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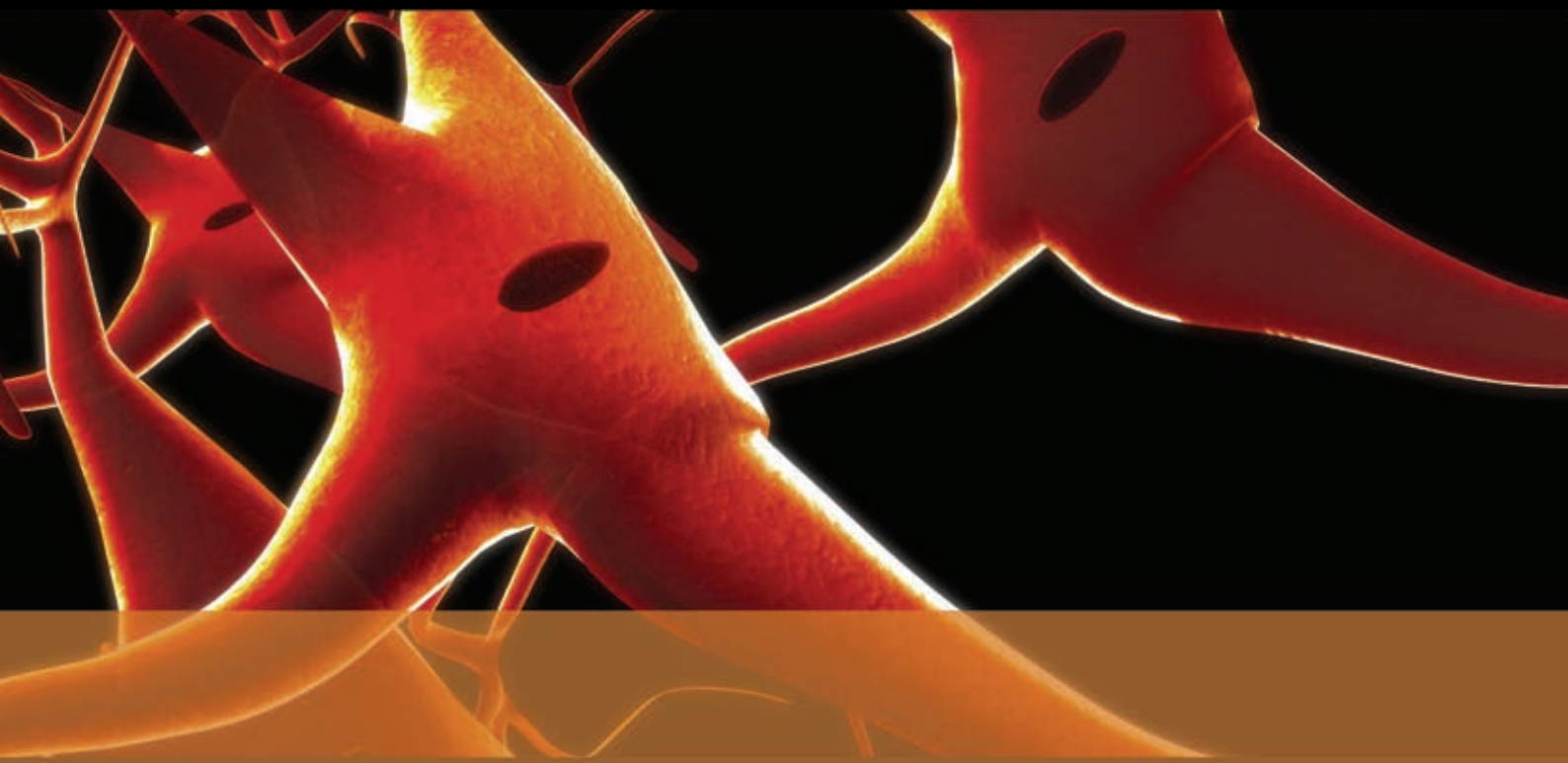

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Electro-clinical analysis of epilepsy patients with generalized seizures on adjunctive perampanel treatment

Francisco Javier Montoya Gutiérrez[a,b,*], Mónica Díaz Román[b], Dolors Cerveró Albert[b]

[a] Epilepsy Unit, Department of Neurology, Hospital General Universitario de Valencia, Tres Cruces Av, 2, 46014, Valencia, Spain
[b] Epilepsy Unit, Department of Clinical Neurophysiology, Lluis Alcanyis Hospital, Carretera Xátiva-Silla, Km 2, 46800, Xàtiva, Valencia, Spain

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ABSTRACT

Quantifying epileptiform discharges before and after the initiation of treatment can be useful for evaluating the efficacy of antiepileptic drugs in generalized epilepsy. The aim of this study was to determine if the selective α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonist perampanel alters the electroencephalographic signals in patients with drug resistant generalized seizures (primary or secondary). We also assessed the clinical efficacy, safety and tolerability of perampanel as an adjunctive treatment for patients with refractory generalized seizures after 3, 6 and 12 months of treatment to determine if there is an electro-clinical correlation. We carried out a 1-year retrospective, unicentric, observational, descriptive and non-interventional study to analyze changes in epileptiform discharges, seizure frequency and adverse effects in patients with generalized seizures taking perampanel as an add-on treatment. Perampanel significantly reduced the total number, total duration, maximal duration and average duration of epileptiform discharges in patients with primary generalized epilepsy (n = 44). In patients with focal onset epilepsy and secondary generalized seizures (n = 8) significant decreases in the maximal duration and average duration of epileptiform discharges were found. These findings correlate with the significant decrease in seizure frequency and clinical improvement observed after taking perampanel as an adjunctive therapy for 3, 6 and 12 months. To our knowledge, this is the first study to show that perampanel reduces epileptiform activity, and that this effect correlates with patients' clinical improvement. Analysing patients' electroencephalographic activity in response to perampanel could be useful for assessing the drug's efficacy and optimising adjunctive treatments.

