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A 3.5-year clinical experience with perampanel for refractory epilepsy

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Abstract. – OBJECTIVE: This study aimed to evaluate the efficacy and tolerability of perampanel, which was used in a cohort of patients with refractory epilepsy for up to 3.5 years in a real-world setting in Saudi Arabia.

PATIENTS AND METHODS: Data from the medical records of patients treated with perampanel between March 13th, 2017, and September 6th, 2020, at neurology clinics at King Faisal Specialist Hospital and Research Centre (KFSHRC), Riyadh and Jeddah, Saudi Arabia, was collected. The Liverpool Adverse Events Profile (LAEP) scale was also used to measure the adverse effects of perampanel.

RESULTS: Of the 75 included patients, 66.7% responded to perampanel at the last follow-up, including 22.7% seizure-free for at least the last six months, and 44% of patients responded with a ≥ 50% reduction in seizure frequency from baseline. The overall incidence of adverse effects that led to perampanel discontinuation was 13.3%; the most common adverse effect was aggressive behavior followed by sedation. Pre-existing psychiatric comorbidity was significantly associated with the incidence of psychiatric and behavioral adverse effects on perampanel (p = 0.0206). The mean score of LEAP was 40. The most frequently rated adverse effects in LEAP were "feelings of anger and aggression to others", "nervousness and/or agitation" and "sleepiness". The efficacy and tolerability of perampanel were dose-dependent. Dose 6 mg/day was the most frequently used dose that was taken by about one-third of patients at their last visit.

CONCLUSIONS: Perampanel was effective as an adjunctive treatment for intractable seizures, with a responder rate of 66.7%. The long-term tolerability of perampanel was generally good. Aggressive behavior was the most common reason for perampanel discontinuation. Patients should be counseled and monitored for these adverse effects, particularly those with a history of previous psychiatric and behavioral problems.

Key Words:
Adjunctive therapy, Adverse effects, Aggression, Antiseizure medications, Efficacy, Liverpool Adverse Events Profile (LAEP).

Introduction

About one-third of patients with epilepsy are refractory to treatment[1]. Drug-resistant epilepsy remains a significant burden. It is associated with increased morbidity and mortality[2,3], reduced quality of life with physical, psychological, and social consequences[4,5], and great healthcare costs[6].

Despite the availability of various new antiseizure medications, the number of patients with refractory epilepsy has not substantially reduced in the last three decades[7,8]. Therefore, the development of new antiseizure medications with novel mechanisms of action that can manage intractable seizures is needed[9].

Perampanel is a first-in-class, non-competitive, selective amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor antagonist that inhibits the binding of glutamate to its post-synaptic AMPA receptors[10].

Preclinical studies, randomized clinical trials, and earlier observational studies[10-13] demonstrated that perampanel is a potentially broad-spectrum antiseizure medication with a novel mode of action that can be used as an additional treatment for patients with refractory epilepsy with different types of seizures. Perampanel is currently approved for both focal and generalized epilepsy, as

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monotherapy or adjunctive therapy, and for adults and children from the age of 4 years[14,15].

Perampanel was approved for focal seizures based mainly on the findings of three randomized, double-blinded, placebo-controlled Phase III trials[13,16,17], and for primary generalized tonic-clonic seizures (GTCs) in idiopathic generalized epilepsy based on the results of one randomized, double-blinded, placebo-controlled Phase III trial[18]. In 2020, perampanel was approved for children from the age of 4 years based on the findings of one open-label trial[19].

For a newly approved medication, it is necessary to study its efficacy and tolerability in real-world clinical practice. Real-world studies provide a bridge from the findings of clinical trials to routine practice by including different subgroups of patients, using dosage and titration that are patient-individualized rather than fixed dose protocols, and providing data on long-term outcomes[20,21].

For perampanel, there were several observational studies[22-25] from everyday clinical practice in different countries and regions. However, there were no such studies in Saudi Arabia. Perampanel has been available in Saudi Arabia since January 2017[26]. Therefore, the aim of this study was to evaluate the efficacy and tolerability of perampanel, which was used in a cohort of patients with refractory epilepsy for up to 3.5 years in a real-world setting in Saudi Arabia.

Patients and Methods

Study Design, Patients, and Setting

This was an observational, longitudinal cohort study. The study included patients who were treated with perampanel and followed-up prospectively during a 3.5-year period between March 13th, 2017, and September 6th, 2020, at neurology clinics at King Faisal Specialist Hospital and Research Centre (KFSHRC), Riyadh and Jeddah, Saudi Arabia. Patients with persistent non-adherence to perampanel were excluded from the study. KFSHRC is a tertiary medical center serving the central and western areas of Saudi Arabia.

