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A Russian retrospective multicenter open-label observational study based on medical documentation on the use of perampanel in everyday clinical practice

Objective: *to retrospectively assess the Russian experience with perampanel (PER) in everyday clinical practice as an adjunctive medication for the treatment of patients aged 12 years or older with focal epilepsy (FE).*

Patients and methods. *A multicenter retrospective study was conducted, during which the physicians filled out standard questionnaires assessing the characteristics of the disease and the therapy performed. The maximum follow-up period was 12 months. Each patient was included in the study only once for the duration of the study. A total of 164 cases of pharmacoresistant FE were analyzed. The patients' mean age was 37.7 years; the male to female ratio was 1:1. The disease duration over 10 years was in 68.7% of patients; structural epilepsy was present in 68.2% (temporal and frontal lesions in 53.4 and 39.1%, respectively)*

Results and discussion. *Most (26.6%) patients were prescribed PER after three previous lines of therapy; before PEP administration, there was a maximum of 2 (50.9%) and 3 (29.6%) drugs, respectively, in the combination. The initial frequency of all seizure types reached 9 [3; 34] per month; that of focal-onset bilateral tonic-clonic seizures was 3 [2; 6] per month. Combined therapy including PER could lead to the disappearance of seizures in 22.7% of cases; the responders (by all seizure types) were 52.8%, whereas the remission rate of bilateral tonic-clonic seizures was 60.8% of patients, the responder rate was 27,8%. At 12 months of follow-up, the therapy retention rate reached 80.7% (95% confidence interval, 72.3P89.1). Adverse events (AEs) were noted in 31.3% of patients; the most frequent AEs were drowsiness (10.4%), aggression (9.8%), irritability (6.7%); other AEs were observed in individual cases. The average dose of PER was 8 mg.*

Conclusion. *PER was effective in patients with resistant PEs at a maximum follow-up of 12 months in routine clinical practice. Remission of all seizure types was achieved in 22.7% of cases, the decrease in the number of seizures i50% was seen in 52.8% of cases; the therapy retention rate was 80.7%. The drug had a therapeutic effect in all types of focal seizures and was most effective in focal-onset bilateral tonic-clonic seizures. Along with its good clinical effect, PER demonstrated a predictable safety profile.*

Keywords: *perampanel; pharmacoresistant focal epilepsy; efficacy; tolerance; safety; adverse events; side effects; therapy retention.*

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Perampanel (PER) – 5'-(2-cyanophenyl)-1'-phenyl-2,3'-bipyridinyl-6'(1'H)-on is the newest unique antiepileptic drug (AED), the first in its class selective non-competitive antagonist of ionotropic AMPA-glutamate receptors of the postsynaptic neural membrane [1, 2]. The drug is indicated for the treatment of partial onset seizures in patients aged 12 years and older and is most effective against bilateral tonic-clonic [3] and generalized convulsive [4, 5] seizures. Another indication is adjunctive therapy for primary generalized tonic-clonic seizures in patients with idiopathic generalized epilepsy. Additional positive properties of PER include single daily dose, which remarkably simplifies its use, increases compliance, and reduces drug-drug interactions [6, 7]. The whole new mechanism of PER, unlike any of the currently existing ones, predetermines the achievement of clinical effect when it is added to almost any initial therapy with AED [8]. Previously V. A. Karlov et al. [9] reported the results of treatment with PER in 52 patients, some of them were younger than 12 years. N. Swiderska et al. [10] also administered PER therapy for various epileptic syndromes, including in children under 12 years of age.

The purpose of the study is perform retrospective evaluation of Russian experience of using perampanel (PER) in everyday clinical practice as an adjunctive therapy in patients with partial epilepsy (PE) aged 12 years and older.

Patients and methods. A multicenter retrospective study was conducted, which involved epileptologists from different cities of Russia (Moscow, Barnaul, Izhevsk, Kazan, Krasnoyarsk, Novosibirsk, Orenburg, Samara, Saratov, Saint Petersburg, Perm, Tomsk, Chelyabinsk). There were analyzed 164 cases of pharmacoresistant PE. Patients' age was between 18 and 78 years (average age 37.7±15.2 years), male and female ratio was 1:1. Duration of the disease was over 10 years in 68.7% of patients, 68.2% had structural epilepsy (53.4% had temporal localization of epileptic focus, 39.1% had frontal localization). For each patient, doctors filled out a standard questionnaire, where they recorded information about the type of epilepsy, type and frequency of seizures, duration of disease, previous therapy, the reasons for changing it, current regimen of treatment with AEDs and doses, the scheme of individual titration of PER and its dose, efficacy, tolerability of combination therapy, as well as the data of the General health status questionnaire and the comment of the expert who filled out the questionnaire. The maximum duration of observation was 12 months. Each patient was included in the study only once for the duration of observation.

