Effect and tolerability of perampanel in patients with drug-resistant epilepsy

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Abstract

Objective: Perampanel is one of the most recently approved antiseizure medications. The aim of the present study was to assess clinical efficacy and tolerability, in combination with pharmacokinetic variability, of perampanel treatment in patients at a tertial referral center for epilepsy.

Methods: We performed a retrospective observational study of patients given perampanel as adjunctive treatment in the period January 2013 - February 2019 at the National Center for Epilepsy at Oslo University Hospital, Norway.

Results: Clinical data were available for 175 mainly adult patients with drug-resistant epilepsy with mean treatment duration of 16.1 months. We found that 23% (40 patients) were responders (i.e., achieving more than 50% reduction in seizure frequency), four of whom became seizure free, 29% (51 patients) experienced a modest effect, whereas for 29% (50 patients) perampanel had no seizure-reducing effect. A paradoxical effect, with seizure aggravation, was reported in 9% (15 patients). The responder rate was significantly higher in those with slow vs. fast dosage titration. Logistic regression analysis showed better efficacy among those with generalized vs. those with focal epilepsy. Adverse effects were reported by 135 patients (77%), ranging from mild (34%), to moderate (41%) and severe (2%). In 55 patients (41%), these adverse effects resulted in discontinuation of treatment with perampanel. The most frequent adverse effects were psychiatric symptoms (34%), dizziness (31%), and sleepiness (26%). Of the 31 patients for whom serum concentration measurements were available, the mean daily perampanel dose was 6.3 mg (SD 3.0), with a mean serum concentration at steady state of 1.03 μmol/L (range: 0.15-3.59 μmol/L). There were pronounced differences between patients, as demonstrated by a 12-fold variability in the range of concentration/dose (C/D)-ratios (0.06 to 0.69 μmol/L/mg).

Conclusion: Our results demonstrate that perampanel had a modest seizure-reducing effect in this very treatment-resistant patient group. Predictors of treatment success were generalized epilepsy

and slow dosage titration. In patients without a history of psychiatric problems, clinicians could consider increasing dose of perampanel beyond 6 mg daily, taking co-medication and serum concentrations into account.

1. Introduction

Epilepsy affects about 65 million people worldwide, making it one of the most common neurological diseases globally (1). In Norway, the prevalence of epilepsy is estimated to be 0.65%, i.e., about 35,000 people (2). Although multiple antiseizure medications (ASMs) have been launched over the last two decades, about 1/3 of the patient group is refractory to the currently available drugs (3, 4). Drug-resistant epilepsy is defined by the International League Against Epilepsy (ILAE) as failure to achieve sustained seizure freedom despite adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) (5). Recurrent epileptic seizures are a significant strain on the patients and their families, and drug-resistant epilepsy incurs large healthcare costs (6). Hence, there is still an urgent need for new and more efficacious treatment options.

Perampanel (PER) is approved in Europe and US as adjunctive treatment in patients aged ≥ 12 years with focal onset seizures, and in those with primary generalized tonic-clonic seizures as part of idiopathic generalized epilepsy (7, 8). PER decreases glutamatergic neurotransmission by selective inhibition of post-synaptic AMPA receptors. It is metabolized in the liver, primarily through CYP3A4 and CYP3A5 (9). Thus, its clearance may be increased when used in combination with enzyme-inducing drugs, such as carbamazepine (2.75-fold), oxcarbazepine (1.9-fold), phenytoin (1.7-fold), and topiramate (1.27-fold) (10).

Pharmacokinetic variability has been incompletely studied in clinical trials of newly introduced ASMs and needs further investigation in different patient populations (11, 12). As a relatively new ASM, clinical experience with PER is limited. Therefore, observational studies from a real-life setting, including both clinical information and pharmacokinetic data from therapeutic drug monitoring (TDM), is a valuable approach (13).

The aim of the present study was to assess the clinical efficacy and tolerability, in combination with pharmacokinetic variability, of PER in patients at a tertial referral center for epilepsy.

2. Materials and methods

Patients and data collection

This was a retrospective observational study of patients treated with PER in the period January 2013 - February 2019 at the National Center for Epilepsy at Oslo University Hospital in Norway. Patients with difficult-to-treat epilepsy are referred to the center from the whole country. The patients were retrospectively selected according to the following inclusion criteria: 1) Drug-resistant epilepsy as defined by the ILAE, 2) Patients starting treatment with PER during the study period, 3) Available clinical data on efficacy and tolerability in the medical records.