Data Collection

Data collection included data extraction from patients' medical records using a structured pre-designed form. The Liverpool Adverse Events Profile (LAEP) scale was also used to measure the adverse effects of perampanel.

Demographic and clinical characteristics that were collected at baseline were as follows: year of birth, gender, intellectual disability, prior psychiatric comorbidity, number of prior antiseizure medication regimens, and number of concomitant antiseizure medications. Baseline epilepsy and seizure information included epilepsy type, etiology, and seizure type using the 2017 International League Against Epilepsy (ILAE) classification[27,28]; findings of magnetic resonance imaging (MRI) and electroencephalography (EEG) investigations; family history of epilepsy; seizure frequency at baseline; prior epilepsy surgery; and vagal nerve stimulation (VNS) implantation before perampanel initiation.

Data collected at each visit included the following: number and type of seizures, adverse effects, perampanel dose, and changes in concomitant antiseizure medication. At each clinical visit, physicians asked patients about seizure numbers and the adverse effects they experienced. Patients were strongly encouraged to use a seizure diary to record their seizures.

Patients and/or caregivers filled out the LEAP scale. The LEAP scale was filled once for each patient at the maintenance dose of perampanel during the study period. Permission to use the Arabic version of LEAP was taken from author Dr. Yazed Sulaiman AlRuthia[29]. LEAP is a validated and reliable patient-rated scale that measures the frequency of adverse effects of antiseizure medications experienced by patients with epilepsy within the past four weeks. LEAP consists of 19 items that measure both central nervous system (CNS) adverse effects (unsteadiness, tiredness, restlessness, feelings of anger and aggression toward others, nervousness and/or agitation, blurred vision, difficulty concentrating, dizziness, sleepiness, depression, memory problems), and non-CNS related side effects (headache, hair loss, skin problems, upset stomach, trouble with the mouth or gum, shaky hand, weight gain, disturbed sleep)[30]. LEAP is a 4-point Likert scale. Score 1 indicates the symptom is never a problem, 2 (rarely a problem), 3 (sometimes a problem), and 4 (always a problem). Therefore, the score of individual symptoms and the overall symptom score can be calculated.

Outcome Definitions

The study outcomes were efficacy, adverse effects, and dose of perampanel. Efficacy was assessed by measuring the reduction in seizure number after starting perampanel therapy

compared to that at baseline. Patients were categorized into responders and non-responders based on seizure outcomes at the last follow-up. Responders included seizure-free patients and those whose seizures were reduced by ≥ 50%. Seizure-free was defined as no seizure for the last six months or more. Non-responders were patients who achieved < 50% reduction in seizure number and those whose seizure numbers were increased.

The tolerability of perampanel was assessed by two methods. First, intolerable adverse effects that were reported by patients, evaluated by physicians, and documented in medical records as part of clinical practice. Study investigators evaluated these recorded adverse effects, and only perampanel-related adverse effects were included in the analysis. Intolerable adverse effects in this study were defined as adverse effects that led to perampanel discontinuation or dose reduction. Extracted adverse effects were grouped into the following groups: aggressive behaviors (aggression, agitation, anger, nervousness), sedation effects (drowsiness, lethargy, somnolence), psychosis (hallucination, delusion, psychosis), coordination problems (dizziness, blurred vision), loss of appetite, and others (mood swings, hair loss, bloating, skin rash, weight gain, dandruff). The second approach to tolerability assessment was by using the LEAP scale. The LEAP score of individual symptoms ranges from one to four; larger scores indicate a higher frequency of adverse effects. The overall symptom LEAP score ranges from 19 to 76. Adverse effects are considered mild to moderate if scores are ≤ 45, while scores > 45 are considered severe[29,31].

Perampanel dosage in mg/day at last follow-up, at discontinuation, and adverse effects were reviewed and analyzed. Reasons for perampanel discontinuation were documented and grouped as follows: lack of efficacy, intolerability, both lack of efficacy and intolerability, and others.

Ethical Approval

The IRB approval was obtained from the Research Ethics Committee at KFSHRC (RAC # 2191137). Informed written consent was obtained from patients or their legal representatives before they fill out the LEAP questionnaire. The objective and procedure of the study were described to the patient/caregiver. The patients or caregivers were informed that their participation in the study was voluntary, and they could withdraw at any time or refuse to answer any question without any consequences. The confidentiality of the patients was maintained during the study.