The research protocol was approved by the Ethics Committee of the Federal State Budgetary Educational Institution «Moscow State Medical and Dental University n. a. A. I. Evdokimov». The study is currently ongoing.

Inclusion criteria: signed informed consent to participate in the study; patients with pharmacoresistant PE receiving PER as adjunctive AED; age over 12 years; failure of previous antiepileptic therapy; baseline frequency of seizures >1 per month. Exclusion criteria: severe somatic disease; age under 12 years; non-compliance.

Statistical analysis was performed in the IBM SPSS Statistics 25 program (IBM Corp., USA). Relative (%) and absolute (n) frequencies were calculated for categorical variables. A two-sided 95% confidence interval (CI) was also determined when assessing reduction in the frequency of seizures and development of adverse events (AE). For quantitative variables, the arithmetic mean (M±SD) was calculated, and if the distribution of variables differed from the normal one, the median (Me) [25th; 75th percentiles] or Me (Min–Max) was calculated. To characterize retention on therapy, the cumulative survival analysis using Kaplan–Meyer method was used. The comparison of categorical variables was performed using Fisher's exact test. Differences were considered statistically significant at $p<0.05$.

The main parameters of the disease, previous and concomitant therapy, its effectiveness and tolerability are shown in Tables 1–4.

The data presented indicate a severe course of the disease, in which most of multiple previous attempts of drug therapy were unsuccessful. The average patient included in the study could be characterized as follows: diagnose with predominantly temporal (53.2%) or frontal (39.1%), structural (70.5%) epilepsy with mainly focal seizures with impaired awareness (53%) and bilateral tonic-clonic seizures (44.5%). The baseline frequency of all types of seizures was 9 [3; 34] per month; bilateral tonic-clonic seizures – 3 [2; 6] per month, which indicates an initially high activity of the disease for 4 weeks before the administration of PER.

In most cases, PER was included in the scheme at the 4th stage of therapy (26.6%), while previously patients had already taken a maximum of 2 (50.9%) or 3 (29.6%) AED (except PER), mainly valproate (54.9%), carbamazepine (26.8%) and levetiracetam (23.8%).

Table 1. *Main demographic characteristics of patients with PE (n=164)*

Parameter	Value
Age, years:	
M±SD	37.7±15.2
Me [25th; 75th percentile]	33 (25–49)
Min–Max	18–78
Female, n (%)	83 (50.6)
Male, n (%)	81 (49.4)

Table 2. *Disease characteristic, n (%)*

Parameter	Value
Duration of the disease, years (n=163):	
<5	24 (14.7)
5–10	27 (16.6)
>10	112 (68.7)
Etiology of epilepsy (n=154):	
structural	105 (68.2)
unspecified	44 (28.6)
Localization of the epileptic focus (n=161):	
temporal	86 (53.4)
frontal	63 (39.1)
parietal	5 (3.1)
occipital	3 (1.9)
not identified	9 (5.6)

Note: Here and in Tables 4 and 5: the number of analyzed questionnaires for each parameter is indicated.

Table 3. *Types and frequency of seizures*

Type of seizures (n=164):	Number of patients, n (%)	Baseline frequency of seizures, Me [25th; 75th percentiles]
Focal:		
without altered state of consciousness and transformation into bilateral tonic-clonic	38 (23.2)	10 [6.5; 30]
with altered state of consciousness and transformation into bilateral tonic-clonic	87 (53)	10 [6; 18.5]
Bilateral tonic-clonic with partial onset	73 (44.5)	3 [2; 6]
Combination of partial onset and bilateral tonic-clonic	38 (23.2)	9 [3; 34]
Other	9 (5.5)	8 [5; 300]

Note: One patient could have a combination of different localizations of the focus, as well as different types of seizures.

Results. The effectiveness of therapy for 12 months of follow-up is presented in Table 5. As it appears from Table 5, complete remission of all types of seizures was achieved in 22.7% of cases, and complete remission of bilateral tonic-clonic seizures – in 60.8%. Among the patients who developed remission of all types of seizures over the period of 12 months, the number of female patients was almost 2 times higher (64.3%) than that of male patients (35.7%). Achievement of remission in all types of seizures typically (38.5%) required 3 lines of previous therapy, and the maximum number of combinations before the appointment of PER was 2 (69.2%). It turned out that remission was more often observed in the frontal localization of the epileptic focus (69.2%) and in structural epilepsy (64.3%).

