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Perampanel for the treatment of patients with myoclonic seizures in clinical practice: Evidence from the PERMIT study

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ABSTRACT

Purpose: To investigate the effectiveness, safety and tolerability of perampanel (PER) in treating myoclonic seizures in clinical practice, using data from the PERaMpanel pooled analysIs of effecTiveness and tolerability (PERMIT) study.

Methods: PERMIT was a pooled analysis of 44 real-world studies from 17 countries, in which patients with focal and generalised epilepsy were treated with PER. This *post-hoc* analysis included patients with myoclonic seizures at baseline. Retention and effectiveness were assessed after 3, 6, and 12 months; effectiveness was additionally assessed at the last visit (last observation carried forward). Effectiveness assessments included responder rate (≥50% seizure frequency reduction from baseline) and seizure freedom rate (no seizures since at least the prior visit). Safety and tolerability were assessed by evaluating adverse events (AEs) and discontinuation due to AEs.

Results: 156 patients had myoclonic seizures (59.0% female; mean age, 32.1 years; idiopathic generalised epilepsy, 89.1%; Juvenile Myoclonic Epilepsy, 63.1%; monthly median myoclonic seizure frequency [interquartile range], 1.7 [1.0–10.0]; mean [standard deviation] prior antiseizure medications, 2.9 [2.6]). Retention was assessed for 133 patients (mean time, 12.1 months), effectiveness for 142, and safety/tolerability for 156. Responder and seizure freedom rates were, respectively, 89.5% and 68.8% at 12 months, and 85.9% and 63.4% at the last visit. Incidence of AEs was 46.8%, the most frequent being dizziness/vertigo (19.2%), irritability (18.6%) and somnolence (9.6%). AEs led to discontinuation of 14.0% of patients over 12 months.

Conclusion: PER was associated with reduction in myoclonic seizure frequency in patients with myoclonic seizures treated in everyday clinical practice.

1. Introduction

Myoclonic seizures are involuntary jerks (brief muscular contractions) arising from the central nervous system, which can vary in distribution and intensity and may occur in different epilepsy syndromes, including some types of idiopathic generalised epilepsy (IGE), progressive myoclonus epilepsies and epileptic encephalopathies [1,2]. The International League Against Epilepsy includes classifications for myoclonic seizures that are both focal and generalised in origin [3]. Some myoclonic epilepsies, including progressive myoclonus epilepsies

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such as Unverricht–Lundborg Disease, are amongst the most disabling types of epilepsy [4]. Myoclonic seizures are challenging to treat because not all antimyoclonic drugs are antiepileptic and only a limited number of antiseizure medications (ASMs) are antimyoclonic; indeed, some ASMs (e.g., carbamazepine, phenytoin) may induce myoclonic seizures or exacerbate existing myoclonic seizures [2,5]. Treatment is further complicated because myoclonic seizures frequently occur with other seizure types [6]. Correct choice of treatment requires accurate diagnosis of a patient's epilepsy syndrome, and some myoclonic epilepsies are refractory to treatment [5]. Available treatment options are currently limited. Valproate and benzodiazepines, such as clonazepam, have historically been used to treat myoclonic seizures, and work by enhancing γ-aminobutyric acid activity in the brain [5]. Levetiracetam is also used to treat myoclonic seizures [2,7–9], although there have been reports of myoclonic seizure exacerbation in some patients [10–12]. In addition, there are a few reports showing some effectiveness of zonisamide [13,14] and topiramate [15], but side effects have been reported. Piracetam and phenobarbital have also been included in treatment guidelines for myoclonic seizures [16].

Perampanel (PER) is a first-in-class, potent, selective, orally active, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist [17–19]. In clinical trials, PER was effective in treating focal-onset seizures, with or without focal to bilateral tonic-clonic seizures [20,21], and generalised tonic-clonic seizures in patients with IGE [22]. *Post-hoc* analysis of clinical trial data also provided limited evidence of PER's efficacy in treating myoclonic seizures [23]. In Europe, PER is indicated for the adjunctive treatment of focal-onset seizures, with or without focal to bilateral tonic-clonic seizures, in patients aged ≥4 years, and primary generalised tonic-clonic seizures in patients aged ≥7 years with IGE [24]. In the USA, PER is indicated as monotherapy and adjunctive therapy for the treatment of focal-onset seizures, with or without focal to bilateral tonic-clonic seizures, in patients with epilepsy aged ≥4 years, and as adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in patients with epilepsy aged ≥12 years [25].

Real-world data are generally taken to refer to clinical data collected outside the randomised controlled clinical trial setting, and may be derived from a variety of sources, including electronic health records, insurance databases, patient registries, and retrospective or prospective studies conducted under clinical practice conditions [26,27]. Real-world clinical practice data complement evidence from clinical trials by providing information on patients who are more diverse in terms of clinical characteristics than those recruited for clinical trials, as well as insights into the individualised treatment strategies employed in clinical practice [28–30]. Currently, only a few clinical practice studies have investigated PER for the treatment of myoclonic seizures [31–35]. The PERaMpanel pooled analysIs of effecTiveness and tolerability (PERMIT) study is the largest pooled analysis of PER clinical practice data conducted to date, including approximately 5200 patients treated with PER for focal and/or generalised epilepsy [36]. The large size of the PERMIT cohort has allowed meaningful subgroup analyses to be conducted. The objective of this study was to investigate the effectiveness, safety and tolerability of PER when used to treat myoclonic seizures in everyday clinical practice, using data from the PERMIT study.

2. Methods

2.1. Study design

PERMIT was a pooled analysis of real-world data from 44 prospective, retrospective and cross-sectional studies and work groups in which patients with focal and generalised epilepsy were treated with PER, full details of which have been previously published [36]. The studies were identified by a systematic PubMed literature search, supported by searches of abstracts from key epilepsy congresses from 2012 to December 2019 [36]. All of the studies were either previously published or presented at an international conference, with clearly defined inclusion/exclusion criteria. Effectiveness was assessed after 3, 6, and 12 months of PER treatment and at final follow-up (i.e., the last observation of each patient, independent of the timepoint when it occurred [last observation carried forward]; defined as 'last visit'). Safety and tolerability were assessed for the duration of PER treatment. Each study in PERMIT was approved by its own independent ethics committee and letters were sent to these ethics committees to inform them about the PERMIT study; as per current legislation, additional ethics committee approval was not required for participation in PERMIT [36]. A *post-hoc* subgroup analysis was conducted of patients in PERMIT who had myoclonic seizures at baseline.

2.2. Study population

The studies included in PERMIT employed broad inclusion/exclusion criteria, to be representative of patients encountered in clinical practice [36]. The current analysis included all patients who had myoclonic seizures at baseline.

2.3. Study assessments

Retention was assessed after 3, 6 and 12 months of PER treatment. Effectiveness was assessed after 3, 6 and 12 months and at the last visit. Effectiveness assessments comprised number of myoclonic seizures/month, number of days with myoclonic seizures/month, seizure freedom rate, responder rate, and the proportions of patients with unchanged or worsening seizure frequency. Seizure freedom was defined as no myoclonic seizures since at least the prior visit (either 3 or 6 months, depending on the timepoint at which seizure freedom was assessed), and response was defined as ≥50% myoclonic seizure frequency reduction from baseline (i.e., prior to PER initiation). An increase or decrease in seizure frequency of ≤10% was classified as 'unchanged seizure frequency'. Safety and tolerability were assessed by evaluating adverse events (AEs), AEs leading to discontinuation, psychiatric AEs, and psychiatric AEs in patients who discontinued. Information on PER dosing was also assessed.

2.4. Subgroup analyses

Several additional subgroup analyses of patients with myoclonic seizures at baseline were conducted. These included comparisons between: patients diagnosed with versus without IGE; patients with versus without psychiatric comorbidity at baseline; patients for whom a slow (<2 mg/week) versus fast (2 mg/week) PER titration schedule was used; patients treated with 0, 1, 2 and ≥3 previous ASMs; and patients treated with 0, 1, 2 and ≥3 concomitant ASMs. For all subgroup analyses except the last two, assessments included retention, effectiveness (responder and seizure freedom rates, as previously defined) and safety/tolerability (as previously described). For the subgroup analyses based on number of previous and concomitant ASMs, assessments comprised responder and seizure freedom rates only.

