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Perampanel for the treatment of epilepsy; Longitudinal actuarial analysis and dose responses based on monthly outcomes

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ABSTRACT

Purpose: To explore the retention rates and the efficacy and tolerability of perampanel (PER) by using monthly real life data for a period of 12 months.

Methods: Longitudinal outcomes of (PER) usage were assessed using actuarial statistics in an observational nonrandomised multicentre study of 181 people with epilepsy (PWE) refractory to first and second line drugs. Graded seizure outcomes, toxicity and the dose of PER were recorded for each month.

Results: PWE were followed for a mean of 15.1 months. The total cumulative probability for retention on PER at 12 months was 61.7% and for ≥50% improvement was 38.2%. Most improvements in seizure control occurred soon after initiation of PER, 17% by one month, 32% by six months and 38% by twelve months, and mostly at low doses 53% on 2 mg and 90% up to 6 mg. Improvements, when they occurred, were sustained. The most common side effects were neuropsychiatric, occurring in 28%. The emergence of side effects did not appear to be dose related. Although people with intellectual disability (ID) were more likely to remain on PER they did not show improved seizure control and also reported more side effects. Patients treated with VNS and PER had a worse outcome.

Conclusion: Overall around a third of people showed a useful, response to PER therapy. The response to PER is noted usually early in the treatment and for the majority of the patients for doses up to 8 mg.

1. Introduction

Perampanel (PER), one of the newer antiepileptic drugs has a novel antiseizure mechanism acting as a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor antagonist [1]. It was licensed as add-on medication for refractory focal-onset seizures after conduction of 3 phase III double-blinded randomized clinical trials [2–4] followed by an open label extension with a follow-up reaching 4 years [5]. The initial clinical trials had a 6 week titration period and a 13 week follow-up period and showed high retention rates varying from

Abbreviations: FAS, Focal Aware Seizure; FIAS, Focal Impaired Awareness Seizures; GGE, Genetic Generalized Epilepsy; ID, intellectual disability; PER, perampanel; PGTCS, Primary Generalized Tonic-Clonic Seizures; PWE, people with epilepsy; VNS, vagal nerve stimulator

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75% to 92% on different doses [2–4]. The open label extension estimated retention rates for 1,2,3 and 4 years which were 73.5%, 56.4%, 46.2% and 39% respectively showing a trend for reduction of the retention rate with time [5]. Regarding Primary Generalized Tonic-Clonic Seizures (PGTCS) in Genetic Generalized Epilepsy (GGE), PER was licensed based on a double-blinded randomised control trial with a 4-week titration period and a 13-week follow-up period. The retention rate was 84% for the patients receiving PER [6].

A number of real-life studies followed the marketing of PER providing important data about the efficacy and tolerability of the drug. Most of them were retrospective and reported overall retention rates varying from 46% to 77% for patients with refractory epilepsy including both focal (Focal Aware Seizure [FAS], Focal Impaired Awareness Seizures [FIAS] with or without focal to bilateral tonic-clonic seizures) and primary generalized seizures [7–12]. A few studies that exclusively analysed focal epilepsy showed retention rates between 51.9% and 60.6% at the first year [13–15] and only one of these studies was prospectively designed [13].

2. Methods and statistical analysis

We performed a multicentre study of people with epilepsy (PWE) aged 18 or over with chronic epilepsy resistant to first and second line drugs that were commenced on PER. Data were collected retrospectively from the electronic medical documentation and the paper notes for each patient. The number of seizures was extracted from seizure diaries or the clinical record. Only patients that had reliable data for at least one month after the introduction of PER were included. All outcome data to the time of last follow up were recorded.

Outcome data up to 12 months after starting PER were analysed. Sociodemographic and other baseline data, such as age, gender, age at onset of epilepsy, duration of epilepsy, type of epilepsy, type of seizures, frequency of seizures, intellectual disability (ID), details of any resective surgery/VNS implantation, number of previous drugs, baseline drugs and their mechanism of action (only sodium channel blockers, mechanism other than sodium channel blocking and combination of sodium channel blockers and other drugs) were collected. Dose escalation regimes were recorded. The dose of PER for each month was defined as that taken at the middle of the month. For each month seizure outcome was graded as seizure free, 50% or greater reduction in seizures, less than 50% reduction in seizures, no change or worsening of seizure profile (Table 1). Side effects were recorded on a monthly basis and graded as mild, moderate or severe.