Statistical Analysis

Descriptive data was summarized as frequency (n) and percentage (%) for categorical variables and as mean (±SD, standard deviation) and [range] for continuous variables. Fisher's exact test was applied for comparison of proportions; it was used because the expected frequency was < 5. A p-value < 0.05 was considered significant. Microsoft Excel and GraphPad Prism 9.3.1 (GraphPad Software, San Diego, CA, USA) were used for data analysis.

Results

Demographic and Epilepsy Information of Patients

A total of 75 patients were included in this study. Patients' baseline characteristics are summarized in Table I. Patients' ages ranged from 3 to 72 years. Twenty-three patients had one or more prior psychiatric comorbidities as follows: depression and/or anxiety (n = 12), attention-deficit/hyperactivity disorder (ADHD) (n = 7), autism (n = 5), and psychosis (n = 3). The majority of patients (n = 59, 78.7%) had focal epilepsies. There were 13 patients who had myoclonic seizures with or without other seizure types. There were six patients with Lennox-Gastaut syndrome (LGS). The mean monthly seizure frequency at baseline was 61 (SD = 165.9). Twenty-nine (38.7%) patients had prior epilepsy surgery, and 14 (18.7%) patients had implanted VNS.

All included patients received perampanel as add-on therapy, and the most frequently concomitant antiseizure medications were levetiracetam (n = 36, 48%), valproate (n = 26, 34.7%), carbamazepine (n = 26, 34.7%), lamotrigine (n = 15, 20%), and topiramate (n = 18, 24%).

The majority of patients (73.3%) were taking perampanel for more than 12 months. The average duration of perampanel treatment was 1.6 years, ranging from one month to 3.3 years.

During the follow-up, 22 patients (29.3%) needed one or more hospitalizations due to seizures.

Perampanel Efficacy

As shown in Figure 1, out of 75 patients, 66.7% were perampanel responders at the last follow-up.

Table I. Demographic and seizure characteristics of patients at baseline (n = 75).

Variables	Description	Frequency (%)
Demographic and clinical information		
Gender	Female	40 (53.3)
	Male	35 (46.7)
Age at baseline (years)	< 12	2 (2.7)
	12 -17	12 (16)
	18 - 64	60 (80)
	≥ 65	1 (1.3)
	Mean (SD), [range]	26.4 (11.6), [3-72]
Learning disability	Yes	39 (52)
	No	36 (48)
Prior psychiatric comorbidity	Yes	23 (30.7)
	No	52 (69.3)
Number of prior antiseizure medication regimens	≤ 2	25 (33.3)
	> 2	45 (60)
	Not documented	5 (6.7)
Number of concomitant antiseizure medications	≤ 2	37 (49.3)
	> 2	35 (46.7)
	Not documented	3 (4)
Epilepsy and seizure information		
Epilepsy type	Focal epilepsy	59 (78.7)
	Generalized epilepsy	15 (20)
	Unclassified epilepsy	1 (1.3)
Etiology	Genetics	8 (10.7)
	Structural	32 (42.7)
	Unknown	35 (46.7)
Seizure type	Focal seizures only	10 (13.3)
	Focal with secondary GTCs	27 (36)
	Secondary GTCs	20 (26.7)
	Primary GTCs	4 (5.3)
	Myoclonic with or without other seizure types	13 (17.3)
	Absence with or without GTCs	1 (1.3)
MRI	Normal	21 (28)
	Epileptogenic	10 (13.3)
	Abnormal	35 (46.7)
	Not performed	9 (12)
EEG	Normal	6 (8)
	Epileptogenic	31 (41.3)
	Abnormal	21 (28)
	Not performed	17 (22.7)
Family history of epilepsy†	Yes	22 (29.3)
	No	53 (70.7)
Duration of perampanel therapy		
Duration of perampanel treatment (months)	< 3	3 (4)
	3-6	12 (16)
	6.1-12	5 (6.7)
	> 12	55 (73.3)
	Mean (SD), [range]	19.2 (9.6), [1-40]

†Family history of epilepsy in 1st degree relatives. EEG = electroencephalography, GTCs = generalized tonic-clonic seizures, MRI = magnetic resonance imaging, SD = standard deviation.

Perampanel responders included patients who were seizure-free for the last six months or more (22.7%, n = 17/75) and those who responded with a 50% reduction or more in seizure number (44%, n = 33/75). The remaining 25 patients (33.3%) were perampanel non-responders, including patients who achieved less than a 50% reduction in seizure number (28%, n = 21/75) and those whose seizures increased after perampanel initiation (5.3%, n = 4/75).

