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FULL-LENGTH ORIGINAL RESEARCH

Effectiveness and safety of perampanel monotherapy for focal and generalized tonic-clonic seizures: Experience from a national multicenter registry

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Abstract

Objective: To assess the effectiveness and tolerability of perampanel (PER) monotherapy in routine clinical practice for the treatment of focal onset and generalized tonic-clonic seizures (GTCS).

Methods: This multicenter, retrospective, observational study was conducted in patients aged ≥12 years treated with PER as primary monotherapy or converted to PER monotherapy by progressive reduction of background antiepileptic drugs. Outcomes included retention, responder, and seizure-free rate after 3, 6, and 12 months and tolerability throughout the follow-up.

Results: A total of 98 patients (mean age = 49.6 ± 21.7 years, 51% female) with focal seizures and/or GTCS were treated with PER monotherapy for a median exposure of 14 months (range = 1-57) with a median dose of 4 mg (range = 2-10). The retention rates at 3, 6, and 12 months and last follow-up were 93.8%, 89.3%, 80.9%, and 71.4%, respectively. The retention rates according to the type of monotherapy (primary vs conversion) did not differ (log-rank *P* value = .57). Among the 98 patients, 61.2% patients had seizures throughout the baseline period, with a median seizure frequency of 0.6 seizures per month (range = 0.3-26). Responder rates at 3, 6, and 12 months were 79.6%, 70.1%, and 52.8%, respectively, and seizure freedom rates at the same points were 62.7%, 56.1%, and 41.5%. Regarding the 33 patients who had GTCS in the baseline period, 87.8% were seizure-free at 3 months, 78.1% at 6 months, and 55.1% at 12 months. Over the entire follow-up, PER monotherapy was generally well tolerated, and only 16% of patients discontinued PER due to adverse events (AEs). Female patients were found to be at a higher risk of psychiatric AEs (female vs male odds ratio = 2.85, 95% confidence interval = 1-8.33, *P* = .046).

Significance: PER demonstrated good effectiveness and a good safety profile when used as primary therapy or conversion to monotherapy at relatively low doses, in a clinical setting with patients with focal seizures and GTCS.

KEYWORDS
effectiveness, epilepsy, monotherapy, perampanel, tolerability

1 | INTRODUCTION

Perampanel (PER) is a once daily antiepileptic drug (AED) with a unique mechanism of action, since it is a selective and non-competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.[1] Based on the proven efficacy and the safety profile shown in several clinical trials,[2–5] PER has been approved in Europe and the USA as adjunctive therapy for focal onset seizures (FOS) with or without secondarily generalization and for primary tonic-clonic seizures in patients with epilepsy aged ≥ 12 years.[6,7]

More recently, the US Food and Drug Administration has accepted the extrapolation of the efficacy and safety of PER as adjunctive therapy for the treatment of FOS to its use as monotherapy. This new regulatory pathway considerably speeds up the access to monotherapies with new AEDs and therefore enables physicians to use more therapies for the treatment of FOS. Unfortunately, there are still discrepancies among different regulatory agencies, and noninferiority studies, where the new drug in monotherapy is compared to carbamazepine, are still requested by the European Medicines Agency.

As expected, many AEDs that demonstrated efficacy as adjunctive therapy have also been shown to be efficacious and safe when used as monotherapies. For this reason, some have questioned whether a separate monotherapy indication is really needed once an AED has been proved to be efficacious and safe in adjunctive trials.[8] Due to these restrictions and discrepancies among different regulators, open-label trials and observational studies are needed to support monotherapy use. Such real-world data become of great interest, as patients who are usually included in clinical trials do not necessarily represent everyday clinical practice and therefore dosing and titration might considerably differ from those used in the more rigid context of clinical trials.[9]

There are limited data regarding clinical experience with PER when used as monotherapy. In this regard, few open-label

and retrospective studies[10–13] have reported preliminary experiences with a limited number of patients receiving PER as monotherapy, who were followed for a short period of time. Besides this, data from these studies focused principally on patients who received PER after conversion to monotherapy, as very few patients were initially treated with PER monotherapy. In addition, clinical experience with PER monotherapy in different types of seizures (particularly generalized tonic-clonic seizures) and in the elderly has not been specifically addressed.

The aim of the present study was to gather real-life data on the retention, effectiveness, and safety of PER when it is administered as monotherapy, including conversion to monotherapy and initial monotherapy, in patients with FOS and generalized tonic-clonic seizures (GTCS) evaluated during the first year of treatment.

Key Points

- Ninety-eight people with focal seizures and/or GTCS were treated with PER monotherapy (primary or conversion monotherapy), and 80% remained on treatment at 1 year
- PER improved seizures in most patients at low doses and was effective regardless of epilepsy syndrome and seizure type (focal seizures and GTCS)
- Responder rates at 6 and 12 months were 70.1% and 52.8%, respectively, and seizure freedom rates at the same points were 56.1% and 41.5%
- Few patients had worsening of any seizure type once converted to PER monotherapy
- PER monotherapy was generally well tolerated, and only 16% of patients at the last follow-up reported transient adverse events that caused discontinuation of treatment

2 | MATERIALS AND METHODS

2.1 | Study design and settings

This was a retrospective, observational, noninterventional study in patients with FOS and/or GTCS (both primary and secondary generalized) conducted under conditions of normal clinical practice at 20 hospitals in Spain. Patients were eligible for inclusion if they met the following criteria: male or female patients aged ≥12 years with focal or idiopathic generalized epilepsy (IGE), in whom PER monotherapy was considered to be the best choice of treatment by the treating physician based on patient profile and epilepsy clinical characteristics. Patients with an inaccurate diagnosis of epilepsy and/or unreliable clinical records according to participating physicians were excluded from the study.