Primary outcome measures were retention time on PER and time to achieve more than 50% improvement in seizure frequency using Kaplan-Meir survival statistics. The log-rank test was used to test for the effect of gender, age of onset, type of epilepsy, localization of focal epilepsy, intellectual disability, VNS, number of baseline drugs and their mechanism of action on retention time and 50% response. Categorical variables were constructed about the age of epilepsy onset, the duration of epilepsy and the number of baseline drugs.

The incidence of different side effects, the association with

Table 1
Patients' characteristics and longitudinal outcomes of the retention on PER at 12 months and the ≥50% response.

	N (%)	Mean ± SD	Actuarial % Retention At 1 year	p	Actuarial 50% improvement at one year	p
Gender						
Male	88 (48.6)		61.8	0.975	34.2%	0.842
Female	93 (51.4)		61.7		41.2%	
Age of Onset		13.8 ± 11.8				
0.5–10 years	87 (48.1)		65.1%	0.573	34.6	0.544
11–20 years	50 (27.6)		57.8%		35.9	
> 20 years	44 (24.3)		59.8%		48.7	
Focal vs Generalized Epilepsy						
Focal	134 (74.0)		66.2	0.182	40.8	0.498
Generalized	44 (24.3)		50.4		31.1	
Unclassified	3 (1.7)		.00		All censored	
Intellectual Disability						
Yes	80 (44.2)		70.4	**0.028**	39.2	0.768
No	101 (55.8)		55		37.7	
Classification of Intellectual Disability						
Mild	50 (62.5)		80.2	**0.031***	38.8	0.906
Moderate	11 (13.8)		68.2		56.4	
Severe	19 (23.7)		45.7		33.0	
Number of drugs at initiation of PER						
1	22 (12.2)		71.8	0.80	35.5	0.929
2	81 (44.8)		55.1		39.1	
3 or more	78 (43.1)		65.2		37.3	
Duration of epilepsy		27.5 ± 13.7				
0.5–10 years	17		61.4	0.188	58.1**	0.274
11–20 years	52		77.4		41.0	
21–30 years	45		53.1		35.0	
> 30 years	67		56.4		31.5	
Current Drug Mechanism						
SC	35 (19.3)		69.8***	0.792	29.2	0.118
Non-SC	17 (9.4)		32.7		32.1	
Mixture	126 (69.6)		62.5		41.3	
VNS						
No	124 (68.5)		60.1	0.489	45.2	**0.009**
Yes	57 (31.5)		65.4		23.1	
All cases	181 (100)					

* The difference in retention amongst the different levels of ID is significant between patients with mild and severe ID (p = 0.024 for paired test between these 2 groups).

** Analysis shows that the cumulative probability of ≥50% response is decreased as the duration of the epilepsy is longer but this trend was not significant.

*** Combination of PER with drugs that act to the sodium channels lead to higher probability for retention on PER. (SC: drugs acting on Sodium Channels, Non-SC: drugs that their main action is not on Sodium Channels, VNS: vagal nerve stimulator).

Table 2
Monthly seizure outcome and number followed each month.

Month	Number Followed	Seizure free	50% responders	< 50% Improvement	No change	Deterioration in seizure control
1	181	7	25	47	92	10
2	172	8	24	50	78	12
3	164	7	27	54	68	8
4	151	4	29	51	62	5
5	137	4	26	53	47	7
6	125	7	24	48	41	5
7	116	7	21	44	37	7
8	105	6	19	41	35	4
9	101	6	19	40	32	4
10	96	5	20	36	30	5
11	92	5	19	37	27	4
12	89	5	18	38	26	2

concomitant AEDs and the effect that side effects had on PER retention were all explored. More specifically, the experience of neuropsychiatric side effects and the relationship with co-administration of Levetiracetam was investigated.

All statistical procedures were performed in SPSS version 22.0 statistical software (Chicago IL). Continuous variables are presented as mean values ± standard deviation, while categorical variables are presented as absolute and relative (%) frequencies. Cumulative probabilities were calculated by using Kaplan-Meir survival statistics. The log-rank test was used to evaluate the significance of observed differences seen in the created Kaplan-Meier survival curves. In addition we performed univariate analyses using Student *t*-test or Pearson correlations and chi-square tests for interval and categorical variables, respectively. The level of significance for all the performed analysis was set at 0.05.

