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The impact of perampanel treatment on quality of life and psychiatric symptoms in patients with drug-resistant focal epilepsy: An observational study in Italy

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ABSTRACT

An observational, prospective study has been conducted to evaluate the effects of adjunctive treatment with perampanel (PER) on psychological functioning and quality of life (QoL) in patients with drug-resistant focal epilepsy. Fifty-six adult patients treated with PER in addition to antiepileptic drugs (AEDs) were recruited in 2 Italian Epilepsy Centers. Irritability in Adult Patients with Epilepsy (I-EPI), Quality of Life in Epilepsy (QOLIE-31), Beck Depression Inventory II (BDI-II), and State–Trait Anxiety Inventory Y-1 and Y-2 (STAI) questionnaires were administered at baseline and 3 and 6 months after the treatment onset. Adverse events (AEs) were collected during the observational 6 months period. Retention rate of treatment with PER was 82.1% at 3 months and 64.3% at 6 months. Thirteen patients reported a significant seizure frequency reduction, and one seizure freedom case was observed after 4 months of PER treatment. Perampanel was stopped because of inefficacy or paradoxical effects in 28.6% of cases and because of AEs in 7.1%. The peak dose was not associated with discontinuation probability. Irritability, QoL, depression, trait, and state anxiety did not change significantly during the PER therapy. A tendency of association between higher level of irritability at baseline and PER discontinuation was found. The results of this observational study have shown that the addition of PER to AEDs may improve seizure control, does not increase levels of irritability, depression, and anxiety, and does not reduce patients' QoL. This study also confirms the importance of a comprehensive clinical assessment, including psychiatric symptoms evaluation before offering a new treatment, to improve therapy compliance.

1. Introduction

Among the most recently marketed drugs, perampanel (PER) is the first-in-class, highly selective, noncompetitive, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type glutamate receptor antagonist [1]. Perampanel is approved in Italy as adjunctive therapy for the treatment of focal-onset seizures and of generalized tonic–clonic seizures in patients with epilepsy aged ≥12 years [2].

The efficacy of PER on focal-onset seizures and generalized tonic–clonic seizures has been demonstrated in a phase III clinical program that included 4 randomized, double-blind, placebo-controlled trials [3–6]. In these trials, as well as in their extension studies [7], treatment with PER was well-tolerated and efficacy was maintained in the long-term period. When evaluated in a real-world setting in a refractory cohort, PER given for one year in patients with focal epilepsy and in patients with idiopathic generalized epilepsy demonstrated a similar efficacy and safety profile to that observed in clinical trials conducted in selected populations [8,9].

Recent studies have described the profile of treatment-emergent adverse effects with PER [10,11]. Dizziness, somnolence, fatigue, and irritability were the most frequently reported adverse effects in phase III studies [10]. In randomized, placebo-controlled clinical trials, the incidence rates for anxiety, aggression, and anger were higher in the 8 and 12 mg PER groups than in the placebo group, whereas the incidence of all other psychiatric disorders, including suicidal ideation, was similar in the PER- and placebo-treated patients [11]. However, clinical trials do not always state how psychiatric adverse events (AEs) were assessed, and whether a context of previous psychiatric disturbances may contribute to the occurrence of these symptoms and their changes over time.

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Furthermore, there are scarce data on the effects of PER on behavior and quality of life (QoL) when used in common clinical practice. A recently published retrospective study [12] has shown that long-term adjunctive treatment with PER was associated with improvements in cognitive performances and did not increase irritability or aggression.

Based on this background, we prospectively utilize validated questionnaires to assess the effects of PER on psychological functioning and QoL in patients with drug-resistant focal epilepsy before and during the adjunctive treatment with PER.

2. Patients and methods

The study population included patients aged ≥16 years with drug-resistant focal epilepsy, who were consecutively recruited and followed in our Division (Epileptology Unit of the Neurological Institute Carlo Besta, IRCCS Foundation, Milan, Italy), in collaboration with the Regional Centre for Epilepsy of the San Paolo Hospital of Milan, Italy. The presence of clear cognitive deficits that would not allow a patient to respond to the questionnaires and to give an informed consent was excluded from the study.