Patients received PER monotherapy in two ways:

1. Primary monotherapy (PM): patients not currently taking any other AEDs were started on PER monotherapy. Patients may have taken previously other AEDs, although by the time they were included in the study they were not taking any AED (eg, due to subject choice or AED discontinuation after seizure remission).
2. Conversion monotherapy (CM): patients taking one or more AEDs, including PER, were converted to PER monotherapy by progressive reduction of background AEDs.

The study began with a 3-month baseline period prior to transition to PER monotherapy. During this period, a daily diary was used to record the date, and type and frequency of seizures. Baseline demographics, clinical data, previous AED prescriptions, and reasons for considering PER monotherapy were also recorded. Although screening tests were not used for the identification of psychiatric comorbidities, referring physicians were asked to register relevant psychiatric history. Seizure types were classified according to the 2017 International League Against Epilepsy Classification of Epileptic Seizures.[14] Patients were treated with PER according to the approved package insert and as per the discretion of the physician. The titration and maintenance dose were determined by each clinician according to seizure frequency and severity, and patient tolerability.

The study was designed and conducted in accordance with all local regulations and guidelines. Anonymized information was collected retrospectively from medical records without any involvement or participation of individuals, with a study cutoff date of March 1, 2019. The study was granted approval by the ethics committee of Hospital Ramón y Cajal in Madrid, Spain.

2.2 | Effectiveness assessments

Seizure frequency was recorded as an average per month for the past 3 months at baseline and at each follow-up period for 3, 6, and 12 months, if available. The effectiveness analysis set included all patients who received at least one dose of PER and had any postbaseline seizure frequency data. The primary effectiveness endpoint was the retention rate captured at predefined regular timepoints and at the last follow-up. Secondary efficacy endpoints were (1) the responder and seizure-free rates for total seizures in non–seizure-free patients during the baseline period; (2) the percentage of patients free of GTCS in non–seizure-free patients during the baseline period; and (3) the percentage of patients who, once converted to monotherapy, had an increase of seizures compared to the

baseline period. All secondary endpoints were evaluated at 3, 6, and 12 months of follow-up, when available. Patients achieving ≥50% reduction in the frequency of all seizures per month relative to the baseline phase were considered responders. Seizure freedom was defined as complete seizure control on PER monotherapy since the prior visit, which for the 12-month visit meant no seizures during at least the prior 6 months, and for the 3- and 6-month visits meant no seizures since baseline or 3-month visit, respectively.

For the evaluation of all the objectives, we used an intention-to-treat analysis considering all patients who started PER monotherapy and reached each pre-established evaluation period (eg, patients in whom PER monotherapy was withdrawn for any reason at 4 months were considered nonresponders at 6- and 12-month follow-up).

2.3 | Safety assessments

The safety analysis set included all patients who received at least one dose of PER. Safety and tolerability were determined by the type and frequency of all treatment-emergent adverse events (TEAEs) and discontinuations related to PER that had been recorded at any time from the initiation of PER monotherapy until the last follow-up.

2.4 | Statistical analysis

Statistical analyses were performed using R software (R Project for Statistical Computing, v3.4.4).[15] Retention time on PER was estimated using Kaplan-Meier survival curves, and the log-rank test was performed to evaluate the effect of other variables on this parameter. Both univariate and additive multivariate Cox proportional hazard regression models were used to identify independent predictors for responders and for treatment retention throughout the study period. The association between adverse events (AEs) and other variables was analyzed with logistic regression. Quantitative variables were summarized as mean ± standard deviation, or median with interquartile range or range according to the Kolmogorov-Smirnov test. In all cases, $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Study population and baseline characteristics

A total of 98 patients from 20 hospitals were enrolled in the study (Table 1). The mean age at start of PER monotherapy was 49.6 ± 21.7 years (range = 14-91 years), and 50 patients were female (51%). Patients had a median epilepsy duration of 6.5 years (range = 2-65, mean = 11.5 ± 13.9 years). Epilepsy syndrome was classified as focal in 71 (72.4%) patients, generalized in 24 (24.5%) patients, and indeterminate in three patients. Of the 98 patients, 27 (27.5%) patients had a medical history of psychiatric comorbidities, which consisted of depression (15 patients), irritability (six patients), anxiety (five patients), and obsessive-compulsive disorder (one patient).

PM with PER was prescribed in 20 (25.2%) patients, whereas monotherapy was achieved after conversion to monotherapy in 78 (79.6%) patients. Patients converted to PER monotherapy had taken a median number of two AEDs (range = 1-8, mean = 2.2 ± 1.4 AEDs) in the past. The most common AEDs were levetiracetam (52%), valproic acid (25.5%), and carbamazepine (12.2%). The median PER maintenance dose at the last follow-up was 6 mg for the conversion to monotherapy group and 4 mg for patients who were started initially on PER monotherapy (Table 1); in the whole cohort, 4 mg was the most common dose (48.9%), followed by 6 mg (26.5%), 8 mg (15.3%), 2 mg (6.1%), and 10 mg (3%). In older patients, the daily dose of PER was lower (median dose of 4 mg in patients aged ≥65 years vs 6 mg in younger patients). Titration was considered fast (2 mg every 2 weeks or less) in 76 patients (77.5%) and slow (>2 weeks) in 22 patients (22.5%). Main reasons for PER to be considered were incomplete seizure control and AEs related to previous AEDs (Table 1). In patients who were started on PER directly, the main reason the referring physician chose PER over other AEDs was simplicity in terms of an easy titration schedule and only one dose per day.

