Original article

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Comparison of the effectiveness and tolerability of perampanel and brivaracetam: a real-world, observational, retrospective study

Claudio Liguori [1], Natalia Manfredi [1], Rosaria Renna [2], Francesca Izzi [1], Mauro Pagliuca [2], Francesco Pagliuca [3], Nicola Biagio Mercuri [1,4], Placidi Fabio [1]

[1] Epilepsy Centre, Department of Systems Medicine, University of Rome "Tor Vergata", Rome,
[2] UOC Neurologia, A.O.R.N. "A. Cardarelli", Naples,
[3] Clinica Neurologica, Università "L. Vanvitelli", Naples,
[4] IRCCS Fondazione Santa Lucia, Rome, Italy

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ABSTRACT – *Aim*. Perampanel (PER) and brivaracetam (BRV) are third-generation antiseizure medications. The aim of the present retrospective, double-centre study was to compare the effectiveness and tolerability between PER and BRV in adult patients with epilepsy.
Methods. We reviewed the clinical charts of patients affected by epilepsy, admitted to the Epilepsy Centre at the University Hospital of Rome "Tor Vergata" and the Cardarelli Hospital in Naples, who started BRV or PER as add-on treatment for controlling seizures with a follow-up of 12 months. Seizure freedom, >50% seizure reduction, retention rate, and adverse events reported during follow-up were compared between the two drugs. Moreover, we considered the effects of both drugs in specific subsets of patients: age ≥60 years, male or female, in patients with genetic generalized epilepsy, and considering previous treatment with levetiracetam (LEV).
Results. Forty-three patients treated with BRV and 64 patients treated with PER were included in this study and followed at both sites for 12 months. Similar effectiveness was observed between BRV and PER, with similar rates of seizure freedom (30% vs 31%) and >50% seizure reduction (32% vs 34%) during follow-up. Moreover, PER and BRV discontinuation rates, due to ineffectiveness or adverse events, were similar. Groups of patients who started BRV or PER as first add-on treatments were also compared but no differences in effectiveness or tolerability were identified. Lastly, BRV was shown to be more effective in patients who were not previously treated with LEV.
Conclusions. This retrospective study reveals comparable effectiveness and tolerability between PER and BRV also when used as first add-on treatments, in patients with epilepsy.

Key words: perampanel, brivaracetam, effectiveness, tolerability, first add-on

Correspondence:
Claudio Liguori
Epilepsy Centre, Neurology Unit,
Department of Systems Medicine,
University of Rome "Tor Vergata",
Viale Oxford 81 - 00133 Rome, Italy
<dott.claudioliguori@yahoo.it>

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Anti-seizure medications (ASMs) are the most effective treatment for controlling seizures and improving quality of life in people with epilepsy (PWE). However, prescription of a single ASM cannot control epileptic seizures in one third of PWE, and adjunctive ASMs may be required to achieve seizure freedom (Grant and Shorvon, 2000). A better understanding of different mechanisms of actions (MOAs) is required for clinicians to provide better treatment strategies for epilepsy. Third-generation ASMs are the most recent drugs licensed for the treatment of epilepsy, and are characterized by their MOAs against different targets. Perampanel (PER) is a third-generation ASM, licensed for the treatment of focal and generalized epilepsies (Strzelczyk *et al*., 2015; Brodie and Stephen, 2016). It is a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA) receptor antagonist that has been demonstrated to be efficacious against focal and generalized seizures in randomized controlled trials (RCTs) and real-life clinical studies (Kwan *et al*., 2015; Trinka *et al*., 2016; Liguori *et al*., 2018). Brivaracetam (BRV) is one of the latest ASM approved for treating epilepsy (Klein *et al*., 2015; Villanueva *et al*., 2019). Like levetiracetam (LEV), BRV acts as a synaptic vesicle protein 2A ligand with a 15 to 30-fold higher binding potential than that of LEV (Ben-Menachem *et al*., 2016). No studies have directly compared third-generation ASMs, and comparison based on the literature between these drugs is exclusively indirect. Moreover, recent advances in understanding the pharmacotherapy of epilepsy suggest a potential preference for newer ASMs since these may offer better tolerability, milder adverse events (AEs), fewer drug interactions, and improved pharmacokinetic characteristics compared to conventional ASMs (De Biase *et al*., 2019). The need to better understand the effectiveness of these ASMs in PWE has therefore prompted us to conduct this retrospective, double-centre study, with the aim of comparing the effectiveness and tolerability between PER and BRV in real-life conditions.