3. Results

3.1. Demographics

The study included 88 male and 93 female PWE. The mean age of the patients at the time of PER being commenced was 41.2 years (± 12.8; range 18–77). The mean age at the onset of epilepsy was 13.8 years of age (± 11.8; range 0.5–55) and the mean duration of the epilepsy was 27.7 years (± 13.7; range 4–72). The maximum duration of follow up was 48 months with a mean of 15.13 months. We collected data from 74 patients that were followed for 13 months or more. These patients had a mean follow-up duration of 27.53 months (± 9.93). Follow up data for more than 2 years were available for 42 patients (23.2%).

3.2. Longitudinal outcomes

The patients' characteristics and the longitudinal outcomes regarding the retention on PER at 12 months and the ≥50% response are seen in Table 1. The monthly seizure outcomes with the number of patients followed are presented in Table 2. The total cumulative probability of retention on PER at 12 months was 61.7%. (Fig. 1a) Patients with ID showed significantly higher cumulative probability of retention on PER at the 12th month (70.4%) compared to those with normal intellectual function (55%; p = 0.028) (Fig. 1b). This difference was caused mainly due to the high retention rates of people with mild ID (Table 1). A difference in cumulative probability for retention in PER was also observed between focal epilepsy (66.2%) and generalised epilepsy (50.4%) but this did not reach significance (p = 0.182) (Fig. 1c). However, when this was adjusted for ID, we found that patients with focal epilepsy and ID had significant higher probability (84.7%) of retention on PER at 12 months than those with generalized epilepsy and ID (50.7%; p = 0.013) (Fig. 1d).

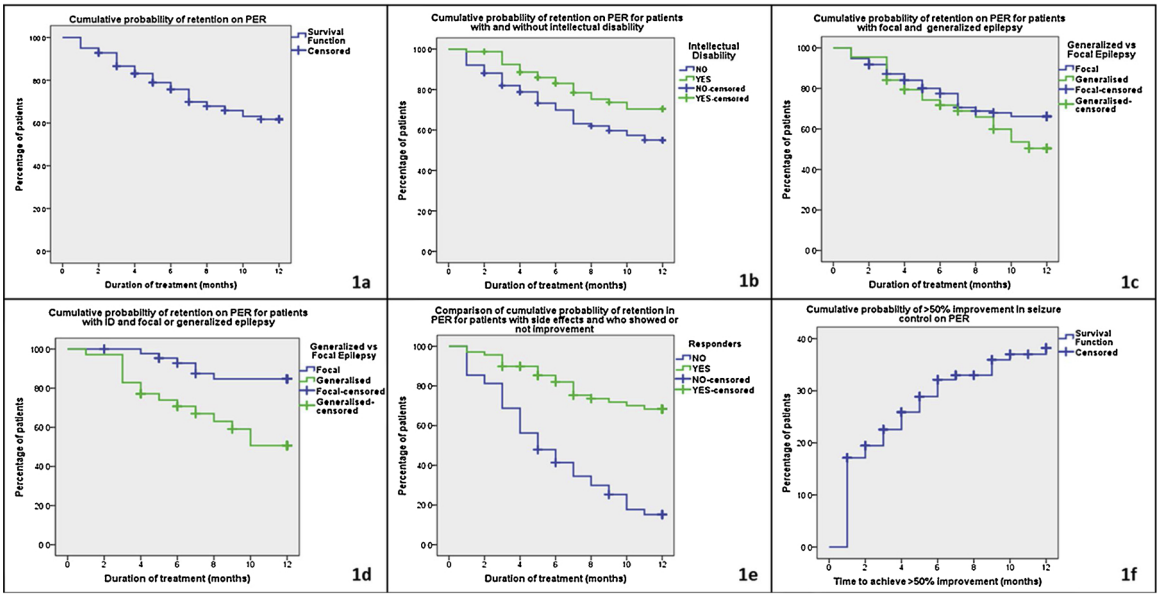

Fig. 1. Longitudinal outcomes regarding retention on PER at 12 months and the ≥50% response. 1a: Cumulative probability for retention on PER at 12 months, 1b: Patients with and without ID, 1c: Patients with focal or generalised epilepsy, 1d: Patients with ID and focal or generalised epilepsy, 1e: Patients with or without side effects, 1f: Cumulative probability for ≥50% improvement in seizure control at 12 months.

PWE that showed any level of improvement at any point during the 12 months after initiation of PER, had higher cumulative probability of retention on PER (79.6%) compared to those that showed no improvement (34.6%; $p < 0.005$). This difference was sustained for those who had any level of improvement even if they experienced side effects (cumulative probability of retention 68.3% compared with 15.2% for those with side effects and no improvement; $p < 0.0005$) (Fig. 1e).