1. Introduction

Current antiepileptic drugs (AEDs) cannot control seizures in 20–30% of patients and many patients require adjunctive therapy if their seizures do not respond to single-drug treatment. However, adjunctive treatments are often chosen based on avoidance of drug–drug interactions and unwanted side effects, rather than on evidence of improved efficacy (French and Faught, 2009).

Electroencephalographic recordings not only aid the diagnosis and classification of epilepsy syndromes, they may also provide a useful objective measure of AED efficacy. Electroencephalographic improvements with antiepileptic drug treatment have been correlated with behavioural improvements in children (Kanemura et al., 2013) and with self-reported improvements in seizure frequency (Pro et al., 2009).

Perampanel — a selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonist that reduces neuronal hyperexcitation associated with seizures by targeting glutamate activity at postsynaptic AMPA receptors — has shown high efficacy and tolerability for the treatment of epilepsy (Steinhoff et al., 2013).

AMPA receptors are critical to the generation and spread of epileptic activity (Rogawski, 2011). Activation of AMPA receptors by glutamate allows the flux of cations across the postsynaptic membrane, resulting in a brief depolarization known as the excitatory postsynaptic potential (EPSP). Summation of EPSPs leads to the firing of action potentials by the postsynaptic neuron and transmission of the synaptic signal. AMPA

Abbreviations: ADHD, attention deficit hyperactivity disorder; AE, adverse event; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AED, antiepileptic drug; CPS, complex partial seizures; EEG, electroencephalogram; EPSP, excitatory postsynaptic potential; FOE, focal onset epilepsy; GTCS, generalized tonic-clonic seizures; IED, interictal epileptiform discharges; IGE, idiopathic generalized epilepsy; JME, juvenile myoclonic epilepsy; LCM, lacosamide; LEV, levetiracetam; PER, perampanel; PGE, primary generalized epilepsy; PGTC, primary generalized tonic-clonic; SGS, secondarily generalized seizures; SPS, simple partial seizures; ZNS, zonisamide

* Corresponding author at: Epilepsy Unit, Department of Neurology, Lluis Alcanyis Hospital, Carretera Xátiva-Silla, Km 2, 46800, Xàtiva, Valencia, Spain.
E-mail address: Javier.Montoya@uv.es (F.J. Montoya Gutiérrez).

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receptor antagonists have shown powerful antiseizure activity in *in vitro* and *in vivo* models (Dichter, 2008; Rogawski, 2013).

Perampanel displayed a broad-spectrum activity across preclinical models of both focal and generalized seizures, and had synergistic effects with other AEDs (Hanada et al., 2011). Various Phase III trials have supported the efficacy, safety and tolerability of once-daily perampanel (4–12 mg) as an adjunctive antiepileptic treatment in patients with focal onset seizures (French et al., 2012, 2013; Krauss et al., 2012). In 2015, a clinical trial in patients with drug-resistant, primary generalized tonic-clonic (PGTC) seizures in the context of idiopathic generalized epilepsy (IGE) demonstrated that 30.9% of perampanel-treated patients achieved PGTC seizure freedom (French et al., 2015). In a Phase III extension study, perampanel was especially effective in reducing the frequency of secondarily generalized seizures; a sustained decrease of 90% was observed after 2 years (Krauss et al., 2014), and 53.6% of patients achieved seizure freedom after 4 years of adjuvant treatment (Krauss et al., 2018). Similar findings were found in the real-world setting FYDATA study, which showed that adjuvant perampanel reduced the frequency of secondarily generalized seizures by 75% after 1 year (Villanueva et al., 2016). More recently, the 12-month GENERAL study (Villanueva et al., 2018) showed that perampanel was effective regardless of epilepsy syndrome, concomitant AEDs, and prior AEDs.

There is growing evidence that perampanel is useful for controlling other kinds of seizures, such as myoclonic seizures in refractory patients (Dirani et al., 2014; Schorlemmer et al., 2013; Steinhoff et al., 2016; Crespel et al., 2017; Gil-López et al., 2018; Villanueva et al., 2018) and specific syndromes related with progressive myoclonus seizures, such as Lance-Adams disease (Steinhoff et al., 2016), Unverricht-Lundborg disease (Crespel et al., 2017) and Lafora disease (Goldsmith and Minassian, 2016).

Perampanel has been used to treat more than 270,000 patients worldwide and is approved in over 60 countries, including the United States, Canada, EU and Japan, as an adjunctive therapy for focal seizures (with or without secondarily generalization) and for PGTC seizures in patients with IGE aged 12 years and older (https://www.eisai.com/news/2020/news202001.html).

Despite the demonstrated efficacy and tolerability of perampanel in patients, nothing is known about the effects of the drug on patients' electroencephalographic profile or epileptiform discharges in the short to medium term.