3.2 | Retention rates

The median length of exposure to PER monotherapy was 14 months (range = 1-57, mean = 14.8 ± 9.1 months). A follow-up of at least 12 months was available in 84 patients (one patient was lost to follow-up). The median maintenance dose of PER was 4 mg (range = 2-12, mean = 5.2 ± 1.9 mg). During the first 12 months of follow-up, PER monotherapy was withdrawn in 16 patients (Figure 1); at the study cutoff date, 27 patients had discontinued PER monotherapy. The retention rates at 3, 6, and 12 months and last follow-up were 93.8%, 89.3%, 80.9%, and 71.4%, respectively (Figure 2). Whereas longer duration of epilepsy was associated with a higher risk of discontinuation of PER monotherapy throughout the study period (hazard ratio = 1.04, 95% confidence interval [CI] = 1.02-1.07), being a predictor in Cox multiple regression analysis ($P = .003$), none of the following variables significantly affected the retention rate: gender, age, epilepsy syndrome, number of failed AEDs, PM versus CM, maximal dose of PER, having seizures during the basal period, and AEs with previous AEDs.

TABLE 1 Demographic and clinical characteristics (n = 98)

Category	Total population, n = 98	Conversion to monotherapy, n = 78	Primary monotherapy, n = 20
Female gender, n (%)	50 (51)	40 (51.2)	10 (50)
Age, y, mean ± SD	49.6 ± 21.7	49.8 ± 21.2	48.5 ± 24
Patients aged ≥65 y, n (%)	32 (32.5)	25 (32)	8 (40)
Age at epilepsy onset, y, median (IQR)	31.5 (18-57)	31 (18-59.2)	32.5 (17.5-53)
Duration of epilepsy, y, median (IQR)	6.5 (2-13)	8 (3-13)	2 (1-9)
Etiology of epilepsy, n (%)			
Focal	71 (72.4)	60 (76.9)	11 (55)
Symptomatic	46 (46.9)	41 (52.5)	5 (25)
Cryptogenic	25 (25.5)	19 (24.3)	6 (30)
Generalized	24 (24.5)	17 (21.8)	7 (35)
Idiopathic generalized epilepsy	23 (23.5)	17 (21.8)	6 (30)
Symptomatic	1 (1)	—	1 (5)
Indeterminate	3 (3)	1 (1.3)	2 (10)
Patients with seizures at baseline, n (%)	60 (61.2)	45 (57.7)	15 (75)
Type(s) of seizures at baseline, n (%)[a,b]			
Generalized tonic-clonic seizures	33 (55)	24 (53.3)	9 (60)
Focal impaired awareness seizures	18 (30)	14 (31.1)	4 (26.6)
Focal aware seizures	14 (23.3)	13 (28.8)	1 (6.6)
Monthly seizure frequency in non–seizure-free patients, Median (IQR)	0.6 (0.3-1.3)	0.6 (0.3-1.3)	0.6 (0.3-1)
Previous AEDs, n (%)[c]			
0	15 (15.3)	0 (0)	15 (75)
1	31 (31.6)	29 (37.1)	2 (10)
≥2	52 (63)	49 (62.8)	3 (15)
Maintenance dose, mg, median (IQR)	4 (4-6)	6 (4-6)	4 (4-4)
Dose titration, n (%)			
≤2 wk	76 (77.5)	60 (76.9)	16 (80)
>2 wk	22 (22.5)	18 (23.1)	4 (20)
Reason(s) to select perampanel, n (%)			
Lack of efficacy with other AEDs	24 (25.2)	24 (30.8)	—
Adverse events with other AEDs	30 (30.6)	29 (37.2)	1 (5)
Lack of efficacy and adverse events	24 (24.5)	24 (30.8)	—
Simplicity	20 (19.7)	1 (1.2)	19 (95)

Abbreviations: AED, antiepileptic drug; IQR, interquartile range; SD, standard deviation.

[a]Percentages of each seizure type are calculated over those patients who had seizures during the 3-month baseline (n = 60). Note that one patient could have several types of seizures.

[b]Absence seizures and myoclonic seizures in patients with idiopathic generalized epilepsy where not quantified.

[c]Patients on primary monotherapy may have previously taken other AEDs, although by the time they were included in the study they were not taking any AED (eg, due to subject choice or AED discontinuation after seizure remission).

Retention time, defined as the probability of remaining on treatment with PER monotherapy, was assessed using Kaplan-Meier survival curves for all patients with 12 months of follow-up (Figure 3). The retention time did not differ by the type of monotherapy (primary vs conversion; log-rank P value = .57) or the type of epilepsy (focal vs generalized; log-rank P value = .18).

