demonstrated that Zonisamide was well tolerated, with adverse effects reported in approximately 24% which were mild-to-moderate intensity. This rate was lower than that reported in previous randomized-controlled trials and observation studies [23,24]**.** The most commonly reported adverse event was a loss of appetite (13.87%) along with other less common were weight loss, dizziness, sedation, rash, viral fever, aggressive behavior and sleep disturbance. No reports were recorded of any deaths, disability, metabolic acidosis, or hospitalization due to adverse events. Zonisamide has a mild inhibitory effect on carbonic anhydrase that might lead to loss of renal bicarbonate and metabolic acidosis [25]. According to the North American AED Pregnancy Registry [26], it was observed that there is an increased risk of major congenital malformations (MCMs) among AEDs which are used during pregnancy. This report suggests that the risks of malformations for "newer generation" AEDs (Lamotrigine, Levetiracetam, Zonisamide, Clonazepam, and Oxcarbazepine) in monotherapy are lower than the risks of malformations for other traditional AEDs (Valproate, Phenobarbital, Phenytoin, and Carbamazepine). In a subgroup analysis of elderly patients [27], it was observed that treatment-emergent adverse event rate (dizziness, somnolence, etc) was only 18% and a lower rate of severe adverse events as compared to young adults with Zonisamide monotherapy which favors its safety/tolerability.

There is limited evidence available on the efficacy and safety of Zonisamide monotherapy in Indian patients in the real-world clinical setting. As this subgroup analysis was of 24 weeks duration, long-term efficacy and safety of Zonisamide initial monotherapy could not be assessed. The difference observed in the responder rate and proportion of patients who achieved seizure freedom in this Zonisamide initial monotherapy subgroup data may be attributable to the inclusion of patients with less severe, long history of seizures and less refractory epilepsies in our study. Median seizure frequency at baseline was three seizures/month and the mean duration of epilepsy in patients was approximately 5 years in this study, which was lower than the studies conducted in real-world clinical settings. But irrespective of certain limitations such as not being long in duration, not conducted in newly diagnosed patients, and also a non-comparative study, the results from this subgroup analysis has provided some useful clinical information which could be of great help for the clinicians who still prefer or believe in the first generation AEDs as monotherapy.

Conclusion

Based on the clinical findings of this subgroup analysis data, it is evident that Zonisamide initial monotherapy is effective and well-tolerated AED in different types of seizures such as focal impaired awareness seizures, generalized motor (tonic-clonic) seizures, and focal to bilateral tonic-clonic in the Indian population which could be possibly due to its multimodal actions [28,29]. Reported evidence suggests that first-generation AEDs are associated with some side effects such as weight gain and risk of major congenital malformations, in contrast, Zonisamide is found to reduce appetite and help with weight loss and also has a low risk for malformations during pregnancy along with safety in the elderly group. Zonisamide is non-inferior to Carbamazepine as an adjuvant and is also well-tolerated as monotherapy for up to 15 years in situations

where first-generation AEDs have certain challenges in special patient populations. Since Zonisamide is not bound to have drug-drug interactions such as an oral contraceptive pill [30], and has the added clinical advantage of once-daily dosing, it could be considered by physicians as a potential initial monotherapy to achieve seizure control in their epileptic patients in real-world clinical settings.

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