The rate of 50% responder and seizure freedom in focal epilepsy was 66.1% (n = 39/59) and

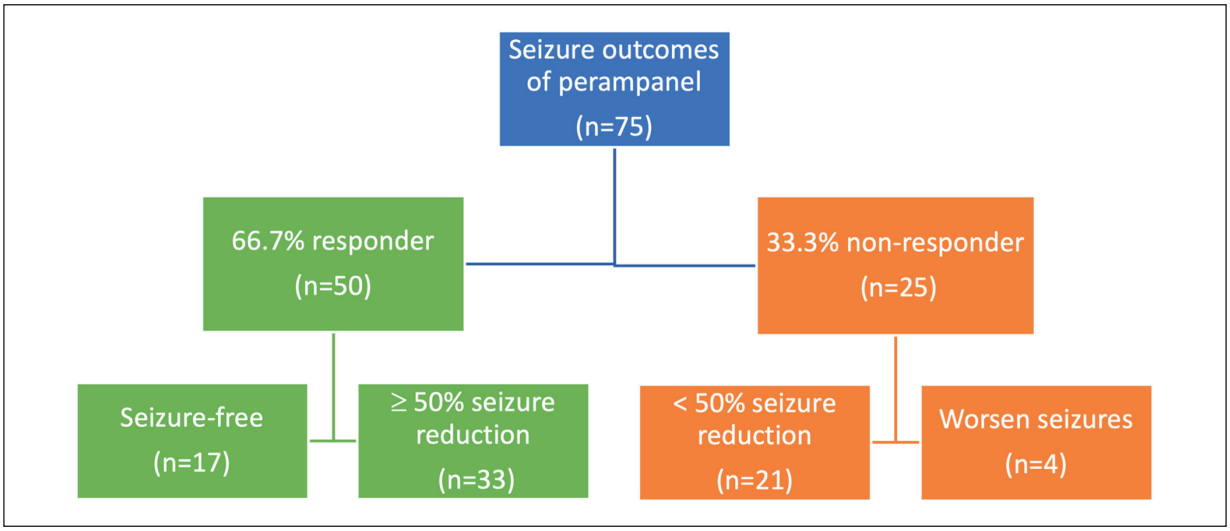

Figure 1. Seizure outcomes of perampanel at last follow-up (n = 75).

Table II. Seizure outcomes of some subgroups.

Subgroups		Responders n (%)	Non-responders n (%)
Learning disabilities	Yes = 39	24 (61.5)	15 (38.4)
	No = 36	26 (72.2)	10 (27.8)
Myoclonic seizures	Yes = 13	8 (61.5)	5 (38.5)
	No = 64	42 (65.5)	20 (31.2)
Lennox-Gastaut syndrome (LGS)	Yes = 6	4 (66.7)	2 (33.3)
	No = 69	46 (66.7)	23 (33.3)

18.6% (n = 11/59), while in generalized epilepsy, it was 73.3 (n = 11/15) and 40% (n = 6/15), respectively.

The perampanel response rate in patients with learning disabilities and patients with myoclonic seizures was 61.5% in each group. While 66.7% of patients with LGS responded to perampanel. Table II shows the seizure outcomes of these subgroups.

During the follow-up, 18 patients discontinued perampanel therapy. Reasons for discontinuation were as follows: adverse effects (n = 10), lack of efficacy (n = 4), patient preference (n = 3), and unavailability of perampanel (n = 1).

Adverse Effects of Perampanel

During the study period, 22 (29.3%) patients had one or more intolerable adverse effects that led to medication discontinuation (13.3%, n = 10/75) or dose reduction (16%, n = 12/75). The majority of adverse effects of perampanel were CNS problems. Aggressive behaviors represented the most frequent side effects, followed by sedation, then psychosis, coordination problems, and loss of appetite (Table III).

The incidence of intolerable psychiatric and behavioral adverse effects, including aggressive behaviors, psychosis, and mood swings, was 12%

Table III. Intolerable adverse effects of perampanel experienced by 22 patients.

Adverse effects	Frequency
Aggressive behaviors	6
Sedation effects	4
Psychosis	3
Coordination problems	3
Loss of appetite	3
Mood swings	1
Hair loss	1
Gastrointestinal adverse effects (bloating)	1
Rash and red eyes	1
Weight gain	1
Dandruff	1

Some patients had more than one problem.