AE were identified in 51 of the 164 analyzed questionnaires, which comprised 31.3% (95% CI 24.5–38.7). The characteristics of AE are presented in Table 6. The most common AE included drowsiness, aggression, irritability, unsteady gait, and vertigo. At the same time, only the frequency of sleepiness exceeded 10%, all other AE were sporadic. Irritability was significantly more frequently observed in women (odds ratio 4.87; 95% CI 1.02–23.29). Aggression was registered only in structural epilepsy (p=0.02, Fisher's exact test), mainly with a daily dose of PER 8 mg, and its reduction to 6 mg resolved this AE in most cases. And only in 2 of 16 cases, aggression developed at a daily dose of PER 4 mg. In 4 patients (3 with frontal and 1 with temporal localization of the epileptic focus), when aggression appeared in combination with other AE and the insufficient effect of the therapy, PER was canceled. However, in all patients with aggression (n=16) the dependence of development of this AE on the location of the epileptic focus, age, and the use of concomitant AED was not revealed.

The retention rate on therapy, which is essentially a derivative of efficacy/tolerability, was 80.7% for 12 months (95% CI 72.3–89.1; Fig. 1). The median of the last effective dose of perampanel was 8 mg/day.

According to the General health status questionnaire, the maximum effect was achieved in the parameters «well-being», «mood», and «energy level» (Fig. 2).

Discussion. The combined results of administration of PER in patients in the Russian Federation obtained in this study indicate that it is highly effective in treatment of PE. The characteristic property of studies conducted in real clinical practice is that the practitioner is not limited by the protocol, as in randomized trials, in which the baseline frequency of seisures, the number of concomitant AED the rate of drug titration, etc. are always fixed.

In general, in this study the subjects managed to achieve remission of all types of seizures in 22.7% of cases; ⩾50% reduction in the frequency of seizures in 52.8%, and retention on therapy for 12 months in 80.7%. These results are comparable to the parameters obtained by K. Sierdzan and H. Hodgson [11], and significantly higher than in other works (Table 7). In this study, the higher efficiency of PER for treat-

Table 4. *Treatment characteristic, n (%)*

Parameter	Value
Number of previous therapy lines (n=158):	
1	19 (12.0)
2	28 (17.7)
3	42 (26.6)
4	18 (11.4)
5	25 (15.8)
>5	26 (16.5)
The maximum number of drugs in a combination before administration of PER (n=159):	
1	23 (14.5)
2	81 (50.9)
3	47 (29.6)
4	8 (5)
Concomitant AEDs (n=159):	
valproates	90 (54.9)
carbamazepine	44 (26.8)
levetiracetam	39 (23.8)
topiramate	28 (17.1)
lamotrigine	25 (15.2)
oxcarbazepine	24 (14.6)
phenobarbital	16 (9.8)
lacosamide	15 (9.1)
benzodiazepines	5 (7.1)
pregabalin	5 (3.3)
zonisamide	1 (1.4)
phenytoin	1 (1.4)
Duration of PER intake, months (n=164):	
1	5 (3.0)
2	11 (6.7)
3	52 (31.7)
6	26 (15.9)
9	18 (11)
12	52 (31.7)

Note: The patient could receive several AEDs at the same time.

ment of PE than in previously published analyses (n=52) [9, 15] is explained by earlier administration of the drug, since the effectiveness depends on the stage-by-stage approach in therapy with AED [16]. The maximum positive result of complex therapy with PER was obtained in bilateral tonic-clonic seizures, which stopped in 60.8% of cases, and ⩾50% decrease in their frequency was achieved in 27.8%, which is comparable to the results of previously published works (see Table 7). And only in the study of E. Shah et al. [17] the maximum improvement was obtained in partial-onset seizures with altered awareness compared to other types of seizures, which is explained by a heterogeneous population (patients not only with PE are represented). The results of pooled analysis of European observational studies of daily clinical practice (n=2396) suggest a higher effect of using PER as an adjunctive AED in the group of patients over 65 years of age: retention rate on the drug for 12 months is 48%, and remission rate is 28% [18]!

The median effective daily dose of PER in this study was 8 mg, and in the previous study – 6 mg [9]. The additional analysis did not allow us to identify the optimal combination for PER, since its effect was manifested independently of the concomitant AED. However, according to a large-scale study conducted in Spain, the use of PER in combination with enzyme-inducing AED reduced the effectiveness of combination therapy [12], which had a pharmacokinetic justification [7].