All patients had already been treated with one or more antiepileptic drugs (AEDs) and showed an inadequate seizure control, as documented by the occurrence of at least one seizure in the month preceding recruitment. Perampanel was administered at a starting dose of 2 mg/day, increased by 2 mg/day weekly or every two weeks, up to maximum dose of 12 mg/day. The target dose was addressed according to clinical response and tolerability.

Patients were evaluated at the start of treatment with PER (t0) and after 3 and 6 months of therapy (t1 and t2, respectively). The study protocol included the collection of baseline sociodemographic and clinical data, and the administration of the following questionnaires: Irritability in Adult Patients with Epilepsy (I-EPI), Quality of Life in Epilepsy (QOLIE-31), Beck Depression Inventory II (BDI-II), and State–Trait Anxiety Inventory Y-1 and Y-2 (STAI).

The I-EPI [13] is an inventory to evaluate irritability in patients with epilepsy, which comprises 4 domains associated with irritability (physical, verbal, epilepsy, and temperamental functioning, each with 3, 5, 5, and 5 items, respectively, made of a 6-point Likert scale). The overall I-EPI score range is 18–108, with higher scores indicating a more intense level of irritability. An overall I-EPI score <41, 41–64, 65–89, and >89 indicates a low, moderate, high, and pathological level of irritability, respectively.

The QOLIE-31 [14] is an epilepsy-specific, 31-item inventory developed to assess 7 domains: overall QoL, seizure worry, emotional well-being, energy/fatigue, cognitive functioning, medication effects, and social functioning. Overall health is reported in an additional question. The scoring procedure converts raw numeric values of items to scores of 0–100, where higher scores reflect a better QoL.

The 21 items of the BDI include alternative statements ranging in order of severity from 0 to 3. The BDI-II [15] includes somatic–affective (items 1–13) and the cognitive (items 14–21) subscales.

The STAI is a commonly used measure of trait and state anxiety [16]. It includes 20 items for assessing trait anxiety and 20 for state anxiety. All items are rated on a 4-point scale, with higher scores indicating greater anxiety.

The occurrence of AEs was collected during the entire 6-month observational period.

The study protocol was approved by the reference Ethic Committee of the two institutions, and participant patients gave their informed consent prior to the start of any study-related procedure.

Continuous variables were reported as means, standard deviation (SD), median, and range; categorical variables were reported as count and percentage. An analysis of variance for repeated measures (ANOVA) was used to test changes from baseline. A further analysis was performed adding as covariates etiology (cryptogenic and idiopathic vs symptomatic and other causes), number of concomitant drugs (two vs three and four AEDs), and seizure outcome (no change vs more than 50% seizure reduction) in the same model. The retention rate of PER after 6-month period was computed using a Kaplan-Meier survival curve. The impact of other factors was evaluated using Cox Proportional Hazard analysis. All statistical analyses were carried out with IBM SPSS Statistics for Macintosh Version 25.0 (Armonk, NY: IBM Corp.).

3. Results

The study population included 56 patients (mean age: 41 years; 51.8% of males) who started treatment with PER between June 2015 and February 2018. Table 1 shows the demographic and other characteristics at baseline. Epilepsy was focal and symptomatic in most of the patients (Table 1).

All patients were treated with two or more AEDs at baseline: 25 patients (44,6%) with two AEDs, 28 (50%) with 3, and the remaining 3 (5.4%) were taking four AEDs.

The retention rate of PER was 82.1% and 64.3% at t1 (3 months) and t2 (6 months), respectively, with a mean dose of 7.8 ± 2.7 mg at terminal follow-up. Discontinuations at t1 were due to inefficacy or paradoxical effect in 9 patients and AEs in 1; discontinuations between t1 and t2 were due to inefficacy or paradoxical effect in 7 patients and AEs in 3. Three patients that completed the entire 6-month observational period did not fill-in the questionnaires and, therefore, were not analyzed with this respect.

Thirteen patients (24.1%) reported a significant reduction of seizure frequency (more than 50% seizure reduction), and one became seizure-free after four months of treatment.