2.5. Statistical analyses

The statistical methodology employed in PERMIT has been published previously [36]. The Full Analysis Set (FAS) included all patients treated with PER. The Retention Population included patients from the FAS whose PER status was known at some point during the first 12 months after starting treatment (including those with ongoing PER treatment at 12 months, those who stopped PER prior to 12 months and those lost to follow-up/end of study follow-up prior to 12 months). The Effectiveness Population included patients from the FAS who had at least one effectiveness measurement available. The Tolerability Population included patients from the FAS for whom data on AEs were available.

There was great heterogeneity in the objectives of each study

included in the pooled analysis and therefore in the information reported. As previously described, PERMIT attempted to combine reported information in the most complete way possible [36]. Missing data were not imputed, except in cross-sectional studies, in which the last visit datum was captured for inclusion in the established cut-off points (3, 6 or 12 months). When the observation timepoint of the study did not match the established cut-off points, the following allocations were made: observations performed between 1.5 and 4.5 months were allocated to the 3-month visit; those performed between 4.5 and 9 months were allocated to the 6-month visit; and those performed between 9 and 15 months were allocated to the 12-month visit. A 'final' variable was created in which the last observation of each patient was included, independently of the moment when it occurred (defined as 'last visit'). No hypothesis was defined, and no systematic review of individual patients was considered, due to the heterogeneity of the individual samples, as well as of the different objectives of each study; therefore, the individual studies were not treated as clusters. Quantitative variables were described as mean, standard deviation (SD), median, minimum and maximum values, together with the number of valid cases and confidence intervals (CIs) or interquartile range (IQR; 25th percentile to 75th percentile). Qualitative variables were described as absolute frequencies and percentages. Data were not available for all patients at every time point; therefore, for each variable, the total number of patients for whom the datum in question was available is stated and this value was used as the denominator for frequency analyses. Retention (on PER treatment) was studied over 12 months using Kaplan–Meier methodology. The numbers of myoclonic seizures/month and days with myoclonic seizures/month were compared between baseline and last visit using the Wilcoxon test. Between-group comparisons of patients with versus without IGE, patients with versus without psychiatric comorbidity at baseline, and patients for whom a slow (<2 mg/week) versus fast (2 mg/week) PER titration schedule was used, were conducted using the Chi-squared test and Fisher's exact test, as appropriate. The significance level was set at 5% and the statistical package SPSS 25.0 was used for all analyses.

3. Results

PERMIT collected information from 5200 patients with epilepsy who initiated PER treatment and the final FAS included 5193 patients [36]. Of the patients included in the PERMIT FAS population, 156 had myoclonic seizures at baseline (median [IQR] monthly frequency, 1.7 [1.0–10.0]; mean [SD] monthly frequency, 7.7 [11.3]). Retention was assessed for 133 of these patients, effectiveness for 142 patients, and safety/tolerability for 156 patients.

3.1. Study population

Fifty-nine percent of the population were female, and the mean (SD) age was 32.1 (13.0) years (Table 1). The mean (SD) age at epilepsy onset was 14.9 (9.5) years and the mean (SD) duration of epilepsy was 17.0 (13.1) years. Most patients (97.4%) had a presumed genetic aetiology, and a range of epileptic syndromes was represented; the most frequent types (>10% of patients) being Juvenile Myoclonic Epilepsy (JME) (63.6%) and other IGE (syndrome unclassified; 25.2%). Overall, 40.5% of patients had learning disability at baseline and 19.4% had psychiatric comorbidity. The most frequently reported psychiatric comorbidities (≥5% of patients) were anxiety (6.3%) and depression (5.6%). Nearly all patients (96.8%) had only generalised-onset seizures at baseline, a minority (3.2%) having both generalised-onset and focal-onset seizures. The mean (SD) number of ASMs patients had been treated with prior to initiating PER was 2.9 (2.6), the most frequently used prior ASMs (≥20% of patients) being valproate (35.8%) and levetiracetam (33.0%). Most patients received one or two concomitant ASMs at PER initiation. The most frequently used concomitant ASMs (≥20% of patients) were levetiracetam (50.0%), valproate (34.7%) and zonisamide (22.0%).

Table 1
Demographic and baseline characteristics (full analysis set/tolerability population).

Characteristic	Full analysis set/tolerability population $N = 156$
Sex	
N[a]	156
Female, n (%)	92 (59.0)
Male, n (%)	64 (41.0)
Age	
N[a]	151
Mean (SD), years	32.1 (13.0)
Median (range), years	30.0 (13.0–78.0)
Age category	
N[a]	156
<12 years, n (%)	4 (2.6)
≥12–<18 years, n (%)	15 (9.6)
≥18–<65 years, n (%)	135 (86.5)
≥65 years	2 (1.3)
Age at epilepsy onset	
N[a]	141
Mean (SD), years	14.9 (9.5)
Median (range), years	13.0 (0.0–58.0)
Duration of epilepsy	
N[a]	141
Mean (SD), years	17.0 (13.1)
Median (range), years	15.0 (0.0–61.0)
Aetiology[b]	
N[a]	152
Genetic, n (%)	148 (97.4)
Structural, n (%)	1 (0.7)
Unknown, n (%)	3 (2.0)
Epilepsy syndrome diagnosis	
N[a]	151
No, n (%)	2 (1.3)
Yes, n (%)	149 (98.7)
IGE, n (%)	139 (92.1)
JME, n (%)	96 (63.6)
Juvenile Absence Epilepsy, n (%)	3 (2.0)
Jeavons Syndrome, n (%)	2 (1.3)
Other IGE (syndrome unclassified), n (%)	38 (25.2)
Not IGE, n (%)	10 (6.6)
MERRF, n (%)	4 (2.6)
Angelman Syndrome, n (%)	2 (1.3)
Progressive Myoclonic Epilepsy, n (%)	2 (1.3)
Lennox-Gastaut Syndrome, n (%)	1 (0.7)
West Syndrome, n (%)	1 (0.7)
Learning disability	
N[a]	42
No, n (%)	25 (59.5)
Yes, n (%)	17 (40.5)
Psychiatric comorbidity	
N[a]	144
No, n (%)	116 (80.6)
Yes, n (%)	28 (19.4)
Seizure type	
N[a]	156
Generalised-onset only, n (%)	151 (96.8)
Focal-onset and generalised-onset, n (%)	5 (3.2)
Number of previous ASMs	
N[a]	143
Mean (SD)	2.9 (2.6)
Median (range)	2.0 (0–13)
Number of previous ASMs	
N[a]	143
0, n (%)	23 (16.1)
1, n (%)	27 (18.9)
2, n (%)	26 (18.2)
3, n (%)	25 (17.5)
4, n (%)	15 (10.5)
5, n (%)	9 (6.3)
≥6, n (%)	18 (12.6)
Number of concomitant ASMs	
N[a]	151
Mean (SD)	1.8 (1.2)

(continued on next page)

Table 1 (*continued*)

Characteristic	Full analysis set/tolerability population $N = 156$
Median (range)	1.0 (0–5)
Number of concomitant ASMs	
N[a]	151
0, n (%)	17 (11.3)
1, n (%)	59 (39.1)
2, n (%)	33 (21.9)
3, n (%)	27 (17.9)
≥4, n (%)	15 (9.9)
Most frequently used[c] concomitant ASMs	
N[a]	150
Levetiracetam, n (%)	75 (50.0)
Valproate, n (%)	52 (34.7)
Zonisamide, n (%)	33 (22.0)
Lamotrigine, n (%)	25 (16.7)
Clonazepam, n (%)	23 (15.3)
Clobazam, n (%)	17 (11.3)

[a] Number of patients for whom datum in question was available.
[b] International League Against Epilepsy 2017 classification.
[c] ≥10% of patients.
ASM, antiseizure medication; JME, Juvenile Myoclonic Epilepsy; IGE, idiopathic generalised epilepsy; MERFF, Myoclonic Epilepsy associated with Ragged Red Fibres; SD, standard deviation.