Total cumulative probability of more than 50% improvement in seizure control at any point during the first 12 months after starting PER was 38.2% (Fig. 1f). This probability was 17.1% at the 1 st month and 32.1% at the 6th month showing that response is usually achieved early in the treatment course. Patients without VNS had significant higher probability of ≥50% reduction in seizures compared to patients with VNS ($p = 0.009$). This difference remained significant after adjustment for the duration of the epilepsy ($p = 0.01$). For patients with and without VNS, student *T*-test was used to check for possible significant differences in age, duration of epilepsy, age at the onset of epilepsy, number of antiepileptic drugs tried in the past and number of baseline drugs between the 2 groups. Pearson's chi-square test was used to check for significant differences in gender, comorbidity with ID, focal or generalised epilepsy, mechanism of action of baseline drugs and presence of side effects between the same groups. No significant differences were observed in any of the above variables (detailed analysis regarding PER in patients with VNS will be presented in a separate paper). As opposed to the probability of retention on PER, the probability of ≥50% improvement did not show any difference between patients with and without learning difficulties (39.2% and 37.7% respectively).

3.3. Dose dependence of response

The monthly doses of PER are seen in Table 3. Fifty-nine (59) patients achieved ≥50% response at any time during treatment. In 52.5% (n = 31) of cases achieved this response at 2 mg PER, 22% (n = 13) at 4 mg and at 6 mg 15.3% (n = 9). Only 3.4% of the responders showed the response in doses above 8 mg. The Kaplan-Meier analysis for ≥50% response when adjusted for dose showed that the cumulative probability for ≥50% response was 45.5% for doses 1–6 mg and 16.9% for doses 7–12 mg and this difference was significant (log rank $p < 0.0005$).

3.4. Sustainment of response

Fifty-nine patients achieved ≥50% improvement in seizure control at any time during their follow-up. From these patients, 37 (62.7%) sustained the improvement until their last follow-up appointment and 26 (44%) sustained the improvement for at least six months. Only 7 patients with sustained ≥50% improvement withdrew PER of whom 6 withdrew due to side effects. Sustainment of response was not dependent on the time taken to achieve ≥50% reduction in seizures.

3.5. Side effects

Side effects were reported from 117 (64.6%) patients. Fig. 2 shows the frequency of each type of observed side effect. A total of 62 (34.2%) patients withdrew from PER during the 12-month period. The main reason for discontinuation of PER (87.1%) was side effects [alone 53.2% (n = 33) or in combination with lack of efficacy 33.9% (n = 21)]. Of note is that 9.7% (n = 6) of the patients that discontinued PER did so because of an increase in seizure frequency. The emergence of side effects was not dose related (Student's *t*-test $p = 0.309$). The hypothesis was retested by creating a categorical variable with 2 categories for the higher dose of PER that each patient reached (1–6 and 7–12 mg). Analysis with Pearson Chi-square failed to show significant correlation between higher doses of PER and reported side effects ($p = 0.813$). The number of patients that reported for first time side effects for each month and the dose of PER at which the side effects were presented is seen in Table 4. Furthermore, the effect of baseline medication on side effects was tested. The number of baseline drugs did not affect the appearance of side effects (Student's *t*-test $p = 0.162$). We checked this result by splitting the number of baseline drugs into 3 categories (1 drug/2 drugs/≥3 drugs) and again this did not reveal significant differences in the emergence of side effects (Pearson Chi-Square $p = 0.518$) although there was a mild trend suggesting that as the number of the drugs increases the frequency of side effects rises [13/22(59.1%) for patients with 1 drug, 50/81(61.7%) for patients with 2 drugs and 54/78(69.2%) for patients with ≥3 drugs].

Neuropsychiatric side effects (depression, abnormal thoughts, and behavioural changes) were observed in 52 patients (28.2%). Neuropsychiatric side effects were similar in patients treated concomitantly with Levetiracetam (32.7%) compared to those not treated with Levetiracetam (27.4%) $p = 0.470$. There was no significant difference in the overall incidence of side effects between those without (67.3%) and with ID (61.3%). However, neuropsychiatric side effects were less frequent in patients without ID (22.8%) compared to those with ID (36.3%) and this difference was significant ($p = 0.047$).