Table 5. *Effectiveness of therapy for 12 months of follow-up*

Parameter	Number of patients, n (%)	% (95% CI)
All types of seizures (n=163):		
none	37	22.7 (16.8; 29.6)
⩾50% frequency reduction (responders)*	86	52.8 (45.1; 60.3)
<50% frequency reduction	17	10.4 (6.4; 15.8)
lack of dynamics	16	9.8 (6; 15.1)
increase in frequency	7	4.3 (1.9; 8.2)
Bilateral tonic-clonic seizures (n=97):		
none	59	60.8 (50.9; 70.1)
⩾50% frequency reduction (responders)*	27	27.8 (19.7; 37.3)
<50% frequency reduction	2	2.1 (0.4; 6.4)
lack of dynamics	5	5.2 (2; 10.9)
increase in frequency	4	4.1 (1.4; 9.5)

* Responderts – patients who had a decrease in the frequency of seizures ⩾50%, but <100%.

Table 6. *Characteristics of AE*

AE	Number of patients, n (%)	% (95% CI)
Somnolence	17	10.4 (6.4; 15.8)
Aggression	16	9.8 (6; 15.1)
Irritability	11	6.7 (3.6; 11.4)
Unsteady gait	10	6.1 (3.2; 10.6)
Dizziness	8	4.9 (2.3; 9)
Retardation	3	1.8 (0.5; 4.8)
Headache	2	1.2 (0.3; 3.9)
Increased appetite	2	2.9 (0.6; 9.1)
Psychomotor agitation	2	2.9 (0.6; 9.1)
Behavioural disturbance	1	1.4 (0.2; 6.6)
Handwriting disturbance	1	1.4 (0.2; 6.6)
Memory impairment	1	1.4 (0.2; 6.6)
Vision impairment	1	1.4 (0.2; 6.6)
Anxiety	1	1.4 (0.2; 6.6)
Fear	1	0.6 (0.1; 2.8)
Total	51	31.3 (24.5–38.7)

Note: One patient could have several AEs that developed sequentially or simultaneously.

Our study confirmed the good tolerability of PER: AEs were registered in only 31.3% of observations (n=51). The most frequent AE was drowsiness (10.4% of cases), the remaining AEs were observed significantly less frequently. In general, the percentage of AEs in this study was less than in previously published works, probably due to the lack of a rigid protocol, moreover, when minimal signs of AEs appeared the doctor immediately explained to the patient the necessity of taking the drug just before bedtime, and in some instances temporarily reduced the dose of PER or prescribed PER on alternate days for a few days.

Aggression as the most alarming AE (9.8%) was transient and in most cases resolved after reducing the daily dose of PER to 6 mg. Only in 4 cases, when aggression was combined with other AEs and the effect of the therapy was insufficient, PER was discontinued. In all patients, this AE registered as statistically significant (p=0.02) in structural partial epilepsy, but it was not possible to determine its relationship with other characteristics of the disease – age, localization of the epileptic focus and the use of concomitant AED. In the study of B. Renroe et al. [19] aggression during treatment with PER was observed mainly in adolescents, in contrast to the results obtained in Russia, where this AE was registered only in 2 patients aged 15 and 16 years (this might be due to the small total number of adolescents in the sample). More than half of patients with aggression took valproic acid as part of combined therapy, but such mental side effects as depression, psychosis, irri-