3.2. Treatment (FAS/tolerability population)

The mean (SD) PER dose was 2.6 (1.1) mg/day at baseline (median, 2.0 mg/day; range, 2–6 mg/day; $n = 47$) and 5.5 (2.1) mg/day at the last visit (median, 6.0 mg/day; range, 2–12 mg/day; $n = 146$). A fast titration (2 mg/week) was used in 13.5% (7/52) of patients and a slow titration (<2 mg/week) was used in 86.5% (45/52). The mean (SD) number of concomitant ASMs was 1.8 (1.2) at baseline (median, 1.0; range, 0–5; $n = 151$) and 1.3 (0.9) at the last visit (median, 1.0; range, 0–4; $n = 98$). The proportion of patients treated with PER as monotherapy was 11.3% (17/151) at baseline and 11.2% (11/98) at the last visit.

3.3. Retention (retention population)

Retention rates were 94.7% (126/133), 89.0% (113/127) and 80.7% (92/114) at 3, 6 and 12 months, respectively. The mean (95% CI) time under PER treatment was 12.1 (11.4–12.7) months (Fig. 1). Reasons for discontinuation of PER treatment at 12 months included AEs ($n = 13$; 11.4%), lack of efficacy ($n = 5$; 4.4%), both AEs and lack of efficacy ($n = 3$; 2.6%), and unknown ($n = 1$; 0.9%).

3.4. Effectiveness (effectiveness population)

The number of myoclonic seizures per month decreased significantly between baseline and the last visit, the mean decrease being 64.9% ($p<0.001$; Fig. 2A). Similarly, the number of days with myoclonic seizures per month decreased significantly between baseline and the last visit, the mean decrease being 64.8% ($p<0.001$; Fig. 2B). At 12 months, the responder rate was 89.5% (77/86) and the rate of seizure freedom since the previous visit was 68.8% (64/93); the proportions of patients with unchanged and worsening seizure frequency were 5.8% (5/86) and 3.5% (3/86), respectively (Fig. 3). At the last visit, responder and seizure freedom rates were 85.9% (110/128) and 63.4% (90/142), respectively; and the proportions of patients with unchanged and worsening seizure frequency were 10.2% (13/128) and 3.1% (4/128), respectively (Fig. 3).

3.5. Safety and tolerability (tolerability population)

AEs were reported for 46.8% (73/156) of patients (Table 2). The most frequently reported AEs (≥5% of patients) were dizziness/vertigo (19.2%), irritability (18.6%) and somnolence (9.6%). AEs led to discontinuation of 14.0% (16/114) of patients over 12 months. Psychiatric AEs were reported for 24.7% (38/154) of patients and 6.9% (9/131) of patients with psychiatric AEs discontinued. The most frequently reported psychiatric AE (≥5% of patients) in patients who discontinued was irritability (5.3% [7/131]).

3.6. Subgroup analyses

3.6.1. Patients diagnosed with IGE at baseline

Overall, 139/156 (89.1%) patients with myoclonic seizures were diagnosed with IGE and 17/156 (10.9%) were not diagnosed with IGE at baseline. Retention at 12 months and the responder rate at the last visit were not significantly different between subgroups, but the seizure freedom rate at the last visit was significantly higher in patients with versus without IGE (Fig. 4A). The incidences of AEs, AEs leading to discontinuation and psychiatric AEs, and the percentages of patients with psychiatric AEs who discontinued, were not significantly different between patients with versus without IGE (Supplementary Table S1A). As in the overall population, the most frequently reported AEs (≥5% of

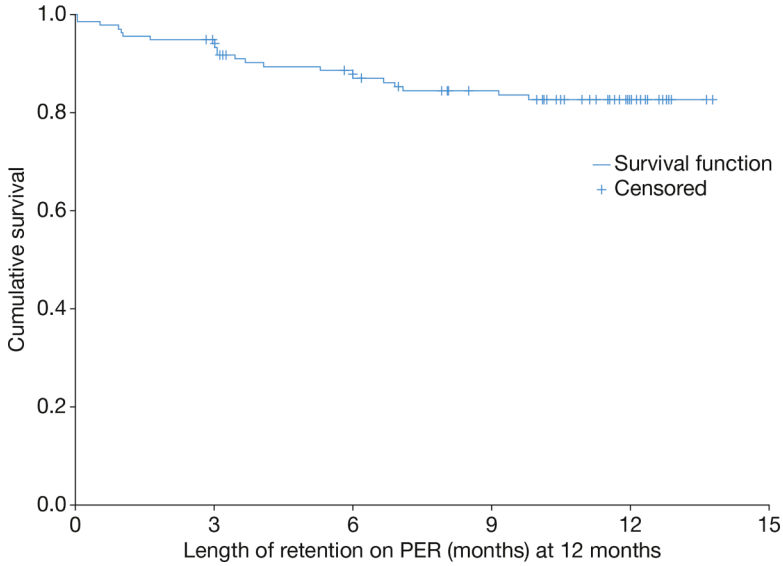

Fig. 1. Kaplan–Meier curve for retention on PER treatment over 12 months (retention population). PER, perampanel.

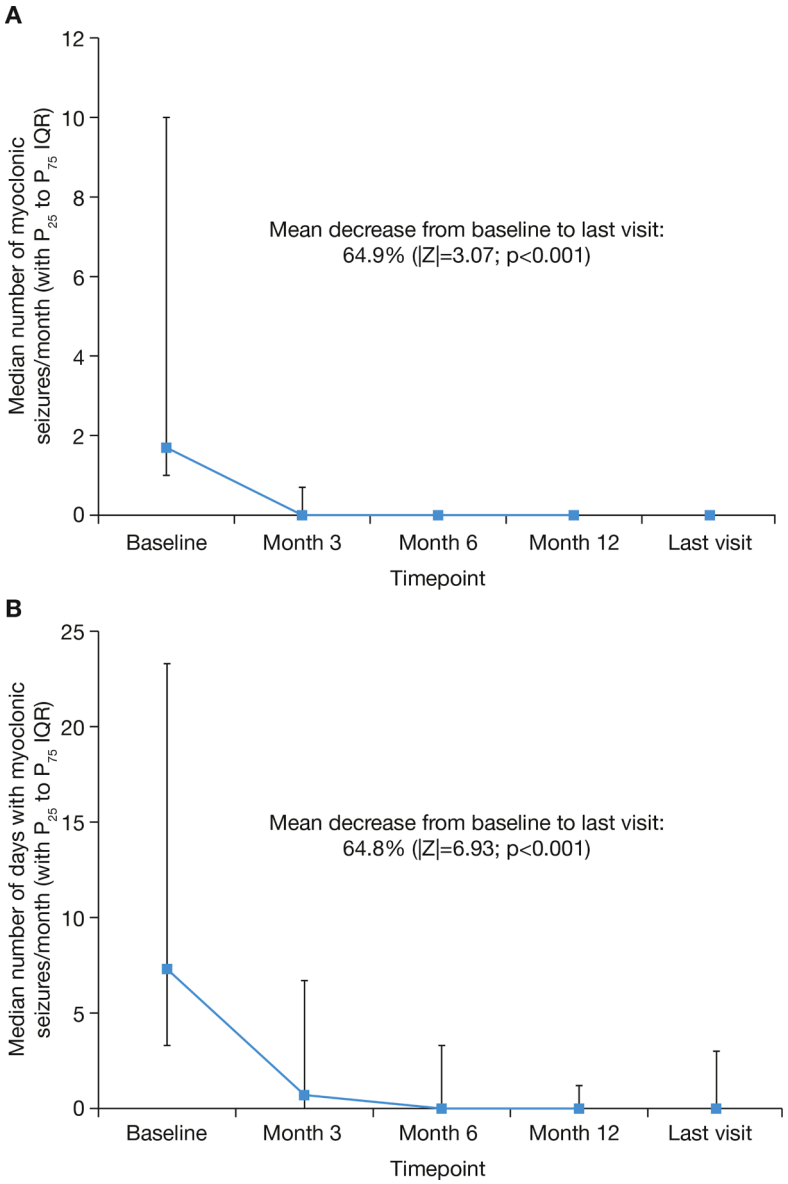

Fig. 2. Median (with P_{25} to P_{75} IQR) number of (A) myoclonic seizures/month and (B) days with myoclonic seizures/month (effectiveness population). IQR, interquartile range; P, percentile.

patients) in patients with IGE were dizziness/vertigo (20.1%), irritability (18.0%) and somnolence (10.1%). Retention, effectiveness and safety/tolerability in the subgroup with IGE were similar to the overall myoclonic population.