Electroencephalography remains the primary diagnostic test of brain function (Binnie and Prior, 1994). Electroencephalograms (EEGs) provide a continuous measure of electrical activity in the cortex, with excellent time resolution, and is especially valuable for assessing patients with known or suspected seizures. Very few studies have examined the effects of AEDs on the epileptiform discharges of patients with generalized epilepsy. Both levetiracetam and valproic acid have been shown to reduce epileptiform discharges and these effects were correlated with clinical and behavioural improvements in patients with generalized epilepsy and children with attention deficit hyperactivity disorder (ADHD) without obvious epilepsy (Pro et al., 2009; Asadi-Pooya and Emami, 2011; Kanemura et al., 2013).

In this study we quantified changes in epileptiform discharges monitored with an EEG in patients with generalized seizures (primary or secondary) treated with adjunctive perampanel. We concomitantly carried out an assessment of the drug's clinical efficacy, safety and tolerability to determine if there is an electro-clinical correlation. Our findings corroborate the effectiveness of perampanel as a broad-spectrum AED and support a correlation between the drug's effectiveness and reduced epileptiform activity in electrophysiological recordings that could be clinically useful for optimizing perampanel use.

2. Materials and methods

2.1. Study design

This was a unicentric, retrospective, observational, open and non-interventional study to evaluate the effects of adjunctive perampanel on epileptiform discharges and seizure frequency after 3, 6 and 12 months in patients with drug-resistant generalized seizures.

The study protocol was approved by the Clinical Research Ethics Committee of the Arnau de Vilanova Hospital in Valencia, and strictly follows the international ethical recommendations for research and clinical studies in humans set out in the Declaration of Helsinki, and the standards of good clinical practice recommended by the Spanish Agency of Medicines and Health Products.

Perampanel was prescribed as an add-on AED in accordance with epilepsy specialists' criteria. Titration was performed according to usual clinical practice; the dose was increased until patients reached the highest tolerated dose or clinical efficacy was achieved.

In our neurology unit, it is standard practice to monitor patients starting treatment with a new AED or an AED in a new indication by performing EEG and a clinical check-up (carried out on the same day) at 3, 6 and 12 months after the start of treatment.

A baseline visit (pre-perampanel) and visits at 3, 6 and 12 months after initiation of perampanel were conducted. The efficacy and tolerability of perampanel were assessed at 3, 6 and 12 months, and the dose was adjusted accordingly. Clinical and demographic data were collected retrospectively from clinical charts between March 2015 and October 2017 and entered into a single database.

At baseline, the following data were collected: patient demographics; seizure type and aetiology of epilepsy; baseline seizure frequency (mean number of seizures per month during the 3-month period prior to perampanel initiation); age at onset; previous and concomitant AEDs; reason for administering perampanel (e.g. poor efficacy or poor tolerability of previous AEDs); and EEG records.

The following information was collected from clinical charts at 3-, 6- and 12-month visits: changes in concomitant AEDs; perampanel dose and titration scheme; adverse events (AEs); responder rate (percentage of patients achieving $\geq$50% reduction in seizure frequency compared to baseline); percentage of seizure-free patients; complete blood count and biochemistry; and EEG analysis.

2.2. Patients

Every patient (or legal representative) is asked to provide written informed consent for the use of their clinical data and history in this or any other retrospective study. Only those who agreed had their data evaluated for the purposes of this project. Inclusion in the study was totally independent of the decision of the specialist to prescribe perampanel.

Patients were considered for inclusion if they were $\geq$12 years old, diagnosed with epilepsy and were taking perampanel as an adjuvant treatment to their antiepileptic therapy. All patients included in this study had non-controlled secondary generalized seizures or primary generalized seizures. Patient data were analysed for up to 12 months after starting perampanel treatment, or until the patient discontinued treatment. Patients enrolled in other clinical studies were excluded, as well as those with inaccessible clinical records.

Patients were classified according to the type of epilepsy: focal onset or primary generalized epilepsy (PGE) (Scheffer et al., 2017). Patients with PGE were further classified into patients with juvenile myoclonic epilepsy (JME), and patients with PGE other than JME (generalized epilepsy with phantom absences, primary generalized tonic clonic seizures only, childhood absence epilepsy, juvenile absence epilepsy).

2.3. Electrical and clinical efficacy assessments

The primary endpoint was variation in number and duration of epileptiform discharges in EEG recordings of patients taking perampanel as adjunctive therapy at 12 months.

The EEG recordings were carried out in the morning and lasted 45 min. Patients were instructed to sleep for at least 7 h the previous 3 days, to take their usual treatment and to not take stimulants or sedatives. Normal (at rest) EEG tracings and EEG tracings recorded during photostimulation and hyperventilation (standard activation procedures) were analysed. Because no differences in EEG discharges were observed during photic stimulation or hyperventilation compared to resting state, entire recordings were analysed.

Epileptic activity, evaluated for each EEG before and during perampanel treatment, was quantified according to the following parameters: 1, total number of discharges in 30 min; 2, total duration in seconds of all registered discharges in 30 min; 3, maximal duration, in seconds, of individual discharges; and 4, average duration, in seconds, of individual discharges. The results are the average discharge counts and measurements made by two neurophysiologists who manually counted and measured the discharges in parallel, blinded to the moment of EEG evaluation (before or after 3, 6 or 12 months of perampanel treatment).