4. Discussion

4.1. Methodology of assessing seizure outcome

Assessing seizure outcome in chronic epilepsy is difficult and few statistical approaches have been proposed. The regulatory trials of anticonvulsants measure short term changes in seizure frequency over a period of around 12 weeks, a method that has been widely criticised as being of limited clinical validity. Trials in newly diagnosed epilepsy assess a binary outcome of "seizures versus no seizures". Follow up is divided into short intervals, for example of one month, and the cumulative probability of achieving 6 months or one or more years seizure freedom is measured using actuarial statistics. The latter approach has the advantage of using all available data in the presence of variable

Table 3
Number of patients on each dose of PER every month.

Month	Number Followed	1mg	2 mg	3 mg	4 mg	5 mg	6 mg	7mg	8 mg	9mg	10mg	12 mg
1	181	10	158		9		3		1			
2	172	3	64		92		6		6			1
3	164	1	41	2	60		50	1	6		1	2
4	151	1	26	1	57		36		26		2	2
5	137	1	23	1	44	3	37		18	1	6	3
6	125	1	20		38		32		26		5	3
7	116	1	17		29	2	34		21	1	7	4
8	105	1	13		33	2	23	1	18	1	7	6
9	101		15		28	1	23	1	20	1	6	6
10	96		12	1	24	1	24		19	1	10	4
11	92		9		23	1	24	1	19	1	8	6
12	89		8		21	2	21	1	22	1	5	8

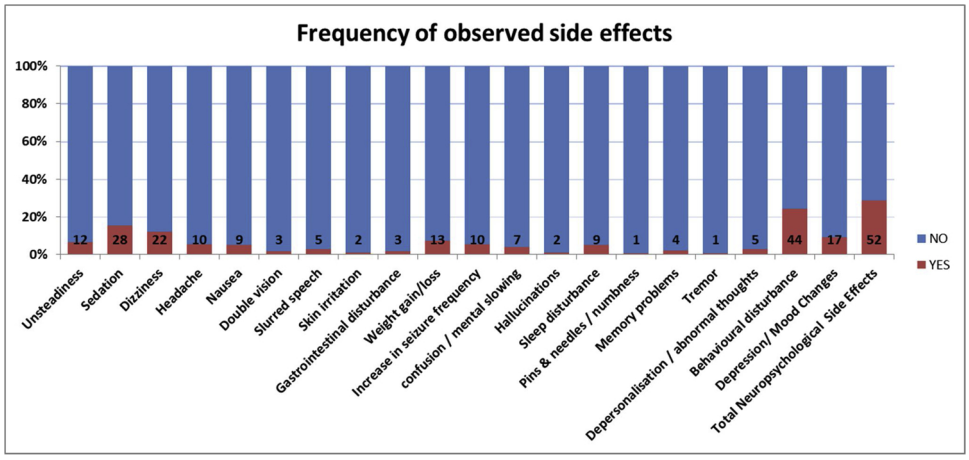

Fig. 2. Graph with the frequency of the different SEs. The last column represents the frequency of neuropsychological SEs in total.

follow-up.

Complete seizure freedom is, however, an unusual outcome in chronic epilepsy and we therefore segregated outcome into five grades ranging from worsening of seizures to seizure freedom. In keeping with regulatory trials, the primary outcome measure was a 50% or more reduction in seizures. Similarly the doses of drugs and presence of side effects was recorded for each month. Unlike previous observational studies we were thereby able to apply actuarial statistics to assess longitudinal changes in seizure control in chronic epilepsy. Furthermore we could assess other important clinical parameters such as dose response, the occurrence of dose related side effects and long term stability of outcome. Most patients were assessed retrospectively and the design was observational, reflecting "real life" outcomes. Assessments were, by necessity, somewhat qualitative and dependant of the assessment of the individual physician. Despite these difficulties it was possible to robustly assess the outcome parameters for each month of follow up.

4.2. Comparison of outcome with regulatory and observation trials

The cumulative probability for retention on PER at 3 months in our study was 86.6% which is comparable with the duration and the findings of the clinical trials. Our cumulative probability for retention on PER at 12 months is 61.7%, in the middle of the results from the observational studies [7–15], but lower than that reported in the trials and the open label extension [2–5].

PER was suggested to have a better efficacy and tolerability for PGTCS, based on the randomized trial of French et al. [6]. Most observational studies have not investigated if this hypothesis is supported by real life data. Our analysis did not entirely confirm those initial results and showed higher actuarial retention rates for patients with focal rather than generalized epilepsy (66.2% vs 52.5%), but without statistical significance.