Methods

The present report is a retrospective, observational, double-centre study. We reviewed data collected from individual charts of patients affected by epilepsy who were prescribed with an add-on ASM (PER or BRV) to control their seizures, based on clinical indication, between June 2018 and November 2018. There were no particular concerns in individual cases regarding the use of BRV or PER to control seizures. For this analysis, we exclusively considered patients who were started on PER or BRV to control their seizures and followed for 12 months. Patients were classified according to the recently proposed classification of seizures by the International League Against Epilepsy (ILAE) (Scheffer *et al*., 2017). In order to increase the significance and homogeneity of our results, and considering the retrospective nature of this study, we chose to collect and analyse data of patients who exclusively completed a follow-up period of 12 months. Moreover, we excluded patients who: had a history of paroxysmal non-epileptic seizures, had a history of status epilepticus, and did not provide all the necessary information during follow-up. The following data were analysed: age, gender, epilepsy type, disease duration, baseline seizure frequency, mean dose of the drug (PER or BRV), failed ASMs, and concomitant ASMs. A titration was performed according to good clinical practice for the administration of PER and BRV. For the statistical analysis, we considered:

– 50% responder rate, defined as the percentage of patients achieving a minimum of ≥50% reduction in seizure frequency compared to baseline;
– seizure freedom (considered as an absence of seizures at the follow-up visit);
– drug retention rate;
– maintenance dose of BRV and PER at 12 months;
– and the occurrence of AEs related to BRV or PER treatment leading to the discontinuation of treatment.

For the analysis of monthly seizure frequency, diaries were considered and rate was based on the last visit. At both centres, patients with epilepsy, after starting PER or BRV as add-on ASM (V0), were visited at three (V1), six (V2), and 12 (V3) months; seizure frequency at the 12-month follow-up visit (V3) was based on the number of seizures experienced during the previous six months (between V2 and V3). Response was defined as reduction of ≥50% in seizure frequency during the period between V2 and V3. Moreover, we performed a secondary analysis in:

– patients who started BRV or PER as first add-on treatment;
– patients aged ≥60 years;
– male and female patients;
– patients who started BRV with or without previous treatment with LEV;
– and in the subgroup of patients affected by genetic generalized epilepsy (GGE).

The Ethical Committee of the University Hospital of Rome "Tor Vergata" approved this observational retrospective study. The statistical analysis was performed using commercial software, Statistica 10.0 program, Statsoft Inc, Tulsa, OK, USA (Liguori *et al*., 2017). Descriptive data were expressed as mean and standard deviation for quantitative analyses. For between-group comparisons of dichotomous variables, the Odds Ratio was calculated, and p value was set at $p<0.05$ for statistical significance. The Student's t-test was used to compare descriptive data.

Table 1. Demographic and clinical data of patients with epilepsy.