3.3 | Responder rates

Of the 98 patients included in this study, 60 (61.2%) patients had seizures throughout the baseline period and 33 (33.6%) patients had GTCS (Table 1). The overall median monthly seizure frequency at baseline was 0.6 seizures per month

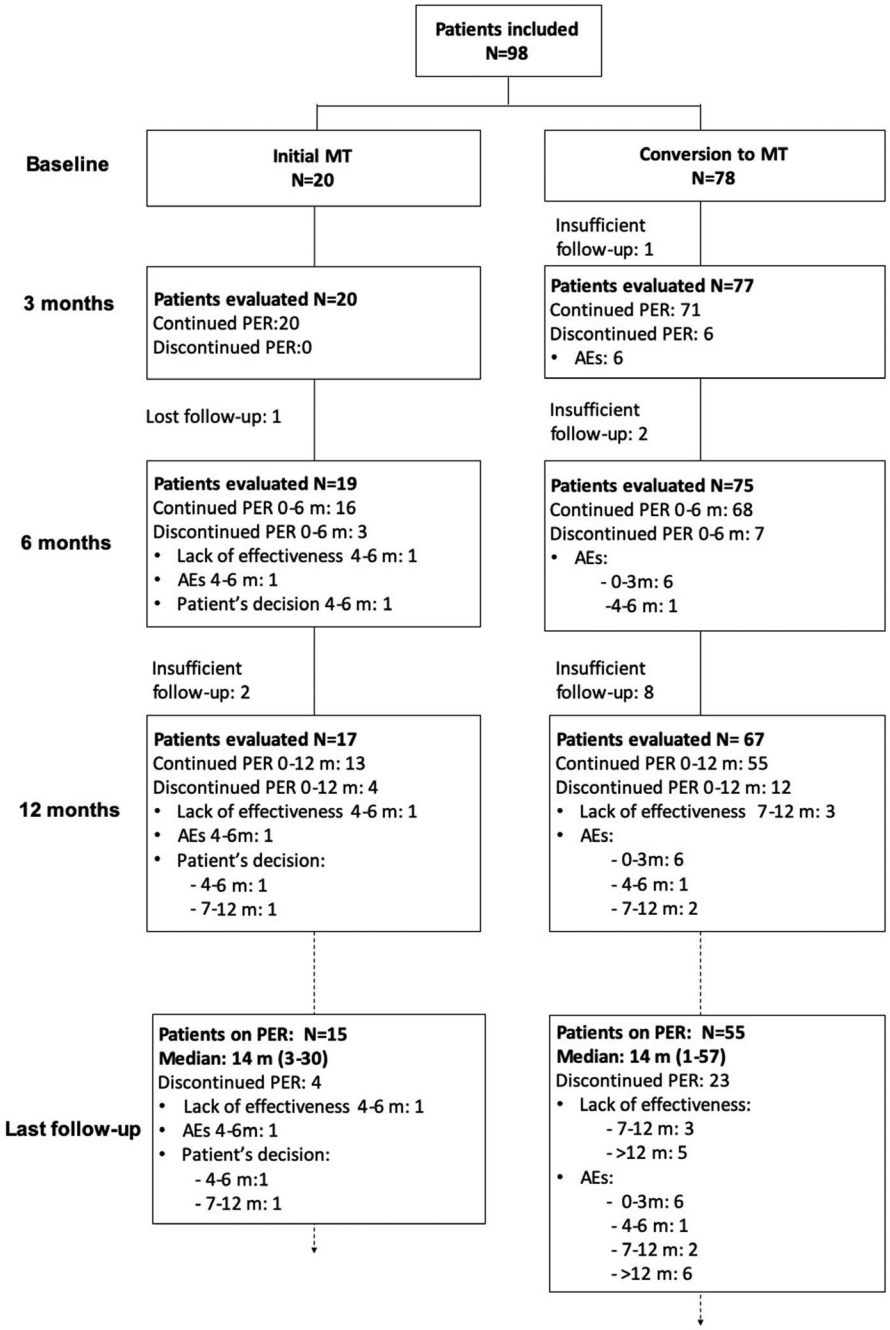

FIGURE 1 Illustration of the number of patients evaluated at each visit who have been treated with perampanel (PER) monotherapy (MT) at some point during the first 12 months and at the last follow-up. AE, adverse event; m, months

(range = 0.3-26, mean = 1.7 ± 3.9), whereas in patients with GTCS, the median frequency of seizures per month was 0.3 (range = 0.3-1.6, mean = 0.5 ± 0.3). On the other hand, among those 38 patients who did not have seizures during the 3-month baseline period, only 15 (39.4%) patients had seizures at some point during the previous 12 months (median = 0.2, range = 0.1-0.5, mean = 0.2 ± 0.1).

In patients with seizures during the baseline period, responder rates for all seizure types at 3, 6, and 12 months were 79.6%, 70.1%, and 52.8%, respectively (Figure 4). Seizure freedom rates at the same points were 62.7%, 56.1%, and 41.5%. Regarding the 33 patients with GTCS, 87.8% were seizure-free at 3 months, 78.1% at 6 months, and 55.1% at 12 months. In a multiple regression analysis, response to PER monotherapy was not found to be associated with age, gender, duration of epilepsy, type of epilepsy, number of previous AEDs, or maintenance dose. Although no significant differences were observed in responder rate or seizure freedom according to the acquisition of monotherapy, seizure freedom rates during the whole observation period were superior in the PM group compared to the CM group (71.4% vs 51.2% at 6 months, 58.3% vs 37.5% at 12 months).

As a secondary objective of the study, we also evaluated the proportion of patients who worsened once they discontinued concomitant AEDs (CM group, n = 78; 79.6%), regardless of whether they had seizures during the baseline period.