Clinical data were collected, including age, gender, age at seizure onset, epilepsy etiology, epilepsy type, comorbidity, number of ASMs tried prior to introduction of PER, concomitant ASMs in use, efficacy and tolerability of PER, and time from initiation to withdrawal of the drug.

Seizure frequency at baseline, i.e., before introducing PER, was compared to seizure frequency at last follow-up. Efficacy was categorized using a modified Likert scale: 1) No effect, 2) Some effect (modest reduction of seizure frequency and/or severity), 3) Good effect (> 50% reduction in seizure frequency, defined as responders), and 4) Complete seizure control over the last year.

Adverse effects were documented in the medical records by the treating physician and categorized as none, mild (no action), moderate (dose adjustment/discontinuation), and severe (hospitalization). The reasons for discontinuing treatment with PER were classified as lack of effect, adverse effects, both of these reasons, or other reasons.

Serum concentrations, dose, and concentration/dose (C/D) ratios were retrieved from the TDM-database at the Section for Clinical Pharmacology and calculated as means or medians with standard deviation (SD)/minimum-maximum range as variability measures. The analyses were routine measurements of validated methods as measured by UPLC-MS/MS by Thermo Scientific, Prelude Endura instrument using the The ClinMass® TDM Platform from RECIPE (MS9000) with the add-on

set for antiseizure drugs (MS9200) (https://recipe.de/products/antiepileptic-drugs-serum/). Blood samples were drawn after drug fasting and before intake of the morning dose. The most recent analysis of serum concentrations at assumed steady-state conditions were used.

All data were anonymized, and the study was approved by the Regional Ethics Committee (2014/160)

Statistical analyses:

IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Possible group differences were tested using the Pearson´s chi-square and independent samples *t*-test for categorical and continuous variables respectively. Variables that differed significantly at $p < 0.05$ (responders, retention rate at 6 months and 1 year, and serious adverse effects) were tested in multiple logistic regression analysis and presented as odds ratios (ORs) with 95% confidence intervals (CIs) and p-values. Dependent variables were moderate or severe adverse events versus none or mild adverse events, responder versus non responder, and on versus off treatment after 6 months and 12 months. Independent variables tested were age, number of concomitant ASMs, drug titration rate, type of epilepsy, PER dose > 6 mg, psychiatric adverse effects, and psychiatric comorbidity.

3. Results

3.1 Patients

In the study period, 237 patients had received PER as adjunctive treatment, but 62 patients were excluded as they were either lost to follow-up or clinical documentation was lacking. The study group therefore consisted of 175 patients with a median age of 32 years (3-75 years), with 54% female. In total, 80% (140 patients) had focal epilepsy, 14% (25 patients) had generalized epilepsy, and 6% (10 patients) had unclassified epilepsy. The epilepsy etiology was known in 50% of the patients. The most common causes were central nervous system (CNS) infection, cortical dysplasia, and presumed genetic etiology (Table 1).

The median number of previously failed ASMs was eight (2-19 drugs). The most common concomitant ASMs in use were lamotrigine (27%), valproate (27%), and levetiracetam (19%). Enzyme-inducing ASMs (phenytoin, phenobarbital, carbamazepine) were used by 15% of the patients. At baseline, 30% of the patients were taking one concomitant ASM, 46% were taking two, 18% used three, and 3% used four concomitant ASMs. Only 3% (5 patients) used PER as monotherapy. A history of psychiatric problems was recorded for 34% (60 patients), 31% (54 patients) had intellectual disabilities, and 8% (14 patients) had autism spectrum disorder (Table 1).

Dose and serum concentrations of PER from 31 of the patients were identified from the TDM-database (Table 1). The average maximum dose of PER was 7.3 mg (2 –16 mg). In 60% (112 patients), the dose titration was rather fast (2 mg every second week, or faster), and in the remaining 40% (76 patients) the dose titration was slow (2 mg every four weeks, or slower).

3.2 Efficacy

We found that 23% (40 patients) were responders (> 50% seizure-reducing effect), of whom four patients had been seizure free for the whole of one year following the treatment. In 29% (51 patients), treatment with PER had a modest effect (< 50% seizure-reducing effect), and in 29% (50 patients) PER had no seizure-reducing effect. A paradoxical effect of seizure aggravation was seen in 9% (15 patients). For the remaining 11% (19 patients), the change in seizure frequency after initiation of PER treatment was uncertain (Table 2).