The primary efficacy endpoint was the reduction in all-seizure frequency, measured by means of responder rates (percentage of patients achieving ≥50% reduction in all-seizure frequency relative to baseline) and seizure freedom (proportion of patients free of all seizures) at 12 months; seizure counts were based on patients' diaries. All efficacy and electrical endpoints comprised all patients who fulfilled the inclusion criteria and had at least one efficacy measurement. Last observation carried forward was used to handle missing data.

To assess clinical efficacy, the number of focal seizures with retained awareness (simple partial seizures, SPS), focal seizures with a loss of awareness (complex partial seizures, CPS), secondarily generalized seizures (SGS), absence seizures, myoclonic seizures or generalized tonic-clonic seizures (GTCS) per month was also analysed.

2.4. Safety assessments

The safety endpoints included the proportion of patients with at least one AE and the proportion of patients with AEs that led to perampanel withdrawal at 3, 6 and 12 months after perampanel initiation. Treatment-associated AEs, their frequency and severity were obtained from patients' clinical records.

2.5. Statistical analysis

All statistical analyses were performed using SPSS version 19.0 (IBM Corporation, Armonk, NY, USA). The threshold of significance was $p < 0.05$. Categorical variables were described with the count and percentage, and continuous variables were provided as mean ± standard deviation (SD) or median with interquartile range (IQR), for normally and non-normally distributed data, respectively. For quantitative variables satisfying a Kolmogorov–Smirnov test for normality, a Student's *t*-test was used, whereas a Mann–Whitney U test was employed for quantitative variables that were found to be not normally distributed. Qualitative variables were analysed using the Chi-square test or Fisher's exact test. The variation in the number of epileptiform discharges and seizure frequency over time were studied using the Friedman test and the Wilcoxon test for pairwise comparisons. The variation between the types of seizures were studied using Cochran's Q test and the McNemar test for pairwise comparisons.

Table 1
Patient baseline characteristics (n = 52).

Male /female (%)	26 (50%) / 26 (50%)
Mean age (min-max)	41.1 (13 − 78) years
Time since diagnosis of epilepsy (mean)	23.4 years
Mean age at epilepsy onset	17.7 years
Type of epilepsy	
Primary generalized epilepsy (PGE)	44 (84.6%)
Juvenile myoclonic epilepsy (JME)	21 (40.4%)
PGE other than JME: primary generalized tonic-clonic (PGTC) epilepsy only 14; generalized epilepsy with phantom absences 5; childhood absence epilepsy 2; juvenile absence epilepsy 2	23 (44.2%)
Focal onset epilepsy with secondarily generalized seizures	8 (15.4%)
Previous AEDs, median (IQR)	4 (1 − 14)
Concomitant AEDs at onset with perampanel, median (IQR)	1 (0 − 4)
Levetiracetam, n (%)	29 (55.8)
Zonisamide, n (%)	17 (32.7)
Lacosamide, n (%)	10 (19.2)
Lamotrigine, n (%)	8 (15.4)
Valproic acid, n (%)	7 (13.5)
Basal EEG activity, n (%)	
Normal activity	6 (11.5)
Focal activity	3 (5.8)
Generalized activity	32 (61.5)
Focal and generalized activity	11 (21.2)

3. Results

3.1. Patient baseline characteristics and disposition

Fifty-two patients with epilepsy were included in the study. Their demographic features and epilepsy-specific medical history are summarized in Table 1. Eight (15.4%) presented with focal onset epilepsy with SGS, and 44 (84.6%) presented with PGE. In 47 of 52 patients the etiology of the disease was unknown. The percentage of psychiatric comorbidity was 15.7%, with depression (5.9%) and psychosis (5.9%) being the most frequent.

All patients started on a 2 mg daily dose of perampanel and doses were increased as the study progressed. In 98.1% of patients the titration scheme was 2 mg every 2 weeks. At the 12-month follow-up 33 patients (70.2%) were on 4 mg/day of perampanel, 12 (25.5%) were on 6 mg/day, 1 (2.1%) was on 8 mg/day and 1 (2.1%) was on 10 mg/day.

Over 12 months, 5 patients (9.6%) discontinued perampanel treatment due to AEs, but none of the patients discontinued due to lack of efficacy (Fig. 1). All 52 patients (100%) had at least a 3 months follow-up; 51 of 52 patients (98.1%) had at least a 6 months follow-up, and 47 patients had a 12 months follow-up. The retention rate at 12 months was 90.4%.

At the start of the study, 51.9% of the patients were taking one AED concomitantly and 34.6% were taking two AEDs. One patient initiated perampanel on monotherapy. The most frequent AED to which perampanel was associated with was levetiracetam (LEV) in 55.8% of patients, followed by zonisamide (ZNS) in 32.7% of patients and lacosamide (LCM) in 19.2% of patients.

3.2. Electrical efficacy in overall population

Baseline EEG recordings showed normal activity in 6 patients (11.5%), generalized epileptiform activity in 32 patients (61.5%), focal epileptiform abnormalities in 3 patients (5.8%), and both generalized and focal epileptiform activity in 11 patients (21.2%).

38.5% of patients (n = 20) showed a normalized EEG (measured by subjective interpretation) after 3 months, 45.1% (n = 23) after 6 months, and 51.9% (n = 27) after 12 months.