The following AEs were reported during the 6-month observational period: dizziness (7 patients, 12.5%), cognitive impairment (5 patients, 8.9%), irritability (4 patients, 7.1%), and mood disturbances (2 patients, 3.6%; one reported depression, the other hypomania). One patient

Table 1
Demographic and epilepsy characteristics of recruited patients at baseline.

	N = 56
Age, years (mean ± SD)	41 ± 13
Sex, N (%)	
Males	29 (51.8%)
Females	27 (48.2%)
Profession	
Employed	30 (53.6%)
Unemployed	18 (32.1%)
Student	5 (8.9%)
Unable to work or retired	3 (5.4%)
Schooling (years)	
≤8	15 (26.8%)
<9 and ≤13	28 (50%)
>14	13 (23.2%)
Type of epilepsy, N (%)	
Focal	48 (85.7%)
Multifocal	7 (12.5%)
Generalized	1 (1.8%)
Etiology of epilepsy, N (%)	
Cryptogenic	23 (41.1%)
Symptomatic	33 (58.9%)
Age at onset of symptoms, years (mean ± SD)	14 ± 11
Duration from diagnosis, years (mean ± SD)	27 ± 14
Frequency of seizures in the last year, N (%)	
Daily	7 (12.5%)
Weekly	22 (39.3%)
Monthly	27 (48.2%)
Type of seizures in the last 3 months, N (%)	
With loss of contact	35 (62.5%)
Without loss of contact	16 (28.6%)
Convulsive	1 (1.8%)
With fall	4 (7.1%)
Number of AEDs at baseline, N (%)	
Two	25 (44.6%)
Three	28 (50.0%)
Four	3 (5.4%)

developed pancreatitis that resolved after PER withdrawal. Overall, 13 patients (23.2%) reported AEs, and in 4 (7.1%), AEs led to PER discontinuation.

The results of I-EPI (Fig. 1) showed no significant changes between t0 and t2 ($p = 0.16$, repeated measures ANOVA), whereas the subscale analysis shows a tendency of reduction of the "Physical functioning" (repeated measures ANOVA $p = 0.02$).

Fig. 2 shows the results of QOLIE-31. No significant changes between t0 and t2 were observed for total QoL and for each domain, except for social functioning. The mean ($\pm$SD) changes from baseline in overall QoL score were 0.14 ± 7.65 at t1 and 0.23 ± 9.82 at t2. The subscale analysis showed a significant improvement in the overall QoL, with a positive change at t2 (after 6 months) of 5.86 ± 8.69 (repeated measures ANOVA $p = 0.002$).

Treatment with PER was not associated with significant changes in depression or in somatic or cognitive subscales (Fig. 3).

There were no clinically and statistically significant changes in mean values of STAI trait anxiety and state anxiety from baseline at both t1 and t2. The mean ($\pm$SD) values at baseline were 43.18 ± 8.96 for trait anxiety and 40.68 ± 9.35 for state anxiety, and the mean ($\pm$SD) STAI score changes at t2 compared with baseline were 0.19 ± 6.86 for trait anxiety and -0.42 ± 8.49 for state anxiety.

We found no significant effect of etiology, number of concomitant drugs, and seizure outcome on changes of QoL, depression, irritability, or anxiety.

Table 2 shows the baseline characteristics of patients that discontinued PER and of those that completed the 6-month treatment period. Patients who continued treatment had a higher QoL (QOLIE-31 total score), lower irritability, and lower anxiety and depression scores, compared with those who discontinued PER during the study. Although none of these factors is significantly different between the two groups, the Cox Proportional Hazard analysis showed a tendency of patients with higher baseline irritability to discontinue PER therapy (hazard ratio: 1033, Confidence interval (C.I.) 95%: 0.99, 1.069, $p = 0.06$). The mean ($\pm$SD) highest daily dose of PER during the study was 7.4 ± 2.6 mg in patients that completed the study and 5.1 ± 1.6 mg in patients that discontinued treatment ($p = 0.002$ between subgroups). Age, disease duration, type of epilepsy and of seizures did not differ between the two groups.