Among those with slow dose titration, the responder rate was significant higher than among those with fast dose titration (p=0.02) (Table 3). This was confirmed by multiple regression analysis (OR 2.67; CI 1.16-6.13, p= 0.02). Logistic regression analysis showed that those with generalized epilepsy experienced better efficacy than those with focal epilepsy (OR 2.70; CI 0.10-7.30 p=0.05) (Table 4).

3.3 Safety and tolerability

Adverse effects were experienced by 135 patients (77%), ranging from mild (34%), to moderate (41%), to severe (2%). In 55 patients (41%), these effects resulted in discontinuation of treatment with PER. The most frequent adverse effects were psychiatric symptoms (34%), dizziness (31%), and sleepiness (26%) (Table 2). The most common psychiatric side effects were irritability, anger, and depression. Five patients experienced suicidal thoughts, and in three of them this led to hospitalization; for one this was due to attempts at suicide, and for two this was due to additional psychoses. One patient was hospitalized due to mental instability with aggression.
Multiple regression analysis showed that the occurrence of moderate or severe adverse effects was higher in patients > 65 years old (OR 10.56; CI 2.51-52.63, p=0.005) and in patients with psychiatric adverse effects (OR 9.57; CI 4.40-20.81, P<0.001), whereas it was lower in patients with dosage of PER > 6 mg (OR 0.36; CI 0.17-0.76, p=0.007). (Table 4).

3.4 Retention rate

The retention rate of PER was 69% at 6 months and 51% at 12 months. PER treatment was withdrawn in 41% (72 patients) due to adverse effects, in 22% (39 patients) due to lack of efficacy, in 7% (12 patients) due to both adverse effects and lack of efficacy, and in 2 % (4 patients) the reason for treatment discontinuation was not specified. At last follow-up, 29% (50 patients) were still using PER (mean treatment duration of 16.1 months).

In those with generalized epilepsy, the retention rate at 12 months was 68% (17 patients) compared with 47% (66 patients) in those with focal epilepsy (p=0.055). Generalized epilepsy was an independent factor for retention at 12 months (OR 2.80; CI 1.06-7.42, p=0.039) (Table 4).

Among patients with intellectual disability, 63% (34 patients) were still using PER at 12 months as compared with 51% in the total study group (p=0.032). Patients having a maintenance dose of PER > 6 mg had a higher retention rate at 12 months than those with a lower dose (p < 0.001). Those who experienced psychiatric adverse effects had a lower retention rate than the total group (p=0.01). These were confirmed as independent factors by multiple logistic regression analysis (Table 4). We

found no significant differences in retention rate between those with slow vs. fast dose titration (Table 3).

3.5 Pharmacokinetic variability

Of the 31 patients for whom serum concentration measurements were available, the mean daily PER-dose was 6.3 mg (SD 3.0) with a mean serum concentration at steady state at 1.03 μmol/L (range 0.15-3.59 μmol/L). There were pronounced differences between patients, as demonstrated by a 12-fold variability in the range of C/D-ratios from 0.06 to 0.69 μmol/L/mg.

The majority of patients had serum concentrations within the reference range of 0.25-2.8 μmol/L (Figure 1a). There were no significant correlations between those who had serum concentrations below, within, or above the reference range and responders vs. non-responders, or those with or without adverse effects. There was, however, a correlation between the serum concentration at steady state for responders (mean 1.22 μmol/L (SD 0.80)) versus non-responders (mean 0.49 μmol/L (SD 0.25), $p<0.01$), but not between those who experienced CNS-related adverse effects and those who did not (mean 0.99 and 1.07 μmol/L (SD 0.71 and SD 0.84, respectively)) (Figures 1b and c) (Table 1).

4. Discussion

The main finding in this observational study of PER, mainly used as an add-on treatment in drug-resistant adult epilepsy patients, was a responder rate of 23%. After the last follow-up, i.e., after a mean of 16.1 months, 29% of the patients were still being treated with PER. In a study by Brigo et al. (14) no significant differences in seizure-reducing efficacy of PER were found as compared with the efficacy of other new ASMs, such as lacosamide, eslicarbazepine, and brivaracetam. Our responder rate was lower than those reported in RCT studies of these ASMs; i.e., a responder rate from 26% - 56% according to study group, medication and dosage (15-19). The discrepancy is most probably due

to differences in the study populations and in duration of the studies. With an average of eight previously failed ASMs, our study cohort consists of patients with very severe and difficult-to-treat epilepsies.

Despite only a modest efficacy, we found a 50% retention rate after 12 months of treatment. This is in concordance with previous studies (7, 20). A higher retention rate was seen among those with generalized epilepsy, with a 65% retention rate after 12 months in our study as compared with 84% in a study by Villanueva et al. (21).