3.6.2. Patients with versus without psychiatric comorbidity at baseline

Of the 159 patients with myoclonic seizures, the presence or absence of psychiatric comorbidity at baseline was known for 144, of whom 28 (19.4%) had psychiatric comorbidity and 116 (80.6%) did not. After 12 months, retention was significantly lower in patients with versus without psychiatric comorbidity, and, at the last visit, responder and seizure freedom rates were significantly lower in patients with versus without psychiatric comorbidity (Fig. 4B). The incidence of AEs and AEs leading to discontinuation were significantly higher in patients with versus without psychiatric comorbidity, but the incidence of psychiatric AEs and the percentages of patients with psychiatric AEs who discontinued were not significantly different between subgroups (Supplementary Table S1B). The incidence of dizziness/vertigo was higher in patients with versus without psychiatric comorbidity (25.0% vs. 12.9%) and the incidence of fatigue was lower in patients with versus without psychiatric comorbidity (0% vs. 5.2%).

3.6.3. Slow (<2 mg/week) versus fast (2 mg/week) titration schedule

Speed of titration was known for 52 of the 156 patients with myoclonic seizures. Of these, 45 (86.5%) were treated with slow titration and seven (13.5%) with fast titration. Rates of retention (Month 12) and seizure freedom (last visit) were higher in patients treated with slow versus fast titration, but these differences were not statistically significant; responder rates (last visit) were similar between subgroups (Fig. 4C). Safety and tolerability assessments were not significantly different between patients treated with slow versus fast titration (Supplementary Table S1C).

3.6.4. Number of previous ASMs

At the last visit, responder rates in patients treated with 0, 1, 2 and ≥3 concomitant ASMs were 100% (1/1), 100% (23/23), 96.0% (24/25) and 80.3% (57/71), respectively. Corresponding seizure freedom rates were 100% (1/1), 82.6% (19/23), 88.0% (22/25) and 52.9% (45/85), respectively.

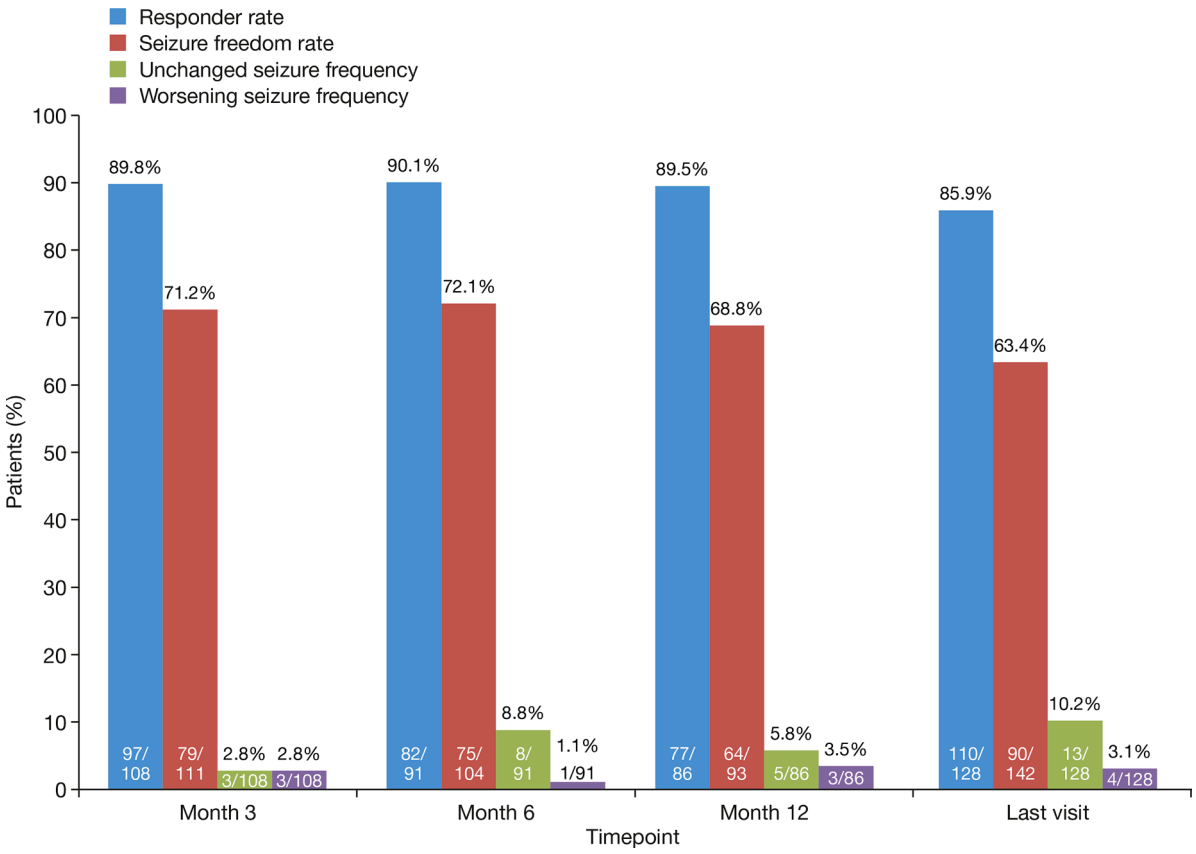

Fig. 3. Responder rate, seizure freedom rate, and percentages of patients with unchanged and worsening seizure frequency (relative to baseline) at Month 3, Month 6, Month 12 and the last visit (effectiveness population). Response was defined as ≥50% seizure frequency reduction from baseline. Seizure freedom was defined as no seizures since at least the prior visit.

Table 2
Summary of safety and tolerability (full analysis set/safety population).

Total patients	*N* = 156
Patients with any AE, n (%)	73 (46.8)
Most frequently reported AEs,[a] n (%)	
Dizziness/vertigo	30 (19.2)
Irritability	29 (18.6)
Somnolence	15 (9.6)
Fatigue	6 (3.8)
Anxiety	4 (2.6)
Depression	4 (2.6)
Instability/ataxia	4 (2.6)
Weight increased	4 (2.6)
Patients with AEs leading to discontinuation, n (%)	16 (14.0)[b]
Patients with any psychiatric AE, n (%)	38 (24.7)[c]
Patients with psychiatric AEs who discontinued[d], n (%)	9 (6.9)[e]
Types of psychiatric AEs in patients who discontinued[d], n (%)	
Irritability	7 (5.3)[e]
Anxiety	1 (0.8)[e]
Behavioural disorders	1 (0.8)[e]
Depression	1 (0.8)[e]
Personality disorder	1 (0.8)[e]

[a] ≥2% patients.
[b] *N*=114.
[c] *N*=154.
[d] These patients had psychiatric AEs but it was not possible to determine if it was these AEs that led to discontinuation.
[e] N=131. AE, adverse event.

3.6.5. *Number of concomitant ASMs*

At the last visit, responder rates in patients treated with 0, 1, 2 and ≥3 concomitant ASMs were 100% (14/14), 96.6% (57/59), 78.6% (22/28) and 63.0% (17/27), respectively. Corresponding seizure freedom rates were 57.1% (8/14), 84.7% (50/59), 71.0% (22/31) and 26.3% (10/38), respectively.

4. Discussion

In this subanalysis of the PERMIT study, PER was shown to be associated with reduction in myoclonic seizure frequency when used to treat patients with myoclonic seizures (primarily IGE) in everyday clinical practice. After 12 months, approximately 80% of patients were retained on PER, 90% had responded to PER treatment, and over two-thirds were seizure free. The proportion of patients who experienced seizure worsening with PER was low (<4%). The most frequent AEs (dizziness/vertigo, irritability and somnolence) were consistent with PER's known safety profile [24], and no new or unexpected safety signals emerged. Psychiatric AEs, which are commonly associated with PER treatment [24], occurred in approximately one quarter of patients, but the only psychiatric AE that occurred in more than one patient who discontinued was irritability, which occurred in 5.3% of patients with psychiatric AEs who discontinued. The findings of this study are encouraging given that myoclonic seizures are challenging to treat and few ASM treatment options are currently available [2,5].