The initial clinical trials had a secondary efficacy point which was the 50% responder rate (patients with ≥50% reduction in seizure frequency). A pooled analysis showed that based on dose, the 50% responders were 28.5% (4 mg); 35.3% (8 mg); 35.0% (12 mg) [16]. Patients with PGTCS and GGE showed a ≥50% responder rate of 64.2%, with seizure freedom rate at 30.9%, which was much higher than that seen in the clinical trials for focal seizures [6]. These results for focal seizures show a higher 50% responder rate in comparison to our cohort where the cumulative probability for ≥50% response at 3 months was 22.6%. The open label extension revealed that the 50% responders' rate was 42.8% for those who were treated for 1 year [5]. Interestingly that study showed that the 50% responder' rate increased year on year. This could perhaps be explained by the exclusion of the patients with no response to PER, resulting in a cohort that had already shown some response to the treatment.

Previous observational studies show significant variability in the ≥50% responder rate ranging from 12.8% to 57.5% [7–15,17]. Shah et al. analysed data from 310 patients and found the highest percentage of responders (57.4% for FIAS, 43.8% for FAS and 57.5% for PGTCS) – this being the only study that shows similar efficacy for FIAS and PGTCS, opposed to the findings of the randomized trials [10]. The actuarial analysis for our cohort showed an overall ≥50% responder rate of 38.2% at 12 months which is almost exactly in the middle of the

Table 4
Number of patients that reported SEs for first time, distributed for each month and the dose of PER at which the side effects were presented.

		Dose at which SEs first reported					
Month of FU	Number of patients	2 mg	4 mg	6 mg	8 mg	10mg	12 mg
1	54	48	4	1	1		
2	17	0	15	0	2		
3	6	0	2	3	1		
4	13	0	3	4	6		
5	7	1	3	1	2		
6	2	0	0	1	1		
7	9	0	0	3	3	1	2
8	2	0	1	0	1	0	0
9	3	0	0	1	1	0	1
10	2	0	1	6	0	0	0
11	2	0	1	0	1		
12	0						
	117 (100%)	49 (41.9%)	31 (26.5%)	15 (12.9%)	18 (15.4%)	1 (0.9%)	3 (2.6%)

range of results from observational studies. Our subanalysis for focal seizures and generalised epilepsy (40.7% and 43.7% respectively) did not show significant differences between these two patient groups.

In our study most improvements in seizure control occurred soon after initiation of PER. The 50% responder rate was 17% by 1 month, 32% by 6 months and 38% by 12 months. This is a finding described in other observational studies where almost the total number of ≥50% responders had shown this response between 4–6 months [9,12,15]. There are, though, other studies in which there is a clear increase in response rate with time, reaching maximum response rates around the 12 months [7,10,18].

4.3. Side effects

The pooled analysis of the 3 phase III clinical trials in focal epilepsy shows that treatment related side effects (SE) were observed in 77% (severe SE in 8.9%), but also in 66.5% of the patients receiving placebo [16]. The most frequent SEs were dizziness, somnolence and headache. Serious psychiatric SE were reported in just 1.2% of the patients receiving PER, most commonly aggression. Observational studies generally show an incidence of side effects between 41.6% and 62.9% and only the study by Shankar et al. has shown a lower percentage of SE at 32% [8,9,11,14,15,17,19]. Apart from dizziness and sedation/somnolence, most of these observational studies have revealed a significant number of patients with behavioral and psychiatric (aggression, irritability, depression, suicidal ideation and psychosis) SE. Brodie and colleagues found that 80.7% of the patients that withdrew from PER did so owing to SE and 11.1% of all patients stopped the treatment due to neuropsychiatric SE [13]. Similarly, 5 studies reported a high incidence of neuropsychiatric side effects and behavioral changes varying from 22.7% to 50% [7,8,14,17,19] which led to discontinuation of PER in many of these patients. Coyle et al. reported that in their cohort, behavioral disturbance including suicidal ideation was the main SE requiring discontinuation of PER [20].

Psychiatric SE with PER are described more frequently in patients with a psychiatric history, but they were also seen in patients free from psychiatric disorders and Maurouset et al. showed that there was no difference in the incidence of psychiatric SE between patients with and without a psychiatric history in their cohort [8].