As reported in other studies (15, 22), we found that many patients (77%) had one or more adverse effects. In phase II and III studies a high incidence of adverse effects was also reported in the placebo group (22, 23).

In our study, multiple regression analysis showed that a dosage of PER > 6mg, age> 60 years, and psychiatric adverse effects were factors associated with discontinuation or dose change of the drug. This is in consensus with the results of previous studies (22-24). On the other hand, if the patient tolerated doses of PER higher than 6 mg, then they tended to continue with the medication. Compared to those with focal epilepsy, those with generalized epilepsy seemed to respond better and tended to remain on PER (21). As in a study of Steinhoff et al. (25), we found that slow dose escalation (> 2 weeks between dosage increases) was beneficial in terms of effect. A history of psychiatric problems seemed to increase the risk of early termination of PER treatment (26, 27).

As we have seen in similar studies at our center (28, 29), PER has extensive pharmacokinetic variability. There does not seem to be a clear correlation between an individual patient's serum concentration of PER and effect/tolerability, but most responders had serum concentrations of > 0.5 µmol/L. Previous studies have also confirmed that the serum concentrations of PER are affected by enzyme-inducing drugs, such as carbamazepine, oxcarbazepine, phenytoin and phenobarbital, and

also by an enzyme-inhibiting drug like valproate (30-32). These apparently all contribute to the pharmacokinetic variability observed.

Methodological considerations

The strength of our study is the large number of patients and the structured follow-up by epileptologists at a tertiary epilepsy center. In our opinion, the combination of clinical and pharmacokinetic data may provide more detailed insights regarding our understanding of factors contributing to the efficacy and tolerability of new ASMs, like PER, in patients with refractory epilepsy.

Observational studies have obvious limitations. A control group without PER treatment, and matched for age, gender, and epilepsy severity would have strengthened our study (33). Moreover, the retrospective nature of the study, and the fact that some of our findings have large confidence intervals, further weaken our results.

In conclusion, our results indicate that PER has a modest seizure-reducing effect in patients with difficult-to-treat epilepsy. Predictors of treatment success are generalized epilepsy and slow dosage titration. In those patients without a history of psychiatric problems, clinicians could consider increasing dose of perampanel of PER beyond 6 mg daily, taking co-medication and serum concentrations into account.

Table 1. Clinical characteristics of patients using perampanel (n=175)

Characteristics	**patients**
Number	175 (94 W, 81M)
Epilepsy onset (mean age, years)	12 (0 – 66)
Age at PER initiation (years), mean	32 (3 – 75)
Type of epilepsy, n (%)	
- Focal	140 (80.0)
- Generalized	25 (14.3)
- Unclassified	10 (5.7)
Etiology, n (%)	
- Known	84 (48)
Assumed genetic	18 (10.3)
Cortical malformation	15 (8.6)
Hippocampal sclerosis	8 (4.6)
Vascular	6 (3.4)
Trauma	2 (1.1)
Tumor	8 (4.6)
Infection	15 (8.6)
Other	12 (6.9)
- Unknown	91 (52)
Intellectual disability, n (%)	54 (30.9)
Psychiatric comorbidity, n (%)	60 (34.3)
Autism spectrum disorder	14 (8.0)

Antiepileptic drugs (ASM)	
Number of previous ASM, median (range)	8 (2-19)
Comedication, n (%)	
Monotherapy	5 (2.7)
1 ASM	49 (29.8)
2 ASM	84 (46.4)
3 ASM	33 (18.1)
4 ASM	4 (2.7)
Concomitant strong enzyme inducing ASMs, n (%) (carbamazepine, phenytoin)	28 (14.9)
Doses and serum concentrations (n=31)	
Mean dose (SD) mg/day	6.3 (SD 3))
Median (range) mg/day	6 mg (2-16)
Mean serum concentration (SD) μmol/L	1.03 (SD 0.77)
Median serum concentration (range) μmol/L	0.8 (0.15-3.59)
Mean C/D-ratio (μmol/L/mg) (range)	0.19 (0.06-0.69) 12-fold variability between min. and max. values

Table 2. Efficacy and tolerability (n=175)