The percentage of patients showing a positive response to treatment (defined as ≥50% improvement in their EEG) was 63.5% (n = 33)

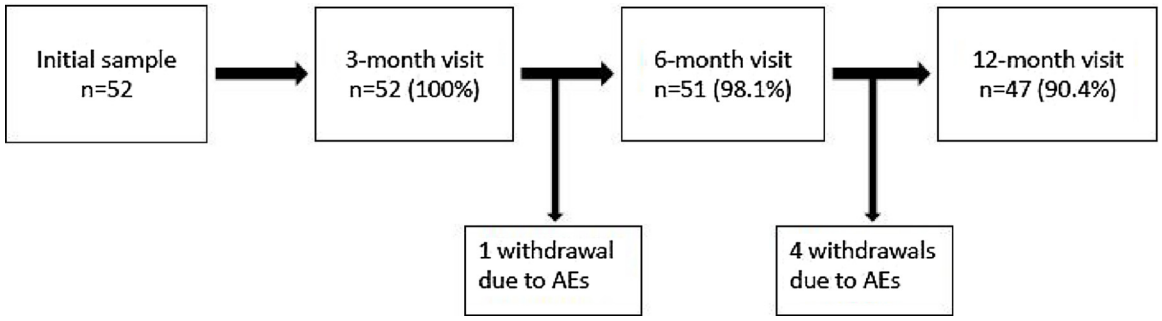

Fig. 1. Patient flow chart from baseline to 12 months.

after 3 months, 68.6% (n = 35) after 6 months and 71.2% (n = 37) after 12 months. Some response to perampanel treatment (< 50% improvement in EEG) was found in 75% (n = 39) of patients after 3 months, 78.4% (n = 40) after 6 months, and 82.7% (n = 43) after 12 months.

No change in EEG was found in 19.2% (n = 10) of patients after 3 months, 21.6% (n = 11) of patients after 6 months, and 13.5% (n = 7) after 12 months. The percentage of patients showing a worsening of their EEG was 5.8% (n = 3) at 3 months, 0% at 6 months and 3.8% (n = 2) at 12 months.

The quantification of epileptic discharges in the 43 patients with generalized epileptiform activity at baseline revealed a 49.3% reduction in the number of epileptiform discharges ($p < 0.001$), and a 79.7% reduction in the total average duration of epileptiform discharges ($p < 0.001$) after 12 months of adjuvant treatment with perampanel (Fig. 2).

The maximum discharge duration was significantly reduced (72.8%) compared to baseline recordings ($p < 0.001$), as was the average discharge duration (79.4%). Significant decreases in all these parameters were also observed at 3 and 6 months compared to baseline.

EEG analysis of patients with focal onset epilepsy with SGS (n = 8) is shown as Supplementary Information. We are wary of drawing conclusions from this population due to the small sample size (n = 5 with basal epileptiform activity).

3.3. Electrical efficacy: EEG analysis of patients with PGE

Of the 44 patients with PGE, six patients had normal basal EEG activity and remained with normal EEG activity during the course of the study thus, the EEGs of 38 patients were analysed. The number, total duration, maximum duration and average duration of epileptiform discharges were significantly reduced along the whole observation period (at months 3, 6 and 12) (Table 2). When each of these items was evaluated at 12 months, significant reductions were observed: the number of epileptiform discharges was reduced by 48.4% ($p < 0.001$); total duration was reduced 79.9% ($p < 0.001$); and maximum and average duration of individual discharges were decreased by 73% ($p < 0.001$) and 79.7% ($p < 0.001$), respectively (Fig. 2).

When the two experts performed subjective interpretation of EEG after 12 months of perampanel initiation, 21 of 44 patients (47.7%) achieved a normalized EEG. The percentage of patients showing ≥50% and < 50% improvement from baseline was 68.2% and 81.8%, respectively. No change or a worsening in EEG was found in 13.6% and 4.5% of the patients, respectively, after 12 months of perampanel initiation.

3.3.1. EEG analysis of patients with JME

Of the 21 patients with JME, 18 patients showed epileptiform activity at the beginning of the study; three had a normal EEG at the start remained with a normal EEG throughout the course of the study.

The quantification of epileptic discharges in 18 patients with JME and generalized basal EEG activity revealed a 53.8% reduction in the number of epileptiform discharges ($p = 0.002$) and a 61.1% reduction in the total duration of epileptiform discharges ($p = 0.001$) after 12 months.

The maximum discharge duration was significantly reduced (39%) compared to baseline recordings after 12 months ($p = 0.019$) (Fig. 2). Significant decreases in all these parameters were also observed at 6