4. Discussion

Our prospective observational study confirms that PER is rather well-tolerated, does not increase irritability, depression, or anxiety, and does not reduce QoL in the 6-month observational period, when these symptoms are measured using standardized scales at baseline and during treatment.

Therapy retention rate at 6 months was 64.3%. Previous observational studies have shown that retention rate for PER at 6 months ranged from 55% up to more than 80% [9,17,18]. Thus, the retention rate of this study seems to be consistent with those previously reported. Retention rate reflects the combined impact of PER effectiveness and its tolerability. It is interesting to note that most treatment discontinuations with PER were due to inefficacy or paradoxical effects and that only 4 patients discontinued PER because of AEs.

The I-EPI is an instrument developed in Italian language developed in a large cohort of more than five hundred patients with epilepsy in Italy for the assessment of irritability in adult patients with epilepsy [13]. Irritability and aggressive behavior in general are related to different AEDs, and they have been associated with topiramate, levetiracetam, and PER therapies [19]. Drug-related neurotransmission and hormonal alteration have been implicated in aggressive behaviors in patients treated with AEDs [19]. Irritability was one of the most frequent treatment-emergent AEs with the use of PER in randomized clinical trial [11] and in retrospective studies [9,20,21]. In our study, an increase of irritability was not observed. Our data confirm preliminary data obtained with a smaller number of patients [22]. In particular, patients in our cohort showed moderate level of irritability at baseline, but no changes over the follow-up period. These results did not confirm the findings of the open-label extension of phase III randomized trials [7]. However, the irritability assessment with a validated tool such as the I-EPI scale [13] allows a more objective and reliable evaluation of this symptom changes.

Our data also show a relation between baseline levels of irritability and PER retention rate. Although this relation does not reach the statistical significance ($p = 0.06$), we think that this tendency suggests the importance of baseline clinical assessment of individual patients before administering PER as adjunctive drug.

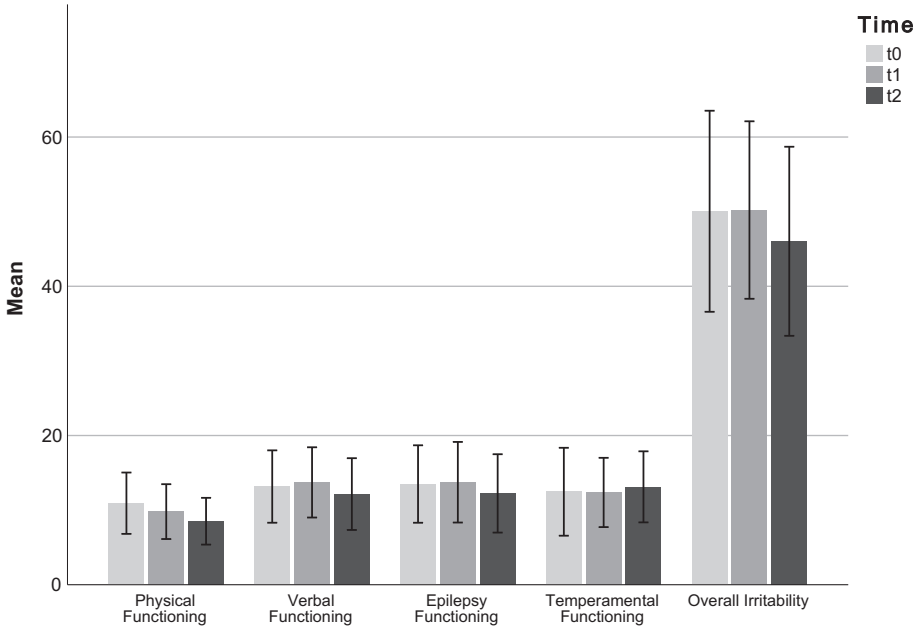

Fig. 1. Results of I-EPI at t0 (before PER treatment; light gray columns), t1 (3 months PER treatment; gray columns), and t2 (6 months PER treatment; dark gray columns). Data are means $\pm$ standard deviation in bars.