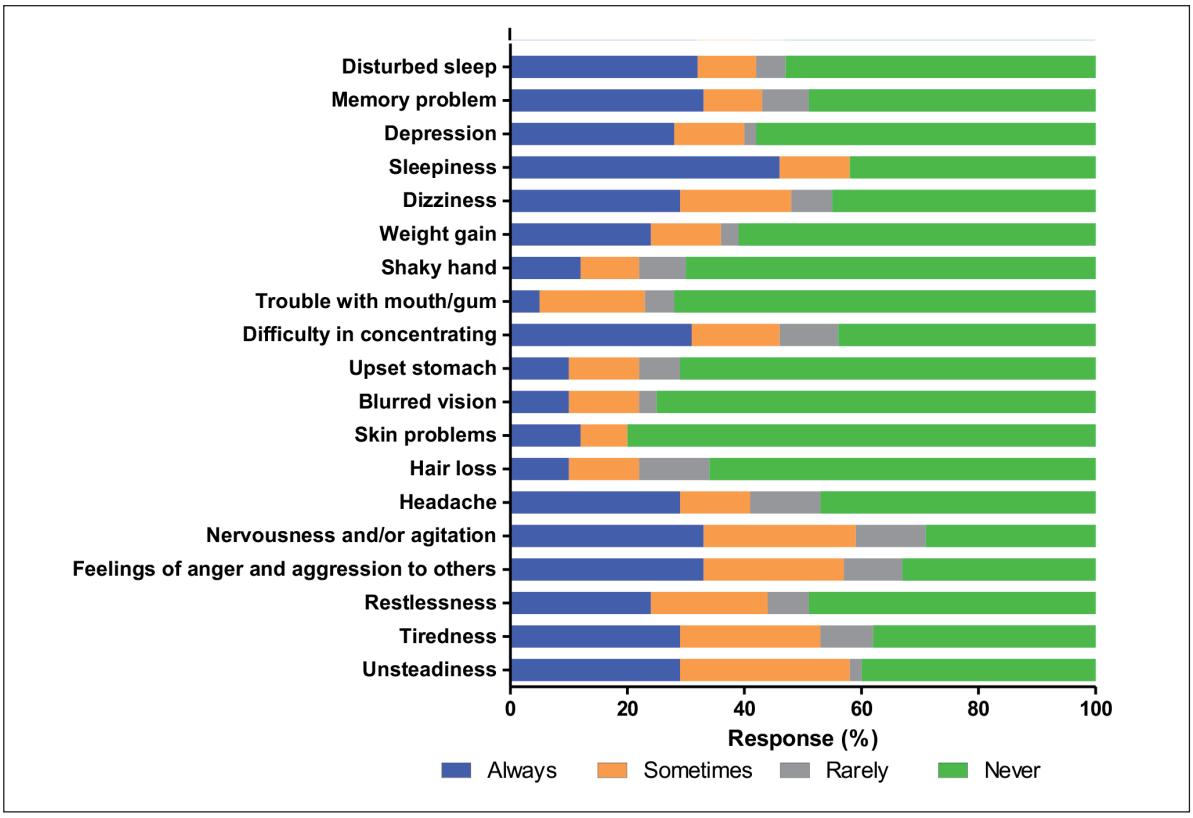

Figure 2. Patient-reported adverse effects of perampanel by Liverpool adverse events profile (LAEP) scale (n = 42).

(n = 9/75). Moreover, patients who had pre-existing psychiatric comorbidity before perampanel therapy experienced more psychiatric and behavioral adverse effects on perampanel (26.1%, n = 6/23) than patients without any prior psychiatric problems (6.1%, n = 3/49); the difference was significant (p = 0.0206).

The tolerability of perampanel was also assessed using the patient-rating LAEP scale. The LAEP scale was filled out by 42 patients. The total mean score of LEAP in this cohort was 40. Out of 42 patients, 13 (31%) had an overall symptoms score > 45. Figure 2 shows the percentage of patients' responses to LEAP. Table IV demonstrates the mean (SD) score of each LEAP item. The most frequently rated adverse effects were "feelings of anger and aggression to others", "nervousness and/or agitation", and "sleepiness", each with a mean score of 2.6. On the other hand, the least commonly rated problem was "skin problems" (mean = 1.5), followed by "blurred vision", "upset stomach", and "trouble with the mouth/gum", each with a mean score of 1.6.

Table IV. Mean scores of Liverpool adverse events profile (LAEP) items (n = 42).