The findings of these studies demonstrate that neuropsychiatric SEs are a major issue in the use of PER, something which was perhaps not so obvious from initial randomized trials and the extension studies. In our study, 64.6% of patients reported at least one SE and one or more behavioral/neuropsychiatric SE were observed in 28.2% (N = 52). More than half of these people (27/52) discontinued PER. Moreover, there were no higher levels of neuropsychiatric SE in those treated with Levetiracetam, a finding that was also noted by Morano et al. [9]. SE effects or their combination with lack of efficacy was the reason for withdrawal in 87.1% of the patients that discontinued PER in our cohort.

The underlying cause for high rates of psychiatric SE is not clear. Antiepileptic drugs with varying distinct mechanisms of action (Topiramate, Levetiracetam, Perampanel, Vigabatrin) may all cause neuropsychiatric adverse effects suggesting a complex underlying pathophysiology. PER suppresses glutamatergic transmission through selective, non-competitive AMPA receptor antagonism. In the last decade there is accumulated evidence that potentiation of AMPA receptor has a beneficial effect on mood disorders [21]. Alterations of AMPA receptors have been described after treatment for depression and Fluoxetine has been shown to increase AMPA receptor signaling [22]. Furthermore, antiepileptics such as Lamotrigine, Riluzole and Valproate has been found to modify the levels of GluR1/2 subunits of AMPA receptor and this may induce their antimanic or antidepressant properties [23]. It could be that PER exerts his action by decreasing the AMPA receptor signaling and in this way it may contribute to dysregulation of mood and appearance of psychiatric side effects. The data are still scarce and the role of glutamatergic transmission on psychiatric disorders seems to be complicated involving different systems of neurotransmitters.

4.4. Dose responses of PER to seizure outcome and side effects

The initial phase III studies showed significant superiority of PER compared to placebo in improving seizure frequency but it was not clear if there was an added benefit from 8 mg to12 mg dose [2,3]. The ≥50% responder rate was 28.5% for 4 mg ; 35.3% for 8 mg and 35% for 12 mg on pooled analysis, revealing that a dose of 12 mg did not offer additional benefit compared to 8 mg [16]. However, analysis demonstrated a clear benefit of PER 12 mg in controlling focal to bilateral tonic clonic seizures compared to PER 8 mg [16]. One other pooled dose-response analysis conducted by Kramer et al. used the data from studies 304, 305 and the extension study 307 to check for dose-related response [24]. The results showed improved efficacy for the patients that increased from 8 mg to12 mg during the extension study with a median percent change in seizure frequency from -32.4% at 8 mg to-44.2% at 12 mg. In observational studies the dose-response relation is not clear-cut. Morano et al. and Juhl et al. have shown that efficacy from PER can be seen at low doses and that there is not necessarily a correlation between dose and outcome [9,14]. Our analysis is in agreement with this latter finding with 89.8% of the patients who achieved ≥50% response doing so with doses up to 6 mg. The actuarial analysis for ≥50% response controlled for the dose of PER supports this, showing a probability of response of 45.5% for doses 1-6 mg and 16.9% for doses 7–12 mg. PER plasma concentration may be lowered by enzyme inducing AEDs but there was no significant difference in the prescription of concomitant enzyme inducing medication between those that achieved ≥50% response when taking a maximum of 1–6 mg PER (49.1%) versus those who took a maximum of 7–12 mg (66.7%; $p = 0.671$).

A connection between PER dose and the presence of SEs has been observed in a series of phase III trials pooled data analyses. Kraus et al. described that the SEs were dose related with a percentage of 65%, 81% and 89% for doses of 4 mg, 8 mg and 12 mg respectively [25]. Interestingly, the majority of the post market observational studies failed to reveal a clear connection between the PER dose and the SEs showing that SEs can occur at low doses or that there was no difference in the mean dose of PER between those with and without SEs [7,9,13–15] In concordance with these results, we found that experience of SEs was not dose related and the majority of these would appear early and at low doses. Only the study of Singh et al. found that the average for those with SEs was 7.3 mg while for those without SEs was 5.5 mg [19].

It remains uncertain as to why efficacy and side effects were seen relatively early during the treatment schedule and at low doses. Pharmacokinetic or pharmacodynamic data do not provide any clear explanation for this observation [26]. As described above, this has been seen in other observational studies of PER whilst a dose related effect was more apparent in the Phase III randomised trials. The latter used very rapid dose escalation which may obscure the effects at lower doses and indeed one of the advantages of observational studies is the delineation of more appropriate dosing regimens.