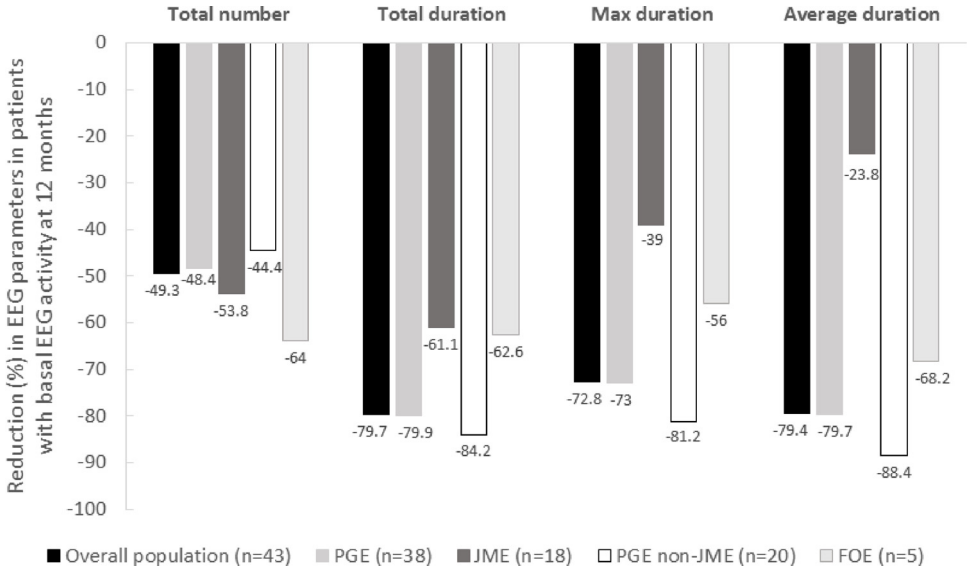

Fig. 2. Percentage reduction in EEG parameters in patients with basal epileptiform activity after 12 months of treatment with perampanel.

Table 2
Mean (± SD) number and duration of epileptic discharges in 38 patients with primary generalized epilepsy and generalized EEG activity at the start of the study who were on adjunctive perampanel treatment. *Denotes a significant change ($p < 0.001$) compared to baseline.

	Baseline	3 months	6 months	12 months
Total number	15.7 (± 17)	9.1 (± 12.4)*	8.3 (± 10.6)*	8.1 (± 12.7)*
Total duration (seconds)	81.1 (± 228.9)	18.7 (± 22.2)*	23.4 (± 53.2)*	16.3 (± 23.1)*
Max duration (seconds)	10 (± 31.1)	3.2 (± 4.6)*	3.6 (± 6.3)*	2.7 (± 3.7)*
Average duration (seconds)	7.4 (± 32.4)	1.9 (± 2.0)*	1.8 (± 2.3)*	1.5 (± 1.7)*

Fig. 3. Change (%) in all seizure frequency in overall population (n = 52).

Table 3
Mean (± SD) frequency of different seizure types per month in patients with primary generalized epilepsy. *Denotes a significant change ($p < 0.05$) compared to baseline, **denotes a significant change ($p < 0.001$) compared to baseline.

	Overall (n = 44)	Seizures at baseline (n = 34)	Absence seizures (n = 12)	Myoclonic seizures (n = 11)	GTCS (n = 18)
Baseline	8.4 (± 16.3)	10.9 (± 17.8)	9.5 (± 23.3)	20.5 (± 15.3)	0.7 (± 0.4)
3 months	2.4 (± 12.6)**	3.1 (± 14.3)**	7.8 (± 23.8)*	0.7 (± 1.6)*	0.1 (± 0.2)*
6 months	2.3 (± 12.7)*	3.0 (± 14.5)*	7.5 (± 23.9)*	0.4 (± 1.4)*	0.1 (± 0.3)*
12 months	0.6 (± 3.8)**	0.8 (± 4.3)**	2.2 (± 7.2)*	0.1 (± 0.3)*	0.02 (± 0.1)**

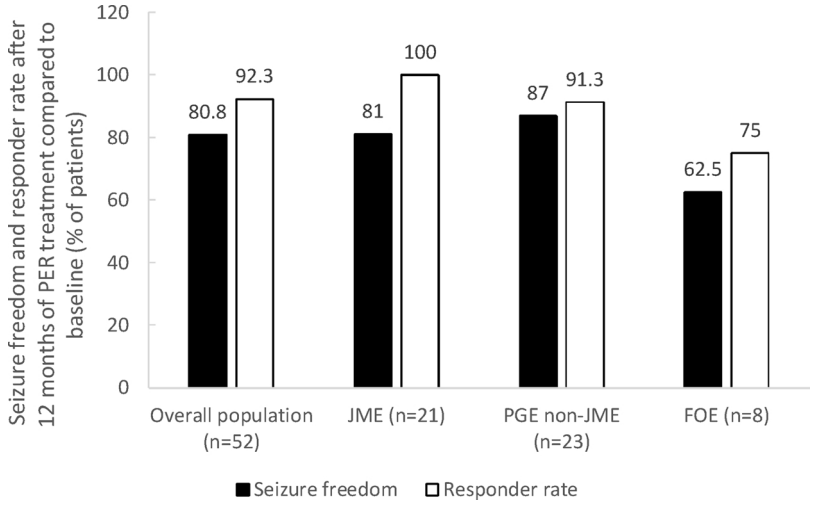

Fig. 4. Percentage of patients free of all seizures, and percentage of patients achieving ≥50% reduction in all-seizure frequency, relative to baseline after 12 months of PER (perampanel) treatment.