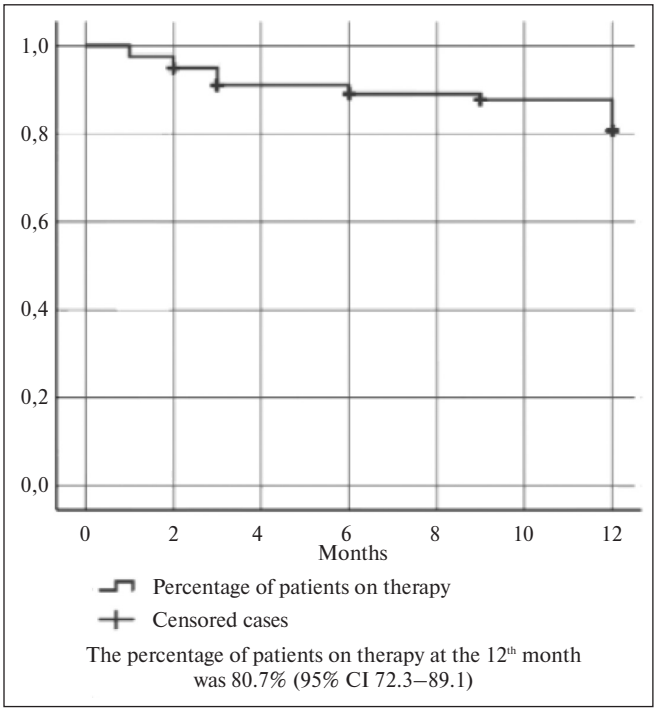

Fig. 1. *Retention rate on therapy*

tability/emotional lability are not typical for patients receiving valproic acid [20]. It is known that irritability and aggression may also develop when levetiracetam and topiramate are used as part of complex therapy [21]. In such circumstances, it is recommended to purposefully collect patient's history of mental/behavioral problems and actively monitor possible manifestations of aggression. This analysis shows that practitioners know that treatment with PER can cause this AE, as evidenced by a slight decrease in its frequency compared to the previous study [9], although the population size increased by 3 times.

In general, patients rated PER very high as part of complex therapy: in most cases, the quality of life improved, and only less than 10% of patients stated that QoL became «definitely worse» or «possibly worse» compared to the beginning of treatment with PER (see Fig. 2). In the questionnaires, patients with epilepsy particularly noted an improvement in mood, a sense of well-being, and a surge of energy. Patients did not feel the effect of PER on concentration and cognitive function, which is consistent with the data of K.J. Meador et al. [22], indicating a minimal effect of PER on cognitive function compared to placebo.

Recent studies of use of PER in early adjunctive therapy allow us to hope for an increase in the effectiveness of complex therapy of PE by almost 2 times compared to the effectiveness with later administration of the drug [23].

Conclusion. Thus, PER was effective in treatment of resistant forms of PE in routine clinical practice with a maximum duration of follow-up of 12 months. Remission of all types of seizures was achieved in 22.7% of cases, ⩾50% reduction in the frequency of seizures – in 52.8% cases, retention on therapy – in 80.7% cases. The drug was effective in all types of partial seizures and was most effective in bilateral tonic-clonic seizures with partial onset. Along with a good clinical effect, PER demonstrated a high and predictable safety profile. It is known that combined therapy is used for pharmacoresistance, which therefore potentially increases the risk of developing