Clinical trial evidence for the use of PER in treating myoclonic seizures is limited to a *post-hoc* analysis of a Phase 3 trial conducted in patients with IGE [22], in which 47/163 (28.8%) patients had myoclonic seizures [23]. In this analysis, the median percent reduction from baseline in 28-day myoclonic seizure frequency was numerically greater with placebo versus PER (52.5% vs. 24.5%), as was the responder rate (60.9% vs. 41.7%), and the seizure freedom rate was similar for placebo versus PER (13.0% vs. 16.7%) (*p*=not significant for all comparisons) [23]. However, the observations were based on small patient numbers and the trial was not powered to detect between-group

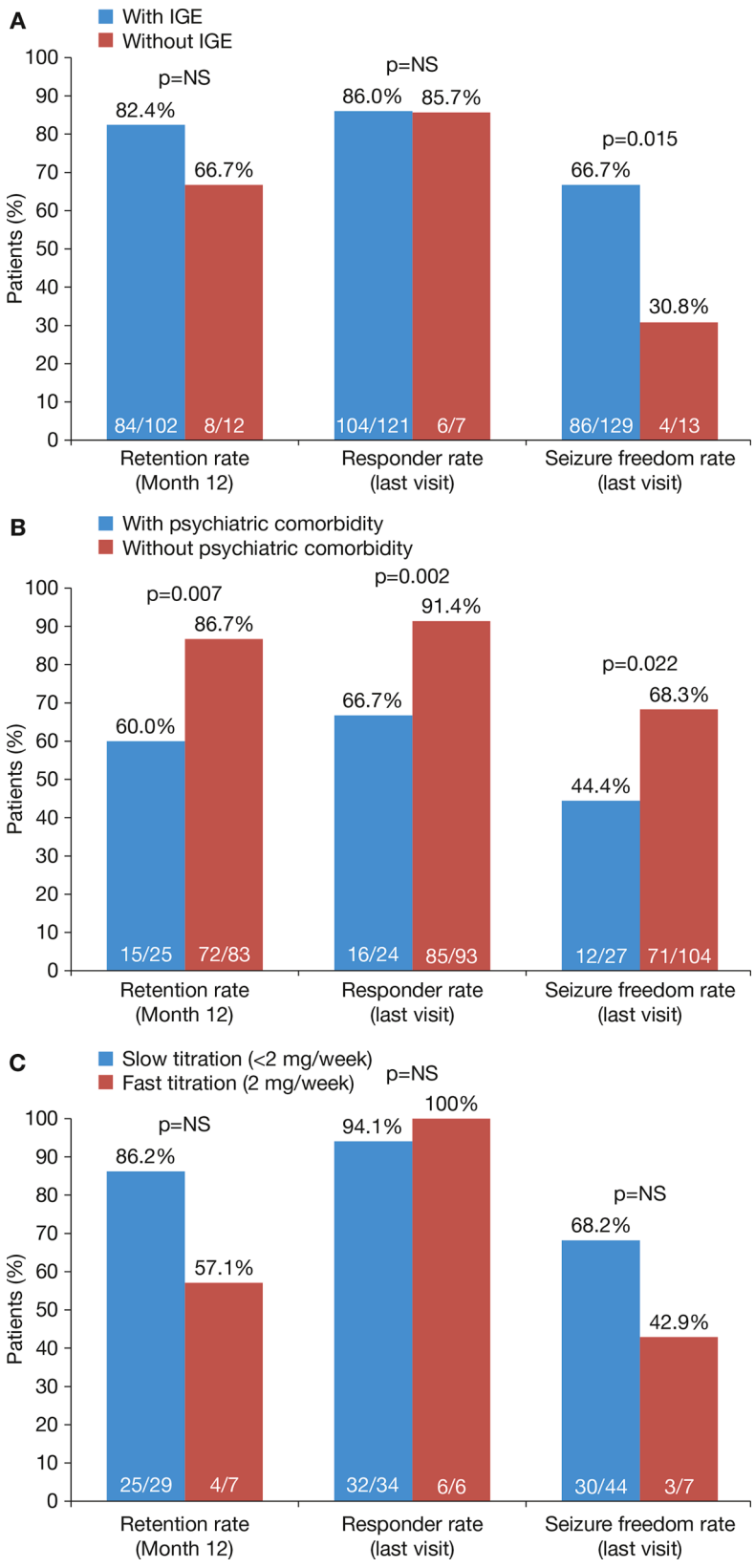

Fig. 4. Retention rate (Month 12), responder rate (last visit), and seizure freedom rate (last visit) in (A) patients with versus without IGE, (B) patients with versus without psychiatric comorbidity at baseline and (C) patients treated with PER using a slow (<2 mg/week) versus fast (2 mg/week) titration schedule. Response was defined as ≥50% seizure frequency reduction from baseline. Seizure freedom was defined as no seizures since at least the prior visit. IGE, idiopathic generalised epilepsy; NS, not significant; PER, perampanel.

differences in these patient subsets [23].

In the clinical practice setting, a Spanish, retrospective, multicentre, observational study specifically assessed the effectiveness and tolerability of adjunctive PER in 31 patients with myoclonic seizures [32]. At 6 months, the responder and seizure freedom rates for myoclonic seizures were 48.4% and 32.3%, respectively (compared with 90.1% and 72.1%, respectively, in the PERMIT cohort), and 39% experienced improvements in functional ability [32]. It should be noted that all these patients had drug-resistant epilepsy, having received a mean of 5.0 ASMs prior to initiating PER (compared to 2.9 in the PERMIT cohort) and a mean of 2.4

concomitant ASMs at the time of PER initiation (compared to 1.8 in the PERMIT cohort) [32], which might partly explain the lower responder and seizure freedom rates observed, in comparison with the current analysis. It is also important to note that all 31 of these patients were included in PERMIT. Since PERMIT was conducted, two other studies reporting the real-world use of PER for treating myoclonic seizures have been published. An Italian multicentre study assessed the impact of PER on cortical myoclonus and seizure frequency in 49 patients with progressive myoclonus epilepsies over 4–6 months [35]. Four patients discontinued during the first 2 months due to psychiatric side effects, but in the remaining patients PER significantly reduced myoclonus severity, assessed using a minimal myoclonus scale ($p<0.001$) and the Unified Myoclonus Rating Scale ($p<0.001$) [35]. In 17 patients who had persistent convulsive seizures before entering the study, PER reduced seizure frequency by over 50% [35]. AEs were reported for 44.8% (22/49) of patients, the most frequently reported AEs (≥5% of patients) being irritability or anxiety (26.5%), drowsiness (20.4%) and aggressiveness (6.1%) [35]. Overall, 77.6% (38/49) of patients continued taking PER at the last observation, for a mean duration of 16.8 months [35]. The remaining patients discontinued PER due to persistent AEs (anxiety and irritability) [35]. It should be noted that all patients included in this study initiated PER while receiving 2–6 concomitant ASMs [35], whereas 16.1% of patients in the PERMIT cohort were treatment-naïve before starting PER treatment. A Spanish, retrospective, single-centre, observational study investigated changes in epileptiform discharges, seizure frequency and AEs in 52 patients with generalised-onset seizures ($n = 44$) and focal-onset seizures with focal to bilateral tonic-clonic seizures ($n = 8$), who received PER treatment for 12 months [33]. As in the Italian study, most patients were treated with PER as an adjunct to existing ASM therapy and only one patient (1.9%) was treated with PER as monotherapy (86.5% of patients were being treated with one or two ASMs when PER was initiated, whereas 37.1% of patients in the PERMIT cohort were treated with one or two concomitant ASMs) [33]. At baseline, 11 patients had myoclonic seizures, with a higher burden than in the PERMIT cohort (mean [SD] monthly frequency, 20.5 [15.3]), the frequency of which decreased significantly after 3, 6 and 12 months ($p<0.05$ for all timepoints); at the last visit, the monthly frequency of myoclonic seizures had decreased by 99.5% from baseline [33]. In a subgroup of 21 patients with JME, the responder and seizure freedom rates at 12 months were 100% and 81%, respectively [33]. Tolerability was only reported for the overall population ($N = 52$) [33]. After 12 months, 36.5% (19/52) of patients had experienced at least one AE, the most frequently reported AEs (≥5% of patients) being irritability (23.1%), somnolence (9.6%), anxiety (7.7%), fatigue (5.8%) and dizziness (5.8%) [33]. Overall, five patients (9.6%) discontinued treatment with PER, including one patient with JME, three patients with primary generalised epilepsy other than JME, and one patient with focal-onset epilepsy [33]. These two reports are broadly consistent with the current findings from the PERMIT study, providing further evidence that PER is associated with reduction in myoclonic seizure frequency when used to treat myoclonic seizures in clinical practice, with no new or unexpected safety signals emerging in this setting. Two single case reports and a small, open-label, multicentre study ($N = 10$) have additionally provided evidence to suggest that PER may be effective in treating patients with Lafora disease, a fatal, intractable, progressive myoclonus epilepsy with onset in adolescence [37–39]. In the multicentre study, seven patients were treated with PER for >9 months and three discontinued treatment after 2–6 months due to undesired effects or lack of efficacy [39]. Four patients experienced >74% reduction from baseline in seizure frequency and seven experienced a major improvement in myoclonus [39].