Characteristics	**Patients**
Discontinuation n (%)	
Total	125 (71.4%)
Adverse effects	72 (41.1%)
Lack of effect	39 (22.3%)
No effect and/or adverse effects	12 (6.9%)
Unknown	2 (1.1%)
Efficacy	
Seizure free/responder rate[1]	4/40 (23%)
Uncertain efficacy:	51 (29.1%)
Lack of effect:	50 (28.6%)
Worsened	15 (8.6%)
No information	19 (10.9%)
Tolerability	
No adverse effects:	34 (19%)
One effects:	45 (26%)
Two or more effects	90 (51%)
Unknown	6 (3%)
Mild effects:	60 (34%)
Moderate:	71 (41%)
Severe:	4 (2%)
Most commonly reported:	
Psychiatric	59 (34%)
- Irritation/aggression	47 (27%)

- Depression	16 (9%)
- Psychosis	3 (2%)
- Suicidal ideation	7 (4%)
Dizziness/unsteadiness	54 (31%)
Reduced seizure control	11 (9%)
Sedation	43 (26%)
Gastrointestinal	6 (3%)
Weight gain	10 (6%)
Cognitive impairment	16 (9%)

[1]Responders were defined as > 50% seizure reduction

Table 3 Pearson´s chi-square and independent samples *t*-test for categorical and continuous variables respectively.

Variable	Responder n (%)	Moderate/severe adverse effects n (%)	On treatment 6 months	On treatment 1 year
Age ≤ 18 Age ≥ 60	12 (26) 1 (7.7)	18 (40.0) **11 (84.6)****	29 (61.7) 9 (69.2)	23 (48.9) 5 (38.5)
Gender (female)	22 (23.4)	44 (47.8)	64 (68.1)	44 (46.8)
Intellectual disability	15 (27.8)	21 (40.4)	41 (75.9)	**34 (63.0)***
Focal epilepsy	29 (20.7)	62 (45.3)	93 (66.4)	66 (47.1)
Generalized epilepsy	9 (36.0)	9 (39.1)	19 (76.0)	17 (68.0)
Symptomatic epilepsy	13(24)	24 (45.3)	37 (68.5)	27 (50.0)
>5 previous ASMs	35 (23.0)	63 (42.9)	102 (67.1)	74 (48.7)
≥2 ASMs	23(19.3)	48 (41.7)	85 (71.4)	63 (52.9)
Psychiatric comorbidity	13 (21.7)	30 (51.7)	**35 (58.3)***	29 (48.3)
Slow drug titration	**16 (36.4)***	21 (51.2)	29 (65.9)	22 (50.0)
Fast drug titration	20 (18.7)	47 (43.9)	73 (68.2)	54 (50.5)
Maintenance dose > 6 mg	20 (22.5)	**28 (32.2)****	**74 (83.1)*****	**58 (65.2)*****
Enzyme inducing ASMs	3 (11.1)	7 (26.9)	20 (74.1)	14 (51.9)
Serum concentration within reference range*	15 (38.5)	10 (26.3)	35 (89.7)	30 (76.9)
Psychiatric adverse effects	18 (30,5)	**44 (74.6)*****	**32 (54.2)****	**22 (37.3)****

*p<0.05, **p<0.01, ***p<0.01

Table 4. Multiple regression analysis for variables associated with responder/non-responder, retention rate at 6 months and 1 year and serious adverse effects.

Variable	OR	CI (95%)	p-value
Responders vs non-responders			
≥2 concomitant ASMs	0.682	0.291-1.594	0.377
Slow drug titration	2.666	1.160-6.134	0.021
Generalized epilepsy	2.702	0.997-7.299	0.051
Serious adverse effects vs some/no adverse effects			
> 6 mg drug dosage	0.363	0.173-0.762	0.007
≥60 years old	10.562	2.507-52.631	0.005
Psychiatric adverse effects	9.573	4.404-20.809	<0.001
On treatment after 6 months vs not on treatment			
Psychiatric adverse effects	0.394	0.201-0.773	0.007
Psychiatric comorbidity	0.522	0.265-1.028	0.060
On treatment after 1 year vs not on treatment			
>6 mg drug dosage	3.267	1.677-6.369	<0.001
Psychiatric adverse effects	0.437	0.218-0.876	0.020
Generalized epilepsy	2.797	1.055-7.418	0.039

Figure legends

Figure 1. Figure 1a shows dose and serum concentration relationships in patients treated with PER (n=31). The reference range is shown in dotted lines (0.25-2.8 μmol/L).

Figure 1b shows responders (n=23) versus non responders (n=8) in relation to daily dose and serum concentration n= in each group

Figure 1c shows CNS-related or psychiatric adverse effects in relation to daily dose and serum concentration (No or mild psychiatric adverse effect n=15, moderate or severe psychiatric adverse effect n=16).