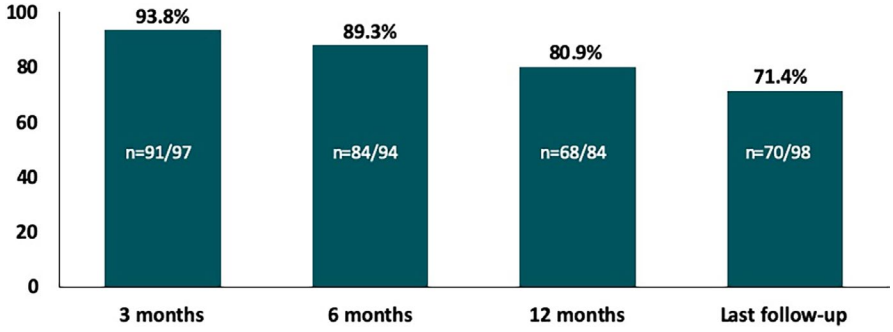

FIGURE 2 Retention rates on perampanel monotherapy

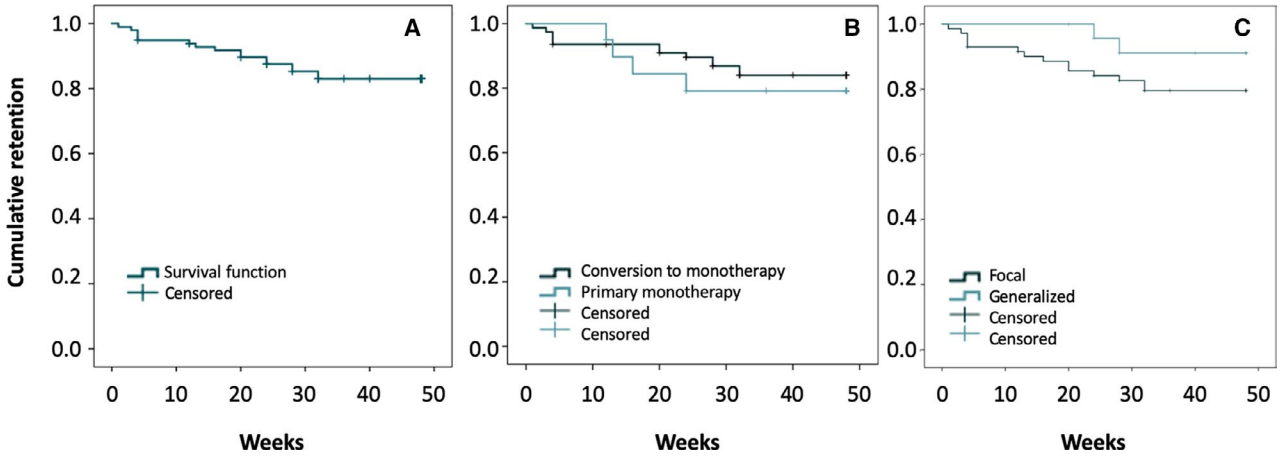

FIGURE 3 Kaplan-Meier plot of retention on perampanel monotherapy in the complete cohort (A), according to the acquisition of monotherapy (B), and according to the type of epilepsy (C)

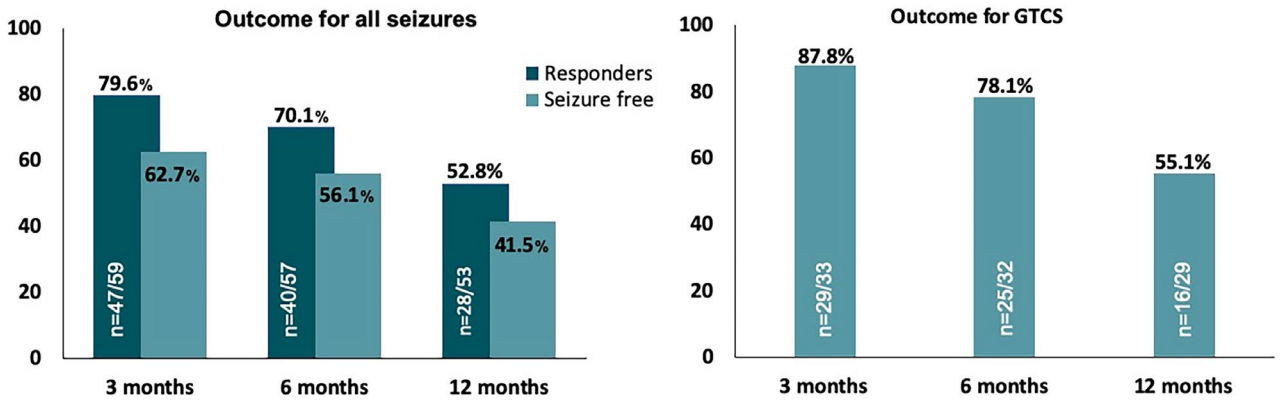

FIGURE 4 Effectiveness outcome on perampanel monotherapy for all seizures (n = 60 patients) and for generalized tonic-clonic seizures (GTCS; n = 33 patients)

For this outcome, 6.5% (5/77) at 3 months, 6.6% (5/75) at 6 months, and 13.4% (9/67) at 12 months had an increase of seizures compared to the baseline period.

3.4 | Safety and tolerability

At the study cutoff (median follow-up = 14 months, range = 1-57 months), 45 patients (45.9%) reported TEAEs at a median daily dose of 4 mg (range = 2-10 mg, mean = 4.8 ± 1.6 mg), which in most cases were rated mild (Table 2). Twenty-eight patients (28.5%) had psychiatric AEs. Irritability was reported by 17 patients, followed by depression in 10 patients and anxiety in one patient. Among nonpsychiatric AEs, mild somnolence and dizziness were the most common, reported by 10 and eight patients, respectively. Other AEs were confusion in one patient and weight gain in another. Although not systematically performed, control blood tests did not show any significant abnormality.