Current ASM treatment options for patients with myoclonic seizures are limited. Valproate has historically been one of the primary treatments, alone or in combination with some benzodiazepines (e.g., clonazepam), based on a long history of clinical experience [2,5,40]. Valproate has been used to treat JME, Lennox-Gastaut syndrome, Doose syndrome, myoclonic absence, photomyoclonic epilepsy, eyelid myoclonia with absence seizures, and post-anoxic myoclonus, and has the advantage of being available in an intravenous formulation for use in myoclonus status epilepticus [5]. However, the use of valproate is affected by its well-established teratogenicity, causing congenital malformations and neurodevelopmental delay, severely limiting its use in females of childbearing potential [41,42]. Levetiracetam was effective in treating myoclonic seizures in placebo-controlled trials [7,43] and open-label studies [44–46], and is licensed in Europe for the adjunctive treatment of myoclonic seizures in adults and adolescents aged ≥12 years with JME [9]. However, there have been reports of myoclonic seizure exacerbation with levetiracetam use, including patients switching from valproate to levetiracetam to avoid the teratogenic risk associated with valproate [10–12]. Lamotrigine was effective in treating patients with JME in open-label and retrospective studies, although less effective than levetiracetam when used as monotherapy [47–52]. However, as with levetiracetam, there have been reports of myoclonic seizure exacerbation with lamotrigine use [53–55]. Topiramate has been investigated as monotherapy and adjunctive treatment for patients with JME in open-label randomised controlled trials and *post-hoc* analysis of double-blind, randomised, placebo-controlled trials [56–58], which have shown that it is as effective as, and better tolerated than, valproate [59], although it has also been shown to result in poorer neuropsychiatric performance than valproate in patients with JME [15]. Open-label and retrospective studies have additionally provided some limited evidence of the effectiveness of zonisamide in treating myoclonic seizures [13,60–62]. Other ASMs with some evidence of use in the treatment of myoclonic epilepsy include piracetam [63–66] and phenobarbital [67,68], both of which have been included in treatment guidelines for patients with myoclonic seizures [16]. In line with current evidence, the ASMs used most frequently in the current study before initiating PER (≥20% of patients) were valproate (35.8%) and levetiracetam (33.0%), and the most frequently used concomitant ASMs at the time of PER initiation were levetiracetam (50.0%), valproate (34.7%) and zonisamide (22.0%), which is line with current evidence.

The subanalyses conducted in the current study provide some additional insights into the potential use of PER in patients with myoclonic seizures. Since almost 90% of patients with myoclonic seizures were diagnosed with IGE at baseline, it is to be expected that results of the IGE subgroup analysis were very similar to those of the overall myoclonic population. The rate of seizure freedom at the last visit was significantly higher in patients diagnosed with versus without IGE, but, otherwise, the effectiveness and safety/tolerability of PER were similar in patients diagnosed with and without IGE. It is also perhaps unsurprising that PER was shown to be significantly less effective and well tolerated in patients who had psychiatric comorbidity at baseline, in comparison with those who did not, since certain psychiatric comorbidities, such as depression, are known to increase seizure frequency in epilepsy patients [69], and the presence of psychiatric comorbidity is associated with poorer response and tolerability to ASM treatment, and an increased risk of drug-resistant epilepsy [70–72]. The incidences of AEs and AEs leading to discontinuation were significantly higher in patients with versus without psychiatric comorbidity, which may relate to those with psychiatric comorbidity most likely using higher levels of polypharmacy than those without psychiatric comorbidity, which may have increased the incidence of drug–drug interactions and associated AEs. Psychiatric AEs are commonly reported with PER;[24] however, although the incidence of psychiatric AEs was numerically higher in patients with versus without psychiatric comorbidity, the between-group difference was not statistically significant, and the proportion of patients with psychiatric AEs who discontinued did not differ significantly between groups. In the subgroup analysis comparing data for patients treated with PER using a slow (<2 mg/week) versus fast (2 mg/week) titration schedule, there was an indication that PER was more effective when slow versus fast titration was used, but none of the between-group comparisons for effectiveness or safety/tolerability were statistically

significant, probably as a result of the low number of patients in the fast titration subgroup, and further research is therefore needed to clarify these observations. Descriptive comparisons of responder and seizure rates in patients treated with 0, 1, 2 and ≥3 previous and concomitant ASMs generally indicated that PER's effectiveness decreased with increasing number of previous and concomitant ASMs, consistent with the idea that the number of previous or concomitant ASMs is a marker of treatment refractoriness, as has been shown in similar analyses with other ASMs (e.g., eslicarbazepine acetate [73]).

This study is limited in being a *post-hoc* analysis of PERMIT, which was itself limited in being a retrospective pooled analysis of studies that were heterogeneous in terms of their objectives and information reported, and which, due to the nature of its design, did not have complete data available for all patients at all timepoints, across all endpoints and assessments [36]. Furthermore, most studies included in PERMIT were uncontrolled retrospective analyses of cases, which are likely to have had selection bias against patients deemed likely to suffer from known side effects of PER treatment, thereby altering the balance between tolerability and efficacy, in comparison with blinded studies [36]. Other sources of potentially significant bias may also have influenced the current findings. A disadvantage of pooled analysis of real-world studies is that the approach may over-estimate the potential clinical value of the product under investigation, since it is not possible to assess to potential impacts of factors such as patient selection, regression to the mean, and the bias inherent in the early dropout from a study of those who fail to respond to the intervention. In addition, as there was no control group, it was not possible to quantify the effectiveness of PER, in comparison with placebo/no drug or the passage of time. Moreover, since myoclonic seizures are brief, sporadic and retrospectively recorded, there may be an influence of time on the recording of myoclonus frequency (i.e., observer fatigue, recall bias), which might exaggerate the effectiveness of a drug in observational studies. As noted in the Methods, the observation timepoints of some studies included in PERMIT did not match those assessed for the overall PERMIT population (i.e., 3, 6 and 12 months), which may have affected the findings for some assessments. In addition, although individual subject data were reviewed by the investigators of the original studies included in PERMIT, they were not reviewed systematically in the current *post-hoc* study. Finally, although the large size of the PERMIT study population allows meaningful subgroup analyses to be conducted, some of the subgroups of the current myoclonic subanalysis cohort were imbalanced, which may have influenced findings, or were too small to allow robust statistical testing.

5. Conclusion

In summary, PER was associated with reduction in myoclonic seizure frequency when used to treat patients with myoclonic seizures in everyday clinical practice, with high rates of retention, response and seizure freedom over 1 year of treatment. The tolerability of PER was consistent with its known safety profile. These findings are encouraging, given the current lack of ASM treatment options for myoclonic seizures, and support the potential use of PER in this setting.

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Declaration of Competing Interest

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Taoufik Alsaadi has received speaker's honoraria from Eli Lilly, Novartis, GlaxoSmithKline, NewBridge, Hikma, Lundbeck and Sanofi; consultancy fees from Eli Lilly, Lundbeck, Merck, Hikma, Novartis and Sanofi; and independent support from Novartis and Merck.

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Rob McMurray is an employee of Eisai Europe Ltd.

Oliver Shastri is an employee of Eisai Europe Ltd.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2022.06.008.