Figure 1a

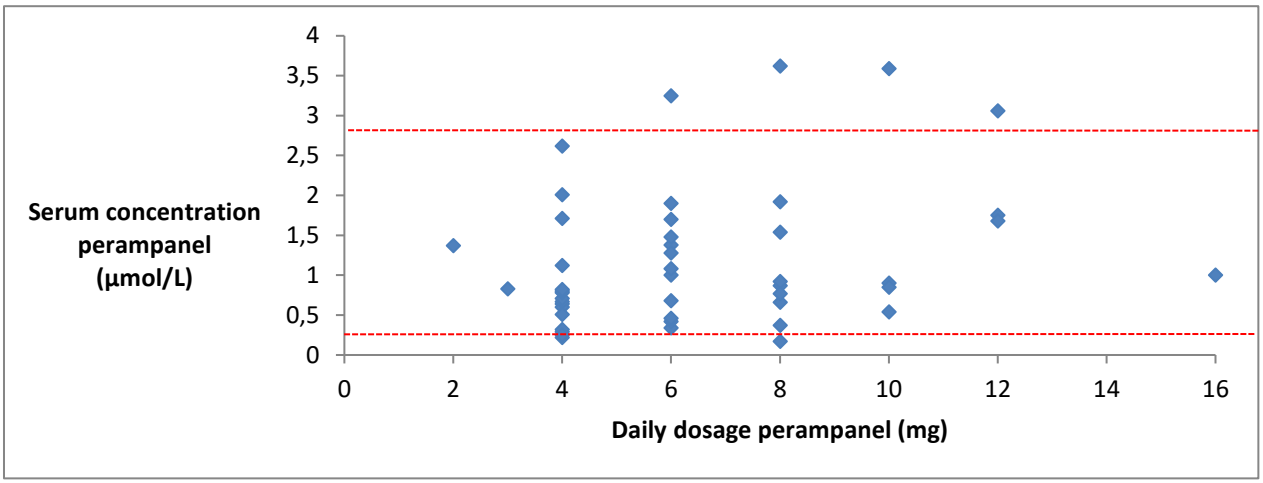


Figure 1b

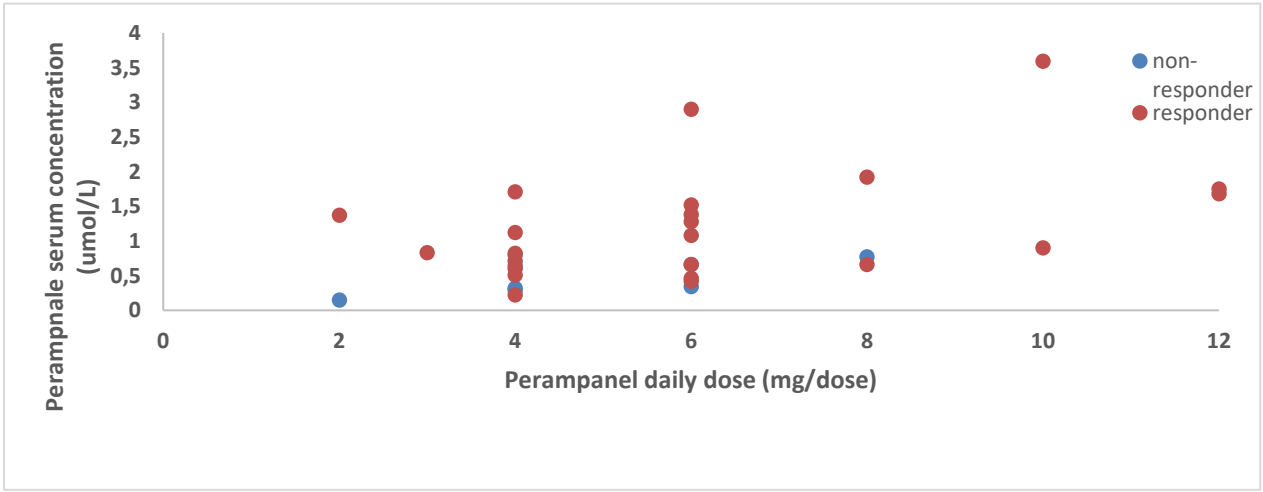
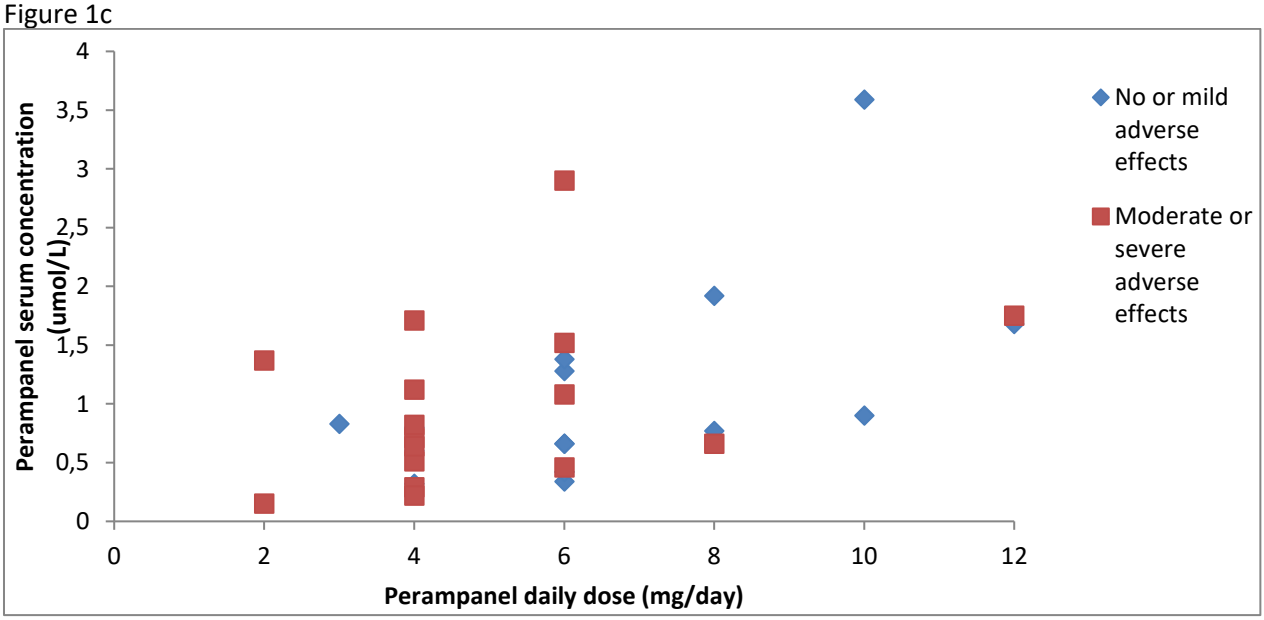


Figure 1c



1. Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology. 2017;88(3):296-303.
2. Syvertsen M, Nakken KO, Edland A, Hansen G, Hellum MK, Koht J. Prevalence and etiology of epilepsy in a Norwegian county-A population based study. Epilepsia. 2015;56(5):699-706.
3. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342(5):314-9.
4. Panayiotopoulos CP. Old versus new antiepileptic drugs: the SANAD study. Lancet. 2007;370(9584):313-4; author reply 5-6.
5. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069-77.
6. Villanueva V, Giron JM, Martin J, Hernandez-Pastor LJ, Lahuerta J, Doz M, et al. Quality of life and economic impact of refractory epilepsy in Spain: the ESPERA study. Neurologia. 2013;28(4):195-204.
7. Steinhoff BJ, Ben-Menachem E, Ryvlin P, Shorvon S, Kramer L, Satlin A, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies. Epilepsia. 2013;54(8):1481-9.
8. 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(16):1751-64.
9. Patsalos PN. The clinical pharmacology profile of the new antiepileptic drug perampanel: A novel noncompetitive AMPA receptor antagonist. Epilepsia. 2015;56(1):12-27.
10. Majid O, Laurenza A, Ferry J, Hussein Z. Impact of perampanel on pharmacokinetics of concomitant antiepileptics in patients with partial-onset seizures: pooled analysis of clinical trials. Br J Clin Pharmacol. 2016;82(2):422-30.