TABLE 2 Characteristics of TEAEs related to perampanel at the last follow-up

TEAEs	n (%)
Any TEAEs	45 (45.9)
Severe TEAEs	4 (4)
Depression	3 (3)
Irritability	1 (1)
TEAEs leading to dose adjustment	
Dose reduction	4 (4)
Psychiatric	3 (3)
Confusion	1 (1)
Withdrawal	16 (16.3)
Dizziness	2 (2)
Psychiatric	14 (14.3)
Most frequent TEAEs (≥5% of patients)	
Irritability	17 (17.3)
Depression	10 (10.2)
Somnolence	10 (10.2)
Dizziness	8 (8.1)

Note.: Median follow-up = 14 months, range = 1-57 months.

Abbreviation: n, number of patients; TEAEs, treatment-emergent adverse events.

During the first 12 months of follow-up, 10 patients (10.2%) discontinued PER monotherapy due to TEAEs, increasing to 16 patients (16.3%) at the last follow-up. Common TEAEs leading to the withdrawal of PER were dizziness (2%) and psychiatric AEs (14.3%); three patients developed depression and another one irritability that were rated severe by the treating physicians. In all cases, these unexpected psychiatric AEs resolved once PER was withdrawn.

Logistic regression analysis showed that the risk of developing TEAEs was higher in patients who previously took a greater number of AEDs (odds ratio [OR] = 1.63, 95% CI = 1.09-2.45, $P = .009$) and in females (female vs male OR = 4.76, 95% CI = 1.85-12.5, $P \leq .001$). Furthermore, females were also at a higher risk of psychiatric AEs (female vs male OR = 2.85, 95% CI = 1-8.33, $P \leq .046$). On the other hand, older patients were at a lower risk of developing psychiatric AEs (OR = 0.97, 95% CI = 0.93-1, $P \leq .034$). Other variables such as type and duration of epilepsy, maximal dose of PER used, titration schedule, and previous psychiatric history (either related to other AEDs or as comorbidities) were not predictive of developing AEs (including psychiatric AEs) with PER.

4 | DISCUSSION

Our study shows the experience acquired during the first year of treatment with PER monotherapy in a relatively large cohort of 98 patients in whom monotherapy was indicated directly (PM) or after progressive withdrawal of concomitants AEDs (CM). The patients in this study represent the real-world epilepsy population, and as such, it is a heterogeneous population in terms of epilepsy syndromes, etiologies, comorbidities, age, and response to previous antiepileptic treatments. Although there is limited information regarding clinical experience with PER monotherapy, recent studies are encouraging in suggesting that PER might be useful as a monotherapy in a selected group of patients. In this regard, a previous European study,[10] with a smaller number of patients and a shorter follow-up, has shown that monotherapy with PER was feasible. Two postmarketing studies[11,12] have already shown that monotherapy with PER could be reached through conversion to monotherapy in up to 4% of patients with either focal seizures or IGE. Additionally, a subanalysis of the open-label extension studies[13] showed that a small proportion of patients with drug-resistant epilepsy were successfully converted to monotherapy.

This study demonstrates that once daily monotherapy with PER was effective and well tolerated in a population with FOS and GTCSs, as most of the patients stayed on monotherapy throughout the whole study (mean exposure = 14.8 ± 9.1 months). The probability of remaining on PER monotherapy was as high as 89% at 6 months and slightly decreased to 80% at 12 months. At the study cutoff date, 71% of patients were still on PER monotherapy at a relatively low dose (median dose = 4 mg). Among the different variables evaluated, longer duration of epilepsy was found to be associated with a higher risk of discontinuation of PER monotherapy. In our population, both patients with focal epilepsy and those with generalized epilepsy presented with similar retention rates; additionally, older patients (≥65 years) benefited similarly to younger patients. Our retention rates are similar to those observed in the study by Gil-Nagel et al,[10] with retention rates of 95% and 74% at 3 and 6 months, respectively. The outcomes presented here are in line with a study of PER as early add-on treatment in patients with focal epilepsy (retention rate of 80.5% at 12 months)[11] and with another study in patients with IGE (retention rate of 83% at 12 months).[12] On the other hand, our data are more optimistic than other observational studies in routine clinical use (retention rates of 48%–60% at 12 months),[16–23] where PER was added to the treatment of patients with focal epilepsy who had a higher degree of refractoriness as revealed by a greater number of previous AEDs, a higher frequency of seizures during the baseline period, and a larger median dose of PER than in our population.

Overall, the responder rates for all seizures were as high as 70% at 6 months and 52% at 12 months. At the same time points, seizure freedom was reached in 56% and 41.5% of patients, with a better response in patients with PM, although it was not statistically significant. Our outcomes were superior

to most observational studies and phase III clinical trials of PER (responder rates of 26.8%-38.9% at 1 year),[16,18,24,25] as patients included in those studies were more resistant to treatment than our population. As expected from extrapolation of results of regulatory and open-label extension trials,[2–5,26] in our population, PER was also efficacious in patients with GTCS, with 78% and 55% of patients rendered seizure-free at 6 and 12 months, respectively. The good response we observed in this study is in line with other observational studies where PER was considered as an early add-on (responder rates of 50% and 68% at 6-12 months),[11] stressing that patients with less resistant epilepsy could benefit from PER at low doses, as shown in this study. Besides this, when considering conversion to monotherapy, caution needs to be taken, because some patients could potentially experience a seizure increase due to the discontinuation of concomitant AEDs.