LAEP items	Mean (SD)
Unsteadiness	2.5 (1.3)
Tiredness	2.4 (1.3)
Restlessness	2.2 (1.3)
Feelings of anger and aggression to others	2.6 (1.3)
Nervousness and/or agitation	2.6 (1.3)
Headache	2.2 (1.3)
Hair loss	1.7 (1.0)
Skin problems	1.5 (1.1)
Blurred vision	1.6 (1.0)
Upset stomach	1.6 (1.0)
Difficulty in concentrating	2.3 (1.3)
Trouble with mouth/gum	1.6 (1.0)
Shaky hand	1.7 (1.1)
Weight gain	2.0 (1.3)
Dizziness	2.3 (1.3)
Sleepiness	2.6 (1.4)
Depression	2.1 (1.3)
Memory problem	2.3 (1.4)
Disturbed sleep	2.2 (1.4)
Total	40 (23.4)
Depression	2.1 (1.3)
Memory problem	2.3 (1.4)
Disturbed sleep	2.2 (1.4)
Total	40 (23.4)

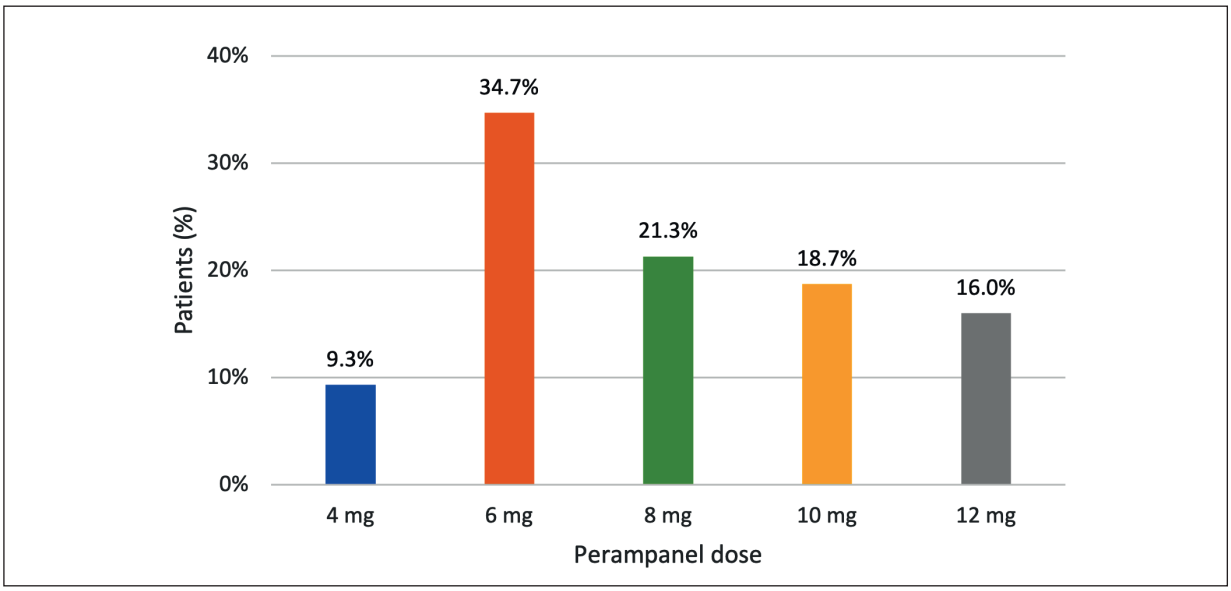

Figure 3. Perampanel dose (mg/day) at last follow-up.

Perampanel Dose

The mean (SD) dose of perampanel at the last follow-up was 7.9 (2.5) mg/day. The most commonly used dose in this cohort was 6 mg/day, which was used by 34.7% of patients (Figure 3).

The responder group was taking a higher dose than the non-responder group; mean (SD) was 8.4 (2.4) and 7.04 (2.5) mg/day, respectively. As demonstrated in Figure 4, there was a positive linear relationship between dose and response (i.e., as the dose increased, the responder rate increased).

The mean (SD) dose for intolerable adverse effects was 8.3 (2.2). As shown in Figure 4, there was a considerable increase in the rate of intolerable adverse effects from 19.2% (at dose 6 mg/day)