Table 4
AEs associated with the treatment in the overall safety population.

	n = 52		
	0 – 3 months	0 – 6 months	0 – 12 months
Any AE, n (%)	14 (26.9%)	19 (36.5%)	19 (36.5%)
Mild	5 (9.6%)	8 (15.4%)	7 (13.5%)
Moderate	9 (17.3%)	10 (19.2%)	11 (21.2%)
Severe	0 (0%)	1 (1.9%)	1 (1.9%)
Discontinuation due to AEs, n (%)[a]	0 (0%)	1 (1.9%)	5 (9.6%)
Individual AEs in > 1 patient, n (%)			
Irritability	7 (13.5%)	10 (19.2%)	12 (23.1%)
Somnolence	4 (7.7%)	5 (9.6%)	5 (9.6%)
Anxiety	1 (1.9%)	2 (3.8%)	4 (7.7%)
Fatigue	3 (5.8%)	3 (5.8%)	3 (5.8%)
Dizziness	2 (3.8%)	3 (5.8%)	3 (5.8%)

[a] Discontinuation due to AEs at month 3 was defined as withdrawal from day 1 to month 3 minus one day; at month 6 was defined as withdrawal from day 1 to month 6 minus one day; and at month 12 was defined as withdrawal from day 1 to month 12 minus one day.

months compared to baseline. No significant change in the average discharge duration was observed at any time-point (there was a reduction of 23.8% after 12 months).

When the two experts performed subjective interpretation of EEG after 12 months of perampanel initiation, 10 (47.6%) patients showed a normalized EEG. The percentage of patients showing ≥50% and < 50% improvement from baseline was 71.4% and 85.7%, respectively. No change in EEG was found in 14.3%, and none of the patients were considered to have worsened after 12 months of perampanel initiation.

3.3.2. EEG analysis of patients with PGE other than JME

Of the 23 patients with PGE other than JME, 20 patients showed generalized epileptiform activity at the beginning of the study. Three patients with PGE other than JME had a normal EEG at the start and remained normal throughout the study course.

The quantification of epileptic discharges in 20 patients with PGE other than JME and generalized basal EEG activity revealed a 44.4% reduction in the number of epileptiform discharges (p = 0.029) and an 84.2% reduction of the total average duration of epileptiform discharges (p = 0.019) after 12 months.

The maximum discharge duration was significantly reduced (81.2%) compared to baseline recordings (p = 0.001), as was the average discharge duration (88.4%; p = 0.001) (Fig. 2). Significant decreases in all these parameters were also observed at 3 and 6 months compared to baseline.

When the two experts performed subjective interpretation of EEG after 12 months of perampanel initiation, 11 (47.8%) patients showed a normalized EEG. The percentage of patients showing ≥50% and < 50% improvement from baseline was 65.2% and 78.3%, respectively. No change in EEG was found in 13%, and 8.7% of the patients were considered to have worsened after 12 months of perampanel initiation.

3.4. Clinical efficacy

In the overall population (n = 52), the ≥50% responder rate was 86.5% at month 3, 84.3% at month 6 and 92.3% after one year of perampanel treatment. Regarding seizure freedom (for all seizures), 73.1%, 74.5% and 80.8% of patients were seizure free at 3, 6 and 12 months, respectively (Fig. 3).

In patients with PGE (n = 44), the frequency of total seizures per month was reduced by 92.9% (92.7% in the 34 patients who suffered seizures at baseline) during the course of the study. At baseline, 12 patients had absence seizures, 11 had myoclonic seizures, and 18 had GTCS. There was a significant decrease in every seizure type during the whole observation period (Table 3). When comparing the number of seizures per month in the last visit to baseline, the numbers of absence, myoclonic seizures and GTCS were decreased by 76.8%, 99.5% and 97.1%, respectively.

From the 44 patients in our sample, 84.1% of patients were seizure free after 12 months of perampanel treatment. The ≥50 % responder rate was 95.5% after 12 months. All patients showed some (< 50%) improvement after 12 months.

During the course of the study, the frequency of seizures per month in patients with JME (n = 21) was significantly reduced by 99.2%. The frequency of seizures per month in patients with PGE other than JME (n = 23) was also significantly reduced by 77.4%. In both cases, significant decreases in the frequency of absence seizures, myoclonic seizures and GTCS were observed.

An analysis of seizure freedom in patients with JME and patients with PGE other than JME showed that after 12 months of perampanel treatment 81% and 87% were seizure-free, respectively (Fig. 4).

In patients with JME, the ≥50% responder rate was 100% after 12 months (Fig. 4). In patients with PGE other than JME, the ≥50% responder rate was 91.3% after 12 months.

In patients with focal onset epilepsy with SGS (n = 8), 62.5% were seizure-free after 12 months of perampanel treatment, and the ≥50% responder rate was 75% after 12 months (Fig. 4, see supplementary information for details on seizure frequency).

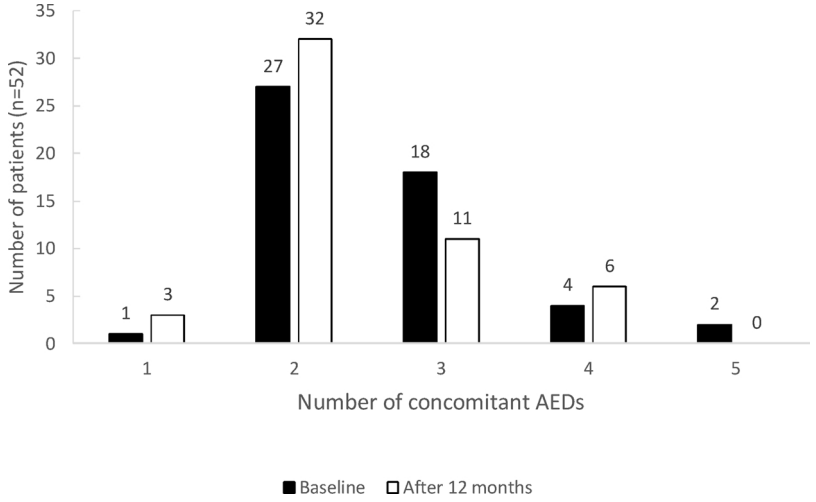

Fig. 5. Number of concomitant antiepileptic drugs (AEDs) before and after perampanel for 12 months (all patients).