11. Patsalos PN, Spencer EP, Berry DJ. Therapeutic Drug Monitoring of Antiepileptic Drugs in Epilepsy: A 2018 Update. Ther Drug Monit. 2018;40(5):526-48.
12. Johannessen Landmark C, Johannessen SI, Tomson T. Host factors affecting antiepileptic drug delivery-pharmacokinetic variability. Advanced drug delivery reviews. 2012;64(10):896-910.
13. Johannessen Landmark C, Johannessen SI, Patsalos PN. Therapeutic drug monitoring of antiepileptic drugs: current status and future prospects. Expert opinion on drug metabolism & toxicology. 2020;16(3):227-38.
14. Brigo F, Bragazzi NL, Nardone R, Trinka E. Efficacy and tolerability of brivaracetam compared to lacosamide, eslicarbazepine acetate, and perampanel as adjunctive treatments in uncontrolled focal epilepsy: Results of an indirect comparison meta-analysis of RCTs. Seizure. 2016;42:29-37.
15. Krauss GL, Serratosa JM, Villanueva V, Endziniene M, Hong Z, French J, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology. 2012;78(18):1408-15.
16. French JA, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology. 2012;79(6):589-96.
17. Biton V, Rogin JB, Krauss G, Abou-Khalil B, Rocha JF, Moreira J, et al. Adjunctive eslicarbazepine acetate: A pooled analysis of three phase III trials. Epilepsy Behav. 2017;72:127-34.
18. Ryvlin P, Werhahn KJ, Blaszczyk B, Johnson ME, Lu S. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. Epilepsia. 2014;55(1):47-56.
19. Chung S, Ben-Menachem E, Sperling MR, Rosenfeld W, Fountain NB, Benbadis S, et al. Examining the clinical utility of lacosamide: pooled analyses of three phase II/III clinical trials. CNS drugs. 2010;24(12):1041-54.