Slow titration seems to be helpful in lowering the SEs rate and improve retention in several studies [7,11,14,15]. Similarly we found that 100% (7/7) of patients that reached a dose of ≥8 mg and 84.6% (11/13) of those with dose of ≥6 mg by the 2nd month experienced side effects. However, in our cohort patients that reached a dose of ≥6 mg by the 3rd month did not experience significantly more side effects than those with slower titration (66.7% and 61.5% respectively). These data might suggest that titrations faster than 2 mg per month associate with an increased risk of side effects although titration at rates slower than 2 mg per month are not necessarily better tolerated than a titration of 2 mg per month. This is perhaps a little speculative as only end point doses were recorded and it is possible that the dose of PER did fluctuate within a given month.

4.5. Perampanel and people with ID

Few published studies have specifically evaluated the efficacy of PER in patients with ID. Shankar et al conducted a retrospective study exploring the difference in response to PER in patients with ID compared to patients with normal intelligence [11]. The authors found that patients with moderate to profound ID had better retention rate of PER compared to those with mild ID or normal intelligence while patients with mild ID had similar withdrawal rate with general population. There was no difference in total SEs between the groups but mental health side effects were increased in the moderate to profound ID group. By contrast, 2 other studies that explored possible differences on the effect of PER in patients with normal intelligence and ID concluded that there were no differences in the retention rates and ≥50% responder rates between the 2 groups [8,9]. Our results are more in keeping with those of Shankar et al. showing that patients with ID have higher actuarial retention rate (70.4%) than those with normal intelligence (55%). However, efficacy was similar with no difference in the ≥50% responder rate (39.2% in people with ID and 37.7% in those without ID). Similarly, no significant difference in the incidence of side effects between those without (67.3%) and with ID (61.3%) was seen although reported neuropsychiatric side effects were more frequent in patients with ID (36.3%) compared to those without ID (22.8%). Despite the fact that efficacy and SE are similar, people with ID withdraw from PER less frequently. This is not easy to explain but there is a possibility that people with ID, who may not be able to advocate for themselves, exert less pressure to withdraw from the drug or alternatively these patients and/or their carers may be prepared to allow more time in evaluating the efficacy of a new medication. Interestingly in our cohort the higher retention rate was mainly seen in patients with mild ID who are usually able to advocate for themselves and take part in medical decisions regarding their treatment.

5. Conclusion

PER is a novel antiepileptic drug and its efficacy and tolerability have been studied through randomised clinical trials and observational studies. We conducted a retrospective study analysing monthly outcomes for up to 12 months of treatment. The retention on PER at 12 months and the percentage of ≥50% responders confirmed the general findings of the clinical trials and other “real life” studies, showing that PER is an effective antiepileptic drug providing reductions in seizure frequency for almost 4 out of 10 patients. In keeping with some previous data from observational studies, PER showed high rates of SEs and the emergence of these was not clearly dose related. Side effects were the reason for discontinuation of the treatment in the vast majority of the patients that withdrew from PER. Neuropsychiatric SEs were prominent in a significant number of patients, and physicians should be alerted for this when they decide to add PER in a patient’s treatment. However, we did not find additive risk for neuropsychiatric SEs with concomitant treatment with Levetiracetam and the combination of these 2 drugs could possibly be used with relative safety. Furthermore, our data provide evidence that the efficacy of PER can be seen fairly soon after initiation, usually during the first 6 months of the treatment, and in low to moderate doses. A small number of patients did show further improvement with up-titration of the drug to doses 10–12 mg.

Our study has significant limitations, as is the case for all retrospective observational studies. The data were collected retrospectively from the records of different centres and thus there is variability in the method of collection and in the way that the physicians created these records. Furthermore, the seizure frequency was based on the diaries that patients and their carers keep which are not always completely accurate. Similarly the classification of the level of ID was based on the clinical letters of the treating neurologist and we were not able to locate neuropsychological reports for many of the patients. People with mild ID are usually close to the limits of normal intelligence. If this is the case the retention rates of our cohort with normal intelligence would be expected to be somewhat higher. Finally, despite the fact that many patients were treated with PER for longer than 12 months, the monthly data beyond one year of treatment were harder to obtain and for this reason we focused our analysis to the period that we had the best data quality.

Overall PER is an effective antiepileptic that can be used as adjunctive therapy in patients with chronic refractory epilepsy, but careful follow up and close monitoring for SEs is recommended.

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