PER monotherapy was relatively well tolerated, with a rate of TEAEs of 45.9% at the last follow-up, which compares favorably with AEs reported in previous observational studies with more refractory patients (50%-67.6% and up to 80% in patients with intellectual disability).[12,16,17,19,21,27] Additionally, we did not observe a higher risk of TEAEs among older patients. When compared with other observational studies where PER was considered as an early add-on or as conversion to monotherapy, the higher rate of TEAEs observed in our study (45.9% vs 20%-41.5%)[10–12] could be explained by a longer follow-up; supporting this is the finding that the discontinuation rate in the first 12 month of follow-up due to TEAEs was similar to those studies (10% vs 7%-15.9%).[10–12] We did not observe any unknown AEs not reported in previous studies, and most of the TEAEs were considered mild and, therefore, did not change substantially the treatment schedule with PER. Up to 8%-10% of patients reported dizziness and somnolence, respectively, which are significantly lower rates than those reported in clinical trials (32% with 8 mg of PER)[24] and could be explained by a lower dose of PER within a more flexible schedule in this study. Moreover, PER dose and titration were not predictive of developing AEs. This finding, which is similar to previous studies,[12,18] has not been found by others[11,16] who described a lower risk of AEs with slow titration and low doses. Discrepancy between studies regarding this potential association might be explained by differences in the definitions used of slow versus rapid titration. Additionally, our conservative dosing, with a low median dose of 4 mg/d, and the similar titration scheme among most of our patients, may also explain why we did not find any statistically significant association when we looked at these variables.

In our population, psychiatric AEs were reported in 28% of patients and led to discontinuation of PER in 14%. Severe psychiatric AEs were seen in only four patients. Irritability and depression were the most common psychiatric AEs (17% and 10%, respectively), with rates similar to the clinical experience reported by others in different observational studies[16,18,28] and slightly superior to what is reported in clinical trials (12.3% hostility/aggression for 8 mg).[29] These differences can be accounted for by the exclusion of patients with antecedent of psychiatric comorbidities in phase III trials as well as the short-term follow-up in these regulatory studies, which are not long enough to unmask these potential emerging psychiatric side effects. Contrary to other studies,[16,28] a previous psychiatric history was not found to be associated with a higher risk of developing psychiatric AEs with PER. These data could be explained by the use of a lower dose of PER in our study compared to studies that evaluated more refractory patients.[16] However, discrepancy between studies may also be due to the inclusion of an insufficient number of patients who had baseline psychiatric comorbidities. In our cohort, older patients were at a lower risk of having psychiatric AEs with PER. This finding could also be explained by the use of a lower dose of PER in this subgroup of patients (median dose of 4 mg in patients aged ≥65 years vs 6 mg in younger patients), which reflects a more conservative approach in older patients. On the other hand, women were found to be at a higher risk of any AEs and especially psychiatric AEs. Although this association has not been reported in other studies of PER with more patients, and therefore could be fortuitous, it has been acknowledged with other AEDs.[30]

Limitations of this study include the retrospective design, which potentially hampers the homogenous collection of information regarding clinical responses and AEs across different centers. However, because all patients were followed by specialized epilepsy departments, it is unlikely that important AEs were missed. It is possible that some of these results may have been influenced by the small numbers of patients in each category, which could limit the detection of a more statistically robust association between the different variables and the outcomes evaluated. Taking these limitations into consideration, the value of our study includes the existence of long-term follow-up data and a real-life picture of the performance of PER monotherapy in routine clinical practice, which includes patients who are not typically evaluated in more rigid studies, providing meaningful information that complements that of clinical trials.

In conclusion, we found that PER is an effective treatment when used as monotherapy at relatively low doses in patients with FOS and GTCS in routine clinical practice. The high retention rate found in our study, which reflects both its tolerability and its effectiveness, combined with its broad-spectrum mechanism of action and attractive posology, supports the proposition that some patients with epilepsy might benefit from monotherapy with PER.

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design, the collection, analysis, and interpretation of the data gathered, the writing of the report, or the decision to submit the article for publication.