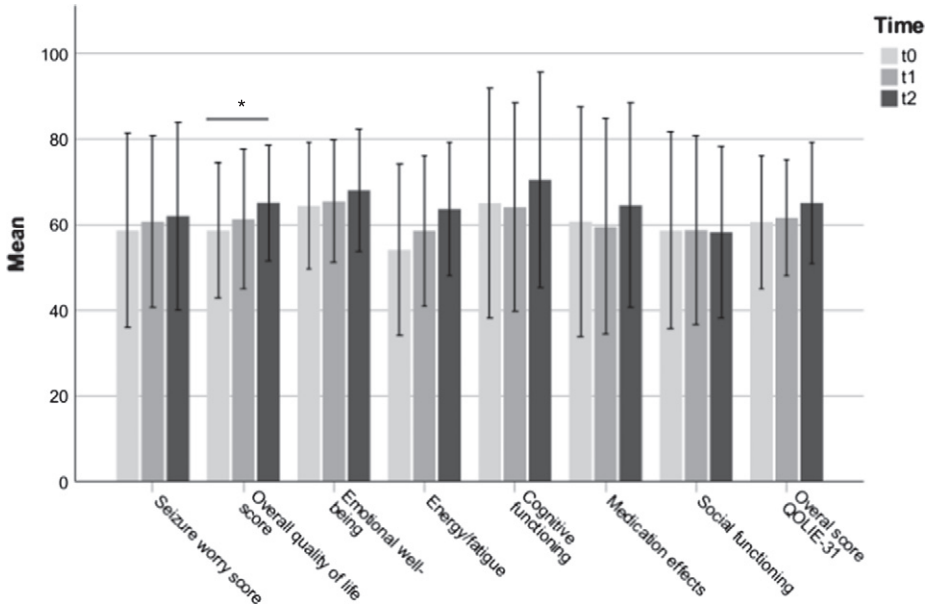

Fig. 2. Results of QOLIE-31 at t0 (light gray columns), t1 (gray columns), and t2 (dark gray columns). Data are means ± standard deviation in bars. *$p < 0.05$.

To our knowledge, this is the first study quantitatively addressing symptoms of anxiety and depression when PER is administered to patients with drug-resistant epilepsy. There were no changes from baseline in anxiety and depression symptoms reported during treatment with PER [9,23]. Baseline scores were indicative of a relatively mild intensity of anxiety, and data at 6 months showed no worsening in this symptom following treatment with PER.

Overall QOLIE-31 score at t0 was similar comparing with a normative epilepsy data collected in a sample of Italian patients with epilepsies comparable with those of this study [24]. No significant changes were found at 6 months follow-up. Quality of life in patients with epilepsy is primarily affected by psychiatric disorder and medication AEs [25]. Therefore, stability of QoL may be considered as an indirect confirmation of the overall tolerability of PER therapy.

Although data were collected in a small number of patients in the two subgroups, patients who discontinued treatment with PER had a tendency to a worse QoL and a higher level of irritability, anxiety, and depression at t0 compared with those that completed the treatment period with PER. These findings are in contrast with those reported in another observational retrospective study, in which retention of treatment with PER was similar in patients with or without psychiatric comorbidities [26]. Further research in a larger cohort would help to better understand which factors are associated with an increased risk of PER therapy discontinuation. Notably, the mean daily dose of PER was higher in patients that completed the study. This finding is probably due to the fact that discontinued patients, particularly those who interrupted treatment in the first three months, did not complete the full titration period.