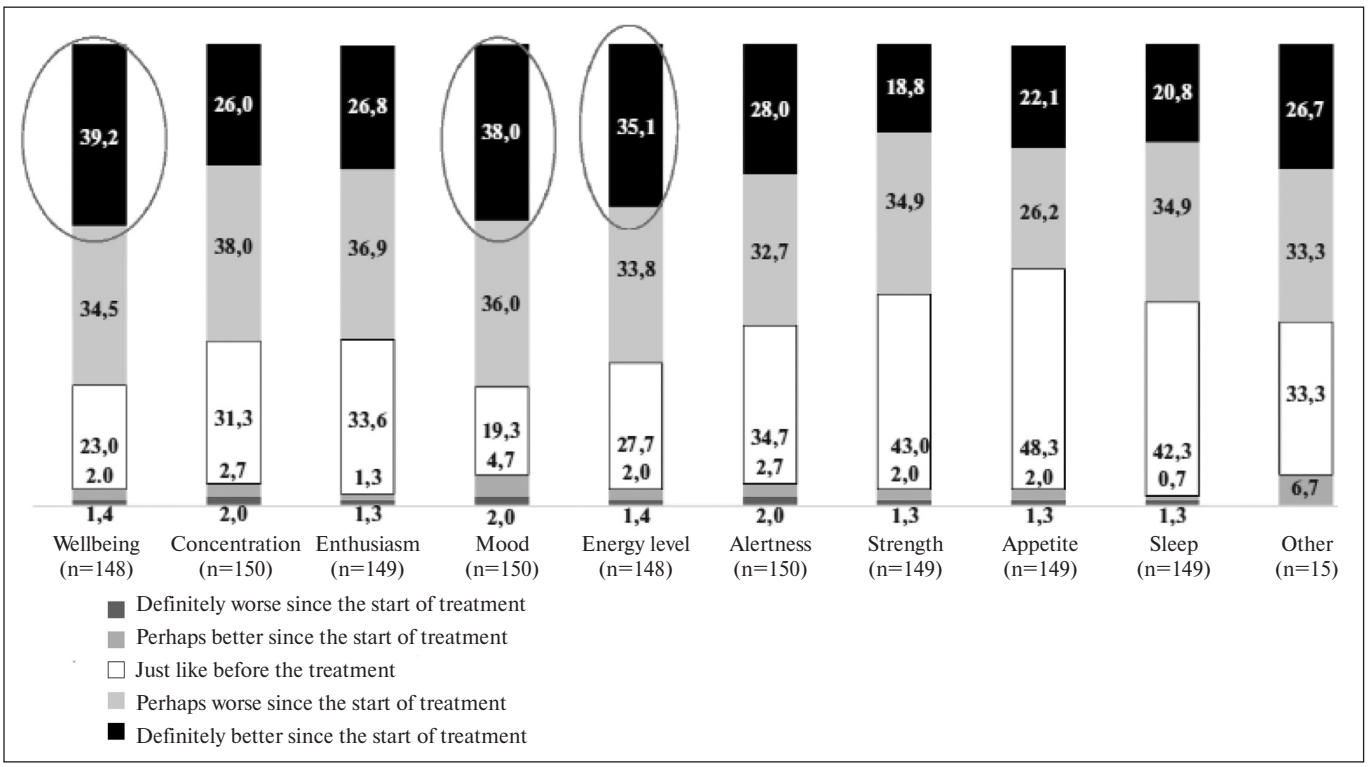

Fig. 2. *Assessment of general health status*

Table 7. *Main studies of comparative effectiveness/tolerability of PER as an adjunctive AED in treatment of PE*

Author, year	Study design	Duration, months	Number of patients	Dose of PER, mg	Effectiveness: seizure free; responders (⩾50%), retention on therapy	AEs (3 most frequent)
V. Villanueva et al., 2016 [12]	Multicenter, retrospective, observational	12	464	2–12 (Me 8)	Seizure free – 7.2%, responders – 26.8%, retention on therapy – 60.6%	Dizziness – 23.2%, drowsiness – 19.8%, irritability – 17.9%. With slow titration, the number of AEs significantly reduced (51.1% of patients at 2 mg/week; 50.5% of patients at 2 mg/2 weeks; 32.0% of patients at 2 mg/3–4 weeks; p=0.006)
B.J. Steinhoff et al., 2014 [13]	Multicenter cross-sectional observational	6	281	4–15 (Me 7,7)	Seizure free in the last 3 months – 15%, responders – 50%, retention on therapy – 60%	Drowsiness – 24.6%, dizziness – 19.6%, followed by ataxia – 3.9%
B.J. Steinhoff et al., 2014 [14]	Retrospective observational	6	A total of 74, including 71 with PE, 3 with Lennox–Gastaut syndrome	4–14 (Me 8,8)	Seizure free – 14%, responders – 46%, retention on therapy – 70%	Drowsiness – 42%, dizziness – 18%, the rest of the AEs – in sporadic observations
K. Sierdzan and H. Hodgson, 2014 [11]	Retrospective observational	14	60	2–12 (Me 6)	Seizure free – 17%, responders – 27%, retention on therapy – 75%	Dizziness – 27%, lability – 17%, behavioural disorders – 8%
V.A. Karlov et al., 2016 [9]	Multicenter retrospective observational	6	52	2–12 (Me 6)	Seizure free – 8%, responders – 58%, retention on therapy – 92.3%	Aggression – 11.5%, drowsiness – 9.6%, unsteady gait – 5.8%. In most cases aggression developed at a dose of PER 8 mg and regressed when the dose decreased
Present study	Multicenter retrospective observational	12	164	2–12 (Me 8)	Seizure free – 22,7%, responders – 52,8%, retention on therapy – 80,7%	Drowsiness – 10,4%, aggression – 9.8%, irritability – 6.7%

AEs, particularly neurotoxicity, with a similar mechanism of action of AEDs. In these cases, administration of the novel AED with a fundamentally different mechanism of action allows personalized approach in pharmacotherapy and is promising in certain groups of patients (age, gender, concomitant somatic pathology, etc.). The use of PER in real clinical practice has shown that after reaching a dose of 4 mg, its effectiveness should be evaluated, and further titration can be performed 2 times or more slowly. In a situation where the doctor is free to choose the dose and rate of PER titration, the effectiveness of the drug was comparable to that obtained in previously published studies, and the tolerability was significantly better. The average PER dose for adult patients is only 8 mg. In 2019, in the United States, PER was approved for use as a monotherapy to treat PE, the reason for this was its high effectiveness and good tolerability.

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