3.5. Safety and tolerability in the overall safety population

During the first 3 months of treatment, 14 patients (26.9%) experienced at least one AE. By 6 and 12 months, 36.5% of patients experienced at least one AE, the majority being mild to moderate. The most frequent AE was irritability (23.1% of patients), followed by somnolence (9.6%) and anxiety (7.7%). Overall, 5 patients discontinued treatment with perampanel: one patient with focal onset epilepsy (FOE) and four patients with PGE (one with JME and 3 PGE other than JME) (Table 4).

3.5.1. Concomitant AED analysis

The number of concomitant AEDs reduced significantly over 12 months (Fig. 5); the average mean number of concomitant AEDs was 1.6 at baseline and 1.4 after 12 months ($p < 0.001$). The doses of lacosamide and levetiracetam were significantly reduced over the course of the study [from a mean average dose of 285 mg/day to 130 mg/day for lacosamide ($p = 0.02$), and from 1696.6 mg/day to 1336.2 mg/day for levetiracetam ($p = 0.003$)].

4. Discussion

To our knowledge this is the first study to demonstrate that the clinical efficacy of perampanel correlates with a decrease in epileptiform activity in patients with generalized seizures, either primary or secondary.

After only 3 months of treatment a significant decrease in the number of epileptiform discharges, the total average duration of epileptiform discharges, the maximum discharge duration and the average discharge duration were found in the EEG recordings of patients with generalized seizures. These improvements were also observed at 6- and 12-month follow-up assessments.

Although it is not possible to determine whether the correlation between epileptiform activity and clinical improvement is statistically significant, due to the small number of non-responders, the reduced electroencephalographic activity correlates well with the clinical efficacy of perampanel. The frequency of total seizures per month significantly reduced after 3, 6 and 12 months in patients with generalized seizures, and 80.8% of patients were free from all seizures after 12 months. IGEs are a well-recognised and common subgroup of PGEs and encompass four well-established epilepsy syndromes: childhood absence epilepsy, juvenile absence epilepsy, JME, and GTCS alone (Scheffer et al., 2017). The effects of perampanel on patients with JME and patients with PGE other than JME were similar to the ones observed in the overall PGE population. In both patients with JME and patients with PGE other than JME there was a significant reduction in EEG epileptiform activity; and after 12 months, the frequency of seizures per month was significantly reduced. Seizure freedom was achieved in 81% of patients with JME and in 87% of patients with PGE other than JME after 12 months of perampanel treatment.The AEDs levetiracetam and valproic acid have also been shown to reduce EEG epileptiform activity in patients with generalized epilepsy and children with ADHD (Pro et al., 2009; Kanemura et al., 2013), supporting the idea that there is an electro-clinical correlation which can be used to assess AED efficacy and determine patient prognosis.

Although perampanel also improved the EEGs of patients with focal onset epilepsy with SGS and significantly reduced the mean frequency of seizures per month after 3, 6 and 12 months, we are cautious about the interpretation of these results as the patient sample was small ($n = 8$).

The clinical efficacy of 4 mg perampanel in this study is comparable to that observed in clinical trials and studies carried out in real-world settings with patients with focal and generalized seizures (Krauss et al., 2014; French et al., 2015; Montoya et al., 2016; Villanueva et al., 2018; Stavropoulos et al., 2019). Interestingly, we found that perampanel treatment reduced the dose and number of concomitant AEDs, suggesting that it could be a first-line drug in the treatment of both focal onset epilepsy with SGS, and in PGE.

Perampanel also showed an excellent safety and tolerability profile, with only 5 patients discontinuing treatment due to AEs during the first 12 months of treatment.

There are a few limitations to this study, including the inherent limitations of the retrospective, observational study design. The small number of patients with focal onset epilepsy with SGS also limits the conclusions we can make about the effects of perampanel on epileptiform discharges in these patients.

In addition to validating the anti-epileptic effects of perampanel in patients with uncontrolled generalized seizures, this study highlights the value of EEG recordings for monitoring AED efficacy and improving seizure control. This translates into a direct benefit to patients, as poorly controlled epilepsy not only increases the risk of accidental injuries that adversely affect patients' quality of life (Salas-Puig et al., 2019), it can also increase the probability of death by SUDEP (sudden death caused by epilepsy) (Aldenkamp and Arends, 2004; Devinsky, 2011 & 2016).

Several studies have found that frequent interictal epileptiform discharges (IED) can impair cognitive performance in both children and adults with different epilepsy syndromes (Ebus et al., 2012; Lv et al., 2013; Glennon et al., 2016) raising the possibility that perampanel could improve patients' cognitive function. Future studies should examine the effects of perampanel on cognition and determine whether perampanel's effect on reducing epileptiform discharges could be particularly beneficial for patients with a high IED frequency but low seizure frequency.

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Declaration of Competing Interest

F.J. Montoya has participated in advisory boards and industry-sponsored symposia for Eisai, UCB, Bial, Esteve and Zambon. D. Cerveró and M. Díaz-Román have no conflict of interests to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2020.106378.

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