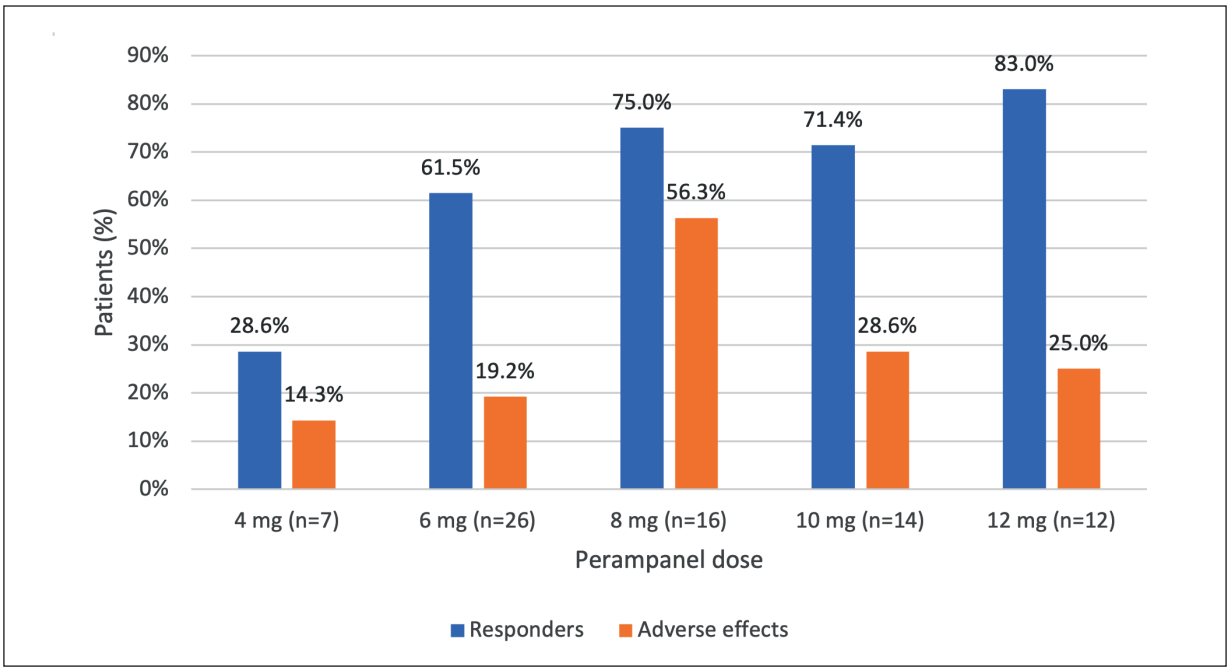

Figure 4. Rates of responders and adverse effects on each perampanel dose.

to 56.3% (at dose 8 mg/day). The rates of adverse effects were higher at doses 10 and 12 mg/day than at doses 4 and 6 mg/day.

Discussion

This study reported efficacy and tolerability outcomes from a cohort of patients with epilepsy treated with perampanel for up to 3.5 years in real-world clinical practice. The degree of refractoriness of patients included in the presented study was higher than that of patients included in perampanel clinical trials[13,16-19]. This study included a relatively large proportion of patients with learning disability, psychiatric comorbidity, high monthly seizure frequency at baseline, failed > 2 antiseizure medication regimens, on > 2 concomitant antiseizure medications, prior epilepsy surgery, and VNS implantation. The KFSHRC is a tertiary healthcare center, and perhaps patients with the most intractable seizures are referred to it.

This study demonstrated that 66.7% of patients responded to perampanel treatment at the last follow-up, including 22.7% seizure-free, and 44% of patients responded with a ≥ 50% reduction in seizure frequency from baseline[31]. A small percentage (5.3%) of patients experienced seizure worsening after starting perampanel treatment. This is consistent with the findings of a pooled analysis of the three-phase III randomized clinical trials[32] of perampanel that showed its efficacy in focal-onset seizures with 50% responder rates from 28.5 to 35% for doses of 4 to 12 mg, respectively. Furthermore, in the randomized trial[18] of perampanel for primary generalized tonic-clonic seizures (GTCs) in idiopathic generalized epilepsy, the 50% responder rate was 64.2%, and 30.9% were seizure-free. The perampanel efficacy observed in this study was also comparable to that reported in the perampanel pooled analysis of effectiveness and tolerability (PERMIT) study[25], which included 44 studies in routine clinical practice from 17 countries of patients with focal and/or generalized epilepsy. The PERMIT study demonstrated that the 50% responder rate and seizure freedom rate were 70% and 20.5% at the last visit, respectively[25]. Likewise, perampanel was found effective as monotherapy and as an add-on treatment for both focal and generalized epilepsy in several other observational studies[22-24,33-36]. There is limited data on perampanel use in some epilepsy sub-populations, including patients with intellectual disabilities, patients with myoclonic seizures, and patients with LGS[37-39]. This study demonstrated that perampanel was effective for these patients.