CONFLICT OF INTEREST

R.T.D. has participated on advisory boards and in industry-sponsored symposia for Eisai, UCB, Bial, Esteve, and GW Pharmaceuticals. I.G.-M. has participated on advisory boards and in industry-sponsored symposia for Eisai, UCB, Bial, and Esteve. B.P.-C. has participated in pharmaceutical industry–sponsored symposia for Bial, Eisai, Esteve, and UCB. E.S. has participated on advisory boards and in pharmaceutical industry–sponsored symposia for Eisai, UCB, Bial, and Esteve. M.T. has received grants and honoraria from Bial, Eisai, and UCB Pharma, and has received honoraria from Cyberonics, Esteve, GSK, and Shire. J.O. has participated on advisory boards and in industry-sponsored symposia for Eisai, UCB, and Bial. J.J.P. has participated on advisory boards and in industry-sponsored symposia for Eisai, UCB, Bial, and Esteve. A.G.-I. has participated on advisory boards and in industry-sponsored symposia for Eisai, UCB, and GW Pharmaceuticals. J.R.-U. has participated on advisory boards for UCB, Eisai, Bial, and Pfizer. A.M. has participated in industry-sponsored symposia for UCB, Bial, Eisai, and Esteve. M.D.C.-V. has participated on advisory boards and in industry-sponsored symposia for Eisai, UCB, Bial, and Esteve. J.Z.S. has participated in industry-sponsored symposia for UCB, Bial, Eisai, and Esteve. A.G.-N. has received speaker honoraria and research grants from Bial, Eisai, and Nutricia, speaker honoraria and advisory fees from Sanofi, speaker honoraria, educational grants, and advisory fees from UCB Pharma, advisory fees from GW Pharma and Esteve, and speaker honoraria from Zogenix. D.C. has participated in industry- sponsored symposia for UCB, Bial, and Eisai. J.A.M.L. has participated in industry-sponsored symposia for UCB, Bial, and Eisai. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Hanada T, Hashizume Y, Tokuhara N, et al. Perampanel: a novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. Epilepsia. 2011;52:1331–40.
2. French JA, Krauss GL, Biton V, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology. 2012;79:589–96.
3. French JA, Krauss GL, Steinhoff BJ, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. Epilepsia. 2013;54:117–25.
4. French JA, Krauss GL, Wechsler RT, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy: a randomized trial. Neurology. 2015;85:950–7.
5. Krauss GL, Serratosa JM, Villanueva V, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology. 2012;78:1408–15.
6. European Medicines Agency. Fycompa® Annex 1: Summary of Product Characteristics. January 2019 [cited 2020 Feb 7]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002434/WC500130815.pdf.oTitle .
7. Food and Drug Administration. Fycompa® Highlights of Prescribing Information. July 2017 [cited 2020 Feb 7]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202834s012,208277s001lbl.pdf.
8. Mintzer S, French JA, Perucca E, et al. Is a separate monotherapy indication warranted for antiepileptic drugs? Lancet Neurol. 2015;14:1229–40.
9. Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. Pharmacoepidemiol Drug Saf. 2017;26:1033–9.
10. Gil-Nagel A, Burd S, Toledo M, et al. A retrospective, multicentre study of perampanel given as monotherapy in routine clinical care in people with epilepsy. Seizure. 2018;54:61–6.
11. Abril Jaramillo J, Estévez María JC, Girón Úbeda JM, et al. Effectiveness and safety of perampanel as early add-on treatment in patients with epilepsy and focal seizures in the routine clinical practice: Spain prospective study (PERADON). Epilepsy Behav. 2019;102:106655.
12. Villanueva V, Montoya J, Castillo A, et al. Perampanel in routine clinical use in idiopathic generalized epilepsy: the 12-month GENERAL study. Epilepsia. 2018;59:1740–52.
13. Kwan P, Mintzer S, Laurenza A, Patten A, Cartwright K. Evaluation of perampanel as monotherapy for focal seizures: experience from open-label extension studies. Epilepsy Behav Case Rep. 2018;9:1–5.
14. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522–30.
15. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.
16. Villanueva V, Garcés M, López-González FJ, et al. Safety, efficacy and outcome-related factors of perampanel over 12 months in a real-world setting: the FYDATA study. Epilepsy Res. 2016;126:201–10.
17. Steinhoff BJ, Bacher M, Bast T, et al. First clinical experiences with perampanel—the Kork experience in 74 patients. Epilepsia. 2014;55:16–8.

18. Rohracher A, Zimmermann G, Villanueva V, et al. Perampanel in routine clinical use across Europe: pooled, multicenter, observational data. Epilepsia. 2018;59:1727–39.
19. Shah E, Reuber M, Goulding P, et al. Clinical experience with adjunctive perampanel in adult patients with uncontrolled epilepsy: a UK and Ireland multicentre study. Seizure. 2016;34:1–5.
20. Juhl S, Rubboli G. Perampanel as add-on treatment in refractory focal epilepsy. The Dianalund experience. Acta Neurol Scand. 2016;134:374–7.
21. Huber B, Schmid G. A two-year retrospective evaluation of perampanel in patients with highly drug-resistant epilepsy and cognitive impairment. Epilepsy Behav. 2017;66:74–9.
22. Takahashi S, Shimizu K, Inaji M, et al. Effectiveness of perampanel as a first add-on antiepileptic drug for the treatment of partial epilepsy. Epilepsy Behav. 2019;100:106492.
23. Steinhoff BJ, Hamer H, Trinka E, et al. A multicenter survey of clinical experiences with perampanel in real life in Germany and Austria. Epilepsy Res. 2014;108:986–8.
24. Steinhoff BJ, Ben-Menachem E, Ryvlin P, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies. Epilepsia. 2013;54:1481–9.
25. Garamendi-Ruiz I, García-García ME, Bertol-Alegre V, et al. One-year clinical experience of perampanel in Spain: a multicentre study of efficacy and tolerability. Epileptic Disord. 2016;18:173–80.
26. Krauss GL, Perucca E, Kwan P, et al. Final safety, tolerability, and seizure outcomes in patients with focal epilepsy treated with adjunctive perampanel for up to 4 years in an open-label extension of phase III randomized trials: Study 307. Epilepsia. 2018;59:866–76.
27. Andres E, Kerling F, Hamer H, et al. Behavioural changes in patients with intellectual disability treated with perampanel. Acta Neurol Scand. 2017;136:645–53.
28. Stephen LJ, Wishart A, Brodie MJ. Psychiatric side effects and antiepileptic drugs: observations from prospective audits. Epilepsy Behav. 2017;71:73–8.
29. Ettinger AB, LoPresti A, Yang H, et al. Psychiatric and behavioral adverse events in randomized clinical studies of the noncompetitive AMPA receptor antagonist perampanel. Epilepsia. 2015;56:1252–63.
30. Josephson CB, Engbers JDT, Jette N, et al. Prediction tools for psychiatric adverse effects after levetiracetam prescription. JAMA Neurol. 2019;76:440–6.

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