References

[1] Striano P, Belcastro V. Treatment of myoclonic seizures. Expert Rev Neurother 2012;12:1411–7. quiz 1418.
[2] Striano P, Belcastro V. Update on pharmacotherapy of myoclonic seizures. Expert Opin Pharmacother 2017;18:187–93.
[3] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, Lagae L, Moshe SL, Peltola J, Roulet Perez E, Scheffer IE, Zuberi SM. 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.
[4] Kalviainen R. Progressive myoclonus epilepsies. Semin Neurol 2015;35:293–9.
[5] Wheless JW, Sankar R. Treatment strategies for myoclonic seizures and epilepsy syndromes with myoclonic seizures. Epilepsia 2003;44(Suppl 11):27–37.
[6] Leppik IE. Classification of the myoclonic epilepsies. Epilepsia 2003;44(Suppl 11): 2–6.
[7] Noachtar S, Andermann E, Meyvisch P, Andermann F, Gough WB, Schiemann-Delgado J, Group NLS. Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. Neurology 2008;70:607–16.
[8] Sharpe DV, Patel AD, Abou-Khalil B, Fenichel GM. Levetiracetam monotherapy in juvenile myoclonic epilepsy. Seizure 2008;17:64–8.
[9] European Medicines Agency Keppra® (levetiracetam) Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/keppra-epar-product-information_en.pdf 2021.
[10] Babtain FA. Levetiracetam may worsen myoclonus in patients with juvenile myoclonic epilepsy: case reports. Clin Neuropharmacol 2012;35:201–2.
[11] Liu YH, Wang XL, Deng YC, Zhao G. Levetiracetam-associated aggravation of myoclonic seizure in children. Seizure 2012;21:807–9.
[12] Makke Y, Hmaimess G, Nasreddine W, Fawaz A, Beydoun A. Paradoxical exacerbation of myoclonic-astatic seizures by levetiracetam in myoclonic astatic epilepsy. BMC Pediatr 2015;15:6.
[13] Kothare SV, Valencia I, Khurana DS, Hardison H, Melvin JJ, Legido A. Efficacy and tolerability of zonisamide in juvenile myoclonic epilepsy. Epileptic Disord 2004;6: 267–70.
[14] Marinas A, Villanueva V, Giráldez BG, Molins A, Salas-Puig J, Serratosa JM. Efficacy and tolerability of zonisamide in idiopathic generalized epilepsy. Epileptic Disord 2009;11:61–6.