This study showed that the long-term tolerability of perampanel in routine clinical practice was good. The overall incidence of intolerable adverse effects that led to perampanel discontinuation was 13.3%, and the mean score of LEAP was 40 in this study. Generally, LEAP scores ≤ 45 are considered mild to moderate adverse effects, while scores > 45 are considered severe[29,31]. This observed mean LEAP score of perampanel adjunctive treatment (40) was lower than that reported in polytherapy (45.6) in a previous study[40] that included a wide range of new and established antiseizure medications. Perampanel was found to be well tolerated in clinical trials and the PERMIT study, with a discontinuation rate of 9.5% and 17.6% due to adverse effects, respectively. The most common intolerable adverse effects in this study were aggressive behaviors and sedation. Similarly, LEAP analysis showed that "feelings of anger and aggression to others", "nervousness and/or agitation" and "sleepiness" were the most frequently rated adverse effects in this study. The most commonly reported adverse events in clinical trials and observational studies were dizziness, somnolence, headache, irritability, behavioral disorders, ataxia, and fatigue[13,16,17,23,25,41].

One of the important findings from this study was that pre-existing psychiatric comorbidity was significantly associated with the incidence of psychiatric and behavioral adverse effects on perampanel. Several previous studies[25] confirmed the relationship between the presence of previous psychiatric comorbidity and the incidence of psychiatric adverse effects of perampanel. However, other studies[38] did not find that pre-existing behavioral problems were a predictor of additional behavioral adverse effects of perampanel. Therefore, it is important to counsel patients and caregivers about the potential risk of psychiatric and behavioral adverse effects of perampanel and monitor patients closely for these adverse effects, especially patients with prior psychiatric problems. Furthermore, in line with previous observational studies[22], psychiatric and behavioral problems were the most common adverse effects requiring discontinuation of perampanel in this study, with a rate of 12%. This was higher than that observed in clinical trials (1.6%)[42]. This could be explained by the fact that epilepsy pa-

tients with psychiatric comorbidities are typically excluded from clinical trials[43], while about 31% of the patients in this study had psychiatric comorbidities at baseline. During this study, there were no reported cases of suicidal ideation.

This study also provides insights into perampanel dose in clinical practice. The mean dose of perampanl at the last follow-up was 7.9 mg/day. Dose 6 mg/day was the most frequently used dose that was taken by about one-third of patients at the last visit. Although there were higher responder rates at doses higher than 6 mg, adverse effects were increased at higher doses as well. Particularly, there was a substantial increase in adverse effects from 19.2% at a dose of 6 mg/day to 56.3% at a dose of 8 mg/day. Therefore, dose 6 mg seemed to be the most effective tolerated dose in a large proportion of patients in this study. In clinical studies[32], the rate of adverse events increased steadily as doses of perampanel increased as follows: 61.7% at 2 mg, 64.5% at 4 mg, 81.2% at 8 mg, and 89% at 12 mg. It should be noted that titration can also influence the incidence of adverse effects of perampanel. Fast titration (2 mg/week) was significantly associated with higher adverse effects than slow titration (< 2 mg/week)[25,44,45].

Conclusions

This study represents perampanel outcomes in a real-world clinical setting with long-term prospective follow-up for up to 3.5 years. Perampanel was effective as an adjunctive treatment for intractable seizures, with a responder rate of 66.7%. Aggressive behavior was the most common reason for perampanel discontinuation. Patients should be counseled and monitored for these adverse effects, particularly those with a history of previous psychiatric and behavioral problems. Future studies are recommended to investigate the effect of combining perampanel with other antiseizure medications that can also aggravate these adverse effects, such as levetiracetam and zonisamide[46].

Authors' Contributions

Concept and design: Abdulaziz Alsemari, Bshra A. Alsfouk. Data collection: Thekra BinTeni, Nouf Almutairi, Sara Abuhaimed, Sara Alaskar, Ghada Alkhamis, Manal Rashed Almarzouqi. Data analysis: Thekra BinTeni, Nouf Almutairi, Saleh Alageel, Bshra A. Alsfouk. Manuscript drafting: Bshra A. Alsfouk. Manuscript critical revision: all authors. Project administration: Abdulaziz Alsemari, Manal Rashed Almarzouqi, Saleh Alageel. Supervision: Abdulaziz Alsemari, Bshra A. Alsfouk. Funding acquisition: Bshra A. Alsfouk.

Conflict of Interest

The authors declare no conflicts of interest. All authors have approved the final version of the manuscript.

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Informed Consent

Informed written consent was taken from the patients.

Ethics Approval

The IRB approval was obtained by the Research Ethics Committee at KFSHRC (RAC # 2191137).

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Availability of Data and Materials

The data of this article is available upon reasonable request to the corresponding author.

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