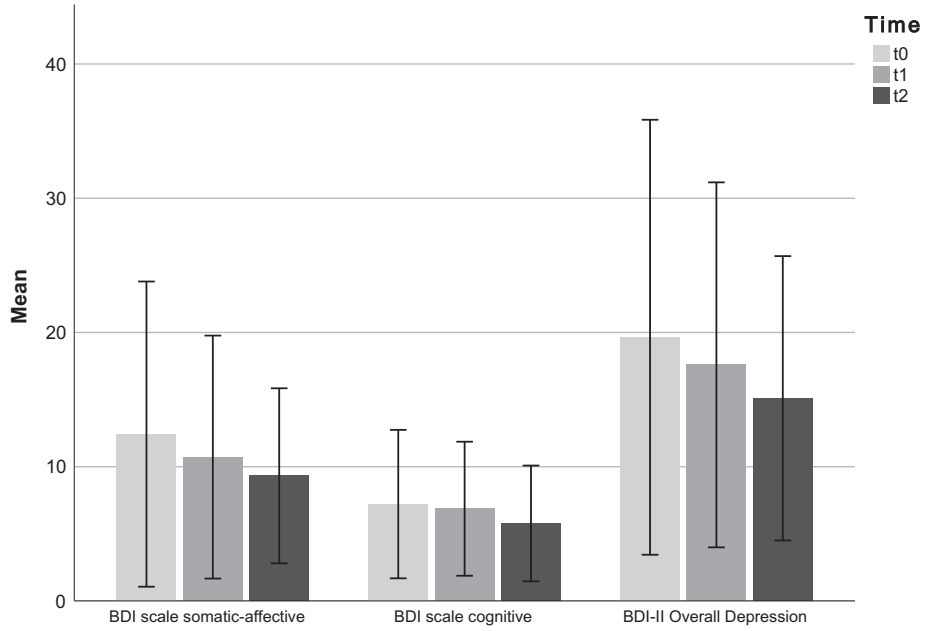

Fig. 3. Results of BDI-II at t0 (light gray columns), t1 (gray columns), and t2 (dark gray columns). Data are means ± standard deviation in bars.

Table 2
Baseline characteristics of patients that discontinued PER or those who completed the 6-month PER treatment period. These measurements were collected at t0, before administering PER.

	Discontinued PER	Completed the 6-month PER treatment period	p*
Age at onset of symptoms, years (mean ± SD)	15.45 ± 12.2	13.4 ± 10.5	0.56
Duration from diagnosis, years (mean ± SD)	27.3 ± 16.9	26.8 ± 12.9	0.91
Age, years (mean ± SD)	42.7 ± 14.1	40.4 ± 12.0	0.58
QOLIE-31, total score (mean ± SD)	55.5 ± 16.4	63.6 ± 14.3	0.97
BDI-II, total score (mean ± SD)	23.8 ± 18.9	17.3 ± 14.2	0.17
STAI trait, total score (mean ± SD)	45.4 ± 10.5	41.9 ± 7.9	0.13
STAI state, total score (mean ± SD)	42.3 ± 10.1	39.8 ± 8.9	0.26
I-EPI, total score (mean ± SD)*	54.5 ± 14.7	47.58 ± 12.24	0.06
Highest daily dose of PER (mean ± SD) [mg]°	5.1 ± 1.6	7.4 ± 2.6	0.002

None of the psychometric baseline characteristics is significantly different between patients that discontinued PER and those who completed the 6-month PER treatment period, however, there is a tendency of higher level of irritability at baseline to be associated with PER discontinuation.
* Cox Proportional Hazard analysis p.
° t-Test p.

Few patients reported AEs related to PER, which generally consisted of dizziness, cognitive, and mood disturbances. Therefore, the results of safety of PER in this study were in line with the known safety profile of the drug, as emerged from randomized clinical trials [23,27].

Our results have shown that the addition of PER to AEDs is well-tolerated considering irritability, overall QoL, and depression, with no increases in severity of anxiety, and with an acceptable safety profile. However, the study has some limitations. The lack of a control group does not allow to compare the effects of PER with a reference standard. The open-label design of the study and the evaluation of effects based on patients' self-rated questionnaires might have determined an overestimation of results. Finally, the relatively short period of observation does not allow to estimate the persistence of PER efficacy and safety over time or to assess the relationship of AEs with PER dose. Nonetheless, the data collected in this study by means of the use of reliable and validated psychometric scales may be useful as a preliminary report for future randomized, controlled, long-term studies on QoL and psychiatric symptoms in patients with epilepsy.

5. Conclusions

In our cohort of patients with drug-resistant focal epilepsy, PER was a rather well-tolerated drug that did not increase the level of irritability, depression, or anxiety. Quality of life was not worsened by the treatment in the six-month observational period. Our study also shows that baseline scale-assessed psychiatric functioning evaluation is useful to predict PER psychiatric tolerability.

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