[15] de Araujo Filho GM, Pascalicchio TF, Lin K, Sousa PS, Yacubian EM. Neuropsychiatric profiles of patients with juvenile myoclonic epilepsy treated with valproate or topiramate. Epilepsy Behav 2006;8:606–9.
[16] National Institute for Health and Care Excellence Epilepsies in children, young people and adults. NICE guideline [NG217]. Available at: https://www.nice.org.uk/guidance/ng217/resources/epilepsies-in-children-young-people-and-adults-pdf-66143780239813 2022.
[17] Rogawski MA, Hanada T. Preclinical pharmacology of perampanel, a selective non-competitive AMPA receptor antagonist. Acta Neurol Scand 2013;127:19–24. Suppl.
[18] Lattanzi S, Striano P. The impact of perampanel and targeting AMPA transmission on anti-seizure drug discovery. Expert Opin Drug Discov 2019;14:195–7.
[19] Di Bonaventura C, Labate A, Maschio M, Meletti S, Russo E. AMPA receptors and perampanel behind selected epilepsies: current evidence and future perspectives. Expert Opin Pharmacother 2017;18:1751–64.
[20] Steinhoff BJ, Ben-Menachem E, Ryvlin P, Shorvon S, Kramer L, Satlin A, Squillacote D, Yang H, Zhu J, Laurenza A. 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.
[21] Ko D, Ramsay RE. Perampanel: expanding therapeutic options for patients with medically refractory secondary generalized convulsive seizures. Acta Neurol Scand 2013;127:36–43. Suppl.
[22] French JA, Krauss GL, Wechsler RT, Wang XF, DiVentura B, Brandt C, Trinka E, O'Brien TJ, Laurenza A, Patten A, Bibbiani F. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy a randomized trial. Neurology 2015;85:950–7.
[23] Brandt C, Wechsler RT, O'Brien TJ, Patten A, Malhotra M, Ngo LY, Steinhoff BJ. Adjunctive perampanel and myoclonic and absence seizures: post hoc analysis of data from study 332 in patients with idiopathic generalized epilepsy. Seizure 2020;80:115–23.
[24] European Medicines Agency Fycompa® (perampanel) Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/fycompa-epar-product-information_en.pdf 2021.
[25] Eisai Inc Fycompa® (perampanel) Prescribing Information. *Available at:* https://www.fycompa.com/-/media/Files/Fycompa/Fycompa_Prescribing_Information.pdf 2021.
[26] Chodankar D. Introduction to real-world evidence studies. Perspect Clin Res 2021;12:171–4.
[27] Makady A, de Boer A, Hillege H, Klungel O, Goettsch W. What is real-world data? A review of definitions based on literature and stakeholder interviews. Value Health 2017;20:858–65.
[28] Tlusta E, Handoko KB, Majoie M, Egberts TC, Vlcek J, Heerdink ER. Clinical relevance of patients with epilepsy included in clinical trials. Epilepsia 2008;49:1479–80.
[29] Arzimanoglou A, Ben-Menachem E, Cramer J, Glauser T, Seeruthun R, Harrison M. The evolution of antiepileptic drug development and regulation. Epileptic Disord 2010;12:3–15.
[30] Steinhoff BJ, Staack AM, Hillenbrand BC. Randomized controlled antiepileptic drug trials miss almost all patients with ongoing seizures. Epilepsy Behav 2017;66:45–8.
[31] Villanueva V, Montoya J, Castillo A, Mauri-Llerda JA, Giner P, Lopez-Gonzalez FJ, Piera A, Villanueva-Hernandez P, Bertol V, Garcia-Escriva A, Garcia-Penas JJ, Garamendi I, Esteve-Belloch P, Baiges-Octavio JJ, Miro J, Falip M, Garces M, Gomez A, Gil-Lopez FJ, Carreno M, Rodriguez-Uranga JJ, Campos D, Bonet M, Querol R, Molins A, Tortosa D, Salas-Puig J. Perampanel in routine clinical use in idiopathic generalized epilepsy: the 12-month GENERAL study. Epilepsia 2018;59:1740–52.
[32] Gil-Lopez FJ, Montoya J, Falip M, Aparicio J, Lopez-Gonzalez FJ, Toledano R, Gil-Nagel A, Molins A, Garcia I, Serrano P, Domenech G, Torres F, Donaire A, Carreno M. Retrospective study of perampanel efficacy and tolerability in myoclonic seizures. Acta Neurol Scand 2018;138:122–9.
[33] Montoya Gutierrez FJ, Diaz Roman M, Cervero Albert D. Electro-clinical analysis of epilepsy patients with generalized seizures on adjunctive perampanel treatment. Epilepsy Res 2020;165:106378.
[34] Trinka E, Lattanzi S, Carpenter K, Corradetti T, Nucera B, Rinaldi F, Shankar R, Brigo F. Exploring the evidence for broad-spectrum effectiveness of perampanel: a systematic review of clinical data in generalised seizures. CNS Drugs 2021;35:821–37.
[35] Canafoglia L, Barbella G, Ferlazzo E, Striano P, Magaudda A, d'Orsi G, Martino T, Avolio C, Aguglia U, Sueri C, Giuliano L, Sofia V, Zibordi F, Ragona F, Freri E, Costa C, Nardi Cesarini E, Fanella M, Rossi Sebastiano D, Riguzzi P, Gambardella A, Di Bonaventura C, Michelucci R, Granata T, Bisulli F, Licchetta L, Tinuper P, Beccaria F, Visani E, Franceschetti S. An Italian multicentre study of perampanel in progressive myoclonus epilepsies. Epilepsy Res 2019;156:106191.
[36] Villanueva V, D'Souza W, Goji H, Kim DW, Liguori C, McMurray R, Najm I, Santamarina E, Steinhoff BJ, Vlasov P, Wu T, Trinka E, participants Ppa. PERMIT study: a global pooled analysis study of the effectiveness and tolerability of perampanel in routine clinical practice. J Neurol 2022;269:1957–77.
[37] Schorlemmer K, Bauer S, Belke M, Hermsen A, Klein KM, Reif PS, Oertel WH, Kunz WS, Knake S, Rosenow F, Strzelczyk A. Sustained seizure remission on perampanel in progressive myoclonic epilepsy (Lafora disease). Epilepsy Behav Case Rep 2013;1:118–21.
[38] Dirani M, Nasreddine W, Abdulla F, Beydoun A. Seizure control and improvement of neurological dysfunction in Lafora disease with perampanel. Epilepsy Behav Case Rep 2014;2:164–6.
[39] Goldsmith D, Minassian BA. Efficacy and tolerability of perampanel in ten patients with Lafora disease. Epilepsy Behav 2016;62:132–5.
[40] Wheless JW, Clarke DF, Arzimanoglou A, Carpenter D. Treatment of pediatric epilepsy: European expert opinion, 2007. Epileptic Disord 2007;9:353–412.
[41] Andrade C. Valproate in Pregnancy: recent Research and Regulatory Responses. J Clin Psychiatry 2018;79.
[42] Beardsley SJ, Dostal I, Cole J, Gutierrez A, Robson J. Valproate use in women aged 15-44 years: an observational study in general practice. BJGP Open 2021;5.
[43] Berkovic SF, Knowlton RC, Leroy RF, Schiemann J, Falter U, Levetiracetam NSG. Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy. Neurology 2007;69:1751–60.
[44] Labate A, Colosimo E, Gambardella A, Leggio U, Ambrosio R, Quattrone A. Levetiracetam in patients with generalised epilepsy and myoclonic seizures: an open label study. Seizure 2006;15:214–8.
[45] Specchio LM, Gambardella A, Giallonardo AT, Michelucci R, Specchio N, Boero G, La Neve A. Open label, long-term, pragmatic study on levetiracetam in the treatment of juvenile myoclonic epilepsy. Epilepsy Res 2006;71:32–9.
[46] Specchio N, Boero G, Michelucci R, Gambardella A, Giallonardo AT, Fattouch J, Di Bonaventura C, de Palo A, Ladogana M, Lamberti P, Vigevano F, La Neve A, Specchio LM. Effects of levetiracetam on EEG abnormalities in juvenile myoclonic epilepsy. Epilepsia 2008;49:663–9.
[47] Machado RA, Garcia VF, Astencio AG, Cuartas VB. Efficacy and tolerability of lamotrigine in juvenile myoclonic epilepsy in adults: a prospective, unblinded randomized controlled trial. Seizure 2013;22:846–55.
[48] Buchanan N. The use of lamotrigine in juvenile myoclonic epilepsy. Seizure 1996;5:149–51.
[49] Milano C, Turco F, Pizzanelli C, Bonanni E, Siciliano G, Fornai F, Giorgi FS. Response to levetiracetam or lamotrigine in subjects with Juvenile Myoclonic Epilepsy previously treated with valproic acid: a single center retrospective study. Epilepsy Behav 2021;115:107706.
[50] Bodenstein-Sachar H, Gandelman-Marton R, Ben-Zeev B, Chapman J, Blatt I. Outcome of lamotrigine treatment in juvenile myoclonic epilepsy. Acta Neurol Scand 2011;124:22–7.
[51] Schimschock JR, Hammer AE, Kustra RP, Messenheimer JA. Effects of lamotrigine monotherapy in patients with newly diagnosed juvenile myoclonic epilepsy: an open-label study. Curr Ther Res Clin Exp 2005;66:230–7.
[52] Morris GL, Hammer AE, Kustra RP, Messenheimer JA. Lamotrigine for patients with juvenile myoclonic epilepsy following prior treatment with valproate: results of an open-label study. Epilepsy Behav 2004;5:509–12.
[53] Guerrini R, Dravet C, Genton P, Belmonte A, Kaminska A, Dulac O. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. Epilepsia 1998;39:508–12.
[54] Carrazana EJ, Wheeler SD. Exacerbation of juvenile myoclonic epilepsy with lamotrigine. Neurology 2001;56:1424–5.
[55] Biraben A, Allain H, Scarabin JM, Schuck S, Edan G. Exacerbation of juvenile myoclonic epilepsy with lamotrigine. Neurology 2000;55:1758.
[56] Biton V, Bourgeois BF. Topiramate in patients with juvenile myoclonic epilepsy. Arch Neurol 2005;62:1705–8.
[57] Levisohn PM, Holland KD. Topiramate or valproate in patients with juvenile myoclonic epilepsy: a randomized open-label comparison. Epilepsy Behav 2007;10:547–52.
[58] Park KM, Kim SH, Nho SK, Shin KJ, Park J, Ha SY, Kim SE. A randomized open-label observational study to compare the efficacy and tolerability between topiramate and valproate in juvenile myoclonic epilepsy. J Clin Neurosci 2013;20:1079–82.
[59] Liu J, Tai YJ, Wang LN. Topiramate for juvenile myoclonic epilepsy. Cochrane Database Syst Rev 2021;11:Cd010008.
[60] Vossler DG, Conry JA, Murphy JV, Group Z-PS. Zonisamide for the treatment of myoclonic seizures in progressive myoclonic epilepsy: an open-label study. Epileptic Disord 2008;10:31–4.
[61] O'Rourke D, Flynn C, White M, Doherty C, Delanty N. Potential efficacy of zonisamide in refractory juvenile myoclonic epilepsy: retrospective evidence from an Irish compassionate-use case series. Ir Med J 2007;100:431–3.
[62] Italiano D, Pezzella M, Coppola A, Magaudda A, Ferlazzo E, Bramanti P, Striano S, Zara F, Striano P. A pilot open-label trial of zonisamide in Unverricht-Lundborg disease. Mov Disord 2011;26:341–3.
[63] Fedi M, Reutens D, Dubeau F, Andermann E, D'Agostino D, Andermann F. Long-term efficacy and safety of piracetam in the treatment of progressive myoclonus epilepsy. Arch Neurol 2001;58:781–6.
[64] Koskiniemi M, Van Vleymen B, Hakamies L, Lamusuo S, Taalas J. Piracetam relieves symptoms in progressive myoclonus epilepsy: a multicentre, randomised, double blind, crossover study comparing the efficacy and safety of three dosages of oral piracetam with placebo. J Neurol Neurosurg Psychiatry 1998;64:344–8.
[65] Ikeda A, Shibasaki H, Tashiro K, Mizuno Y, Kimura J. Clinical trial of piracetam in patients with myoclonus: nationwide multiinstitution study in Japan. The Myoclonus/Piracetam Study Group. Mov Disord 1996;11:691–700.
[66] Obeso JA, Artieda J, Quinn N, Rothwell JC, Luquin MR, Vaamonde J, Marsden CD. Piracetam in the treatment of different types of myoclonus. Clin Neuropharmacol 1988;11:529–36.
[67] Kosaka T, Ohta G, Kometani H, Kawatani M, Ohshima Y. A case of early myoclonic encephalopathy with intractable seizures successfully treated with high-dose phenobarbital. Brain Dev 2019;41:717–20.
[68] Ito S, Nagumo K, Nishikawa A, Oguni H, Nagata S. Low-dose phenobarbital for epilepsy with myoclonic absences: a case report. Brain Dev 2021;43:666–8.
[69] Thapar A, Kerr M, Harold G. Stress, anxiety, depression, and epilepsy: investigating the relationship between psychological factors and seizures. Epilepsy Behav 2009;14:134–40.

[70] Petrovski S, Szoeke CE, Jones NC, Salzberg MR, Sheffield LJ, Huggins RM, O'Brien TJ. Neuropsychiatric symptomatology predicts seizure recurrence in newly treated patients. Neurology 2010;75:1015–21.
[71] Hitiris N, Mohanraj R, Norrie J, Sills GJ, Brodie MJ. Predictors of pharmacoresistant epilepsy. Epilepsy Res 2007;75:192–6.
[72] Kanner AM. Do psychiatric comorbidities have a negative impact on the course and treatment of seizure disorders? Curr Opin Neurol 2013;26:208–13.
[73] Villanueva V, Holtkamp M, Delanty N, Rodriguez-Uranga J, McMurray R, Santagueda P. Euro-Esli: a European audit of real-world use of eslicarbazepine acetate as a treatment for partial-onset seizures. J Neurol 2017;264:2232–48.