20. Shah E, Reuber M, Goulding P, Flynn C, Delanty N, Kemp S. Clinical experience with adjunctive perampanel in adult patients with uncontrolled epilepsy: A UK and Ireland multicentre study. Seizure. 2016;34:1-5.
21. Villanueva V, Montoya J, Castillo A, Mauri-Llerda JA, Giner P, Lopez-Gonzalez FJ, et al. Perampanel in routine clinical use in idiopathic generalized epilepsy: The 12-month GENERAL study. Epilepsia. 2018;59(9):1740-52.
22. French JA, Krauss GL, Wechsler RT, Wang XF, DiVentura B, Brandt C, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy A randomized trial. Neurology. 2015;85(11):950-7.
23. Rugg-Gunn F. Adverse effects and safety profile of perampanel: a review of pooled data. Epilepsia. 2014;55 Suppl 1:13-5.
24. Trinka E, Steinhoff BJ, Nikanorova M, Brodie MJ. Perampanel for focal epilepsy: insights from early clinical experience. Acta Neurol Scand. 2016;133(3):160-72.
25. Steinhoff BJ, Patten A, Williams B, Malhotra M. Efficacy and safety of adjunctive perampanel 4 mg/d for the treatment of focal seizures: A pooled post hoc analysis of four randomized, double-blind, phase III studies. Epilepsia. 2020;61(2):278-86.
26. Hansen CC, Ljung H, Brodtkorb E, Reimers A. Mechanisms Underlying Aggressive Behavior Induced by Antiepileptic Drugs: Focus on Topiramate, Levetiracetam, and Perampanel. Behavioural neurology. 2018;2018:2064027.
27. Mula M. The interictal dysphoric disorder of epilepsy: Legend or reality? Epilepsy Behav. 2016;58:7-10.
28. Svendsen T, Brodtkorb E, Baftiu A, Burns ML, Johannessen SI, Johannessen Landmark C. Therapeutic Drug Monitoring of Lacosamide in Norway: Focus on Pharmacokinetic Variability, Efficacy and Tolerability. Neurochem Res. 2017;42(7):2077-83.
29. Svendsen T, Brodtkorb E, Reimers A, Molden E, Saetre E, Johannessen SI, et al. Pharmacokinetic variability, efficacy and tolerability of eslicarbazepine acetate-A national approach to the evaluation of therapeutic drug monitoring data and clinical outcome. Epilepsy Res. 2017;129:125-31.
30. Steinhoff BJ, Hubers E, Kurth C, Jurges Kehl-Kork U. Plasma concentration and clinical effects of perampanel-The Kork experience. Seizure. 2019;67:18-22.
31. Contin M, Bisulli F, Santucci M, Riva R, Tonon F, Mohamed S, et al. Effect of valproic acid on perampanel pharmacokinetics in patients with epilepsy. Epilepsia. 2018;59(7):e103-e8.
32. Murugesu S, Okayama K, Yamamoto Y, Terada K, Takahashi Y. Changes in serum perampanel concentration profile after discontinuation of carbamazepine. Epileptic disorders : international epilepsy journal with videotape. 2020;22(4):455-61.
33. Perucca E, Wiebe S. Not all that glitters is gold: A guide to the critical interpretation of drug trials in epilepsy. Epilepsia open. 2016;1(1-2):9-21.