		BRV (*n*=43)	PER (*n*=64)
Age (years) (mean ± SD; range)		42.32 ±15.78; 15-73	43 ±17.44; 20-80
Sex		21M / 22F	37M / 27F
Epilepsy type		Focal genetic: 5/43 Focal structural: 18/43 Focal unknown: 2/43 Generalized genetic: 9/43 Combined generalized and focal: 9/43	Focal genetic: 3/64 Focal structural: 25/64 Focal unknown: 17/64 Generalized genetic: 12/64 Combined generalized and focal: 7/64
Disease Duration (years) (mean ± SD)		18.12 ± 14.86	18.78 ± 14.05
Seizures at baseline (mean ± SD)		11.99 ± 14.69	12.04 ± 16.23
Mean dose (mg) (mean ± SD)		116.5 ± 38.23	4.8 ± 1.79
Concomitant ASMs	One add-on ASM	22/43 (9 VPA, 3 PB, 3 OXC, 3 LTG, 2 TPM, 1 CBZ, 1 LCM)	28/64 (12 VPA, 9 LEV, 3 CBZ, 2 LCM, 1 TPM, 1 OXC)
	Two add-on ASMs	11/43 (7 VPA, 4 LCM, 3 CBZ, 2 TPM, 2 CLZ, 1 PB, 1 ESL, 1 LTG, 1 PER)	16/64 (10 VPA, 4 LEV, 4 CBZ, 4 LCM, 3 ZNS, 2 PB, 2 TPM, 1 LTG, 1 CLB, 1 OXC)
	≥Three add-on ASMs	10/43 (5 VPA, 4 LCM, 4 TPM, 3 CBZ, 3 OXC, 2 PB, 2 RUF, 2 PER, 2 ZNS, 1 PRI, 1 CLB, 1 CLZ)	20/64 (10 VPA, 10 PB, 9 LCM, 7 ZNS , 4 LEV, 4 CBZ, 4 CLB, 4 CLZ, 2 TPM, 3 RUF, 1 LTG, 4 OXA, 1 PTH, 1 BRV, 1 PHT, 1 ACZ)
Failed ASMs (*n*) (mean ± SD)		2.56 ± 1.51	2.27 ± 1.42

SD: standard deviation; M: male; F: female; ASM: antiseizure medication; VPA: valproate; PB: phenobarbital; CBZ: carbamazepine; LEV: levetiracetam; LCM: lacosamide; CLZ: clonazepam, ESL: eslicarbazepine; PER: perampanel; BRV: brivaracetam; PRI: primidone; RUF: rufinamide; OXC: oxcarbazepine; LTG: lamotrigine; TPM: topiramate; CLZ: clonazepam; CLB: clobazam; ZNS: zonisamide; PTH: phenytoin, ACZ: acetazolamide.

Results

One hundred and seven patients affected by uncontrolled seizures were included in this retrospective analysis; 17 patients were not included since they did not complete the 12-month follow-up, and were considered lost to follow-up. Of these, 14 patients were not present at the follow-up visit at 12 months (eight with PER and six with BRV) and three patients discontinued the drug before the end of the 12-month follow-up for personal reasons (two with PER and one with BRV). Thirty-three patients were recruited in Naples and 74 patients were recruited in Rome. Overall, 43 patients affected by epilepsy were treated with BRV (19 in Naples and 24 in Rome) and 64 patients were treated with PER (17 in Naples and 47 in Rome). The two groups did not significantly differ in terms of demographic or clinical data (*table 1*). In particular, disease duration, seizure frequency at baseline, and number of previous failed ASMs did not differ between the two groups (*table 1*).

Effectiveness

Considering both groups of patients, no differences were observed between the PER and BRV groups in terms of effectiveness after 12 months of follow-up (*table 2*). In brief, seizure freedom was achieved in 30.3% (13/43) of BRV and 31.3% (20/64) of PER patients after 12 months of follow-up, and 32.5% (14/43) of BRV patients and 34.4% (22/64) of PER patients achieved ≥50% seizure reduction (*table 2*).

Moreover, based on the subgroup analysis, no significant differences were observed between the groups of patients starting PER (*n*=28) and BRV (*n*=22) as first add-on treatment (*table 3*). The same result was observed based on comparison of patients aged >60 years (*table 4*).

Table 2. Overall effectiveness of BRV and PER after 12 months of follow-up.

	BRV	PER
Seizure-free	13/43 (30.3%)	20/64 (31.3%)
Responders (>50%)	14/43 (32.5%)	22/64 (34.4%)
Seizures unchanged	11/43 (25.6%)	12/64 (18.8%)
Discontinuation due to ineffectiveness	3/43 (7%)	6/64 (9.3%)
Discontinuation due to AEs	2/43 (4.6%) Ataxia: 1 (*Rome*) Negative mood: 1 (*Naples*)	4/64 (6.2%) Irritability: 4 (*2 Rome and 2 Naples*)

BRV: brivaracetam; PER: perampanel; AE: adverse event.

Regarding gender, no significant differences were observed in terms of effectiveness for either drug between men and women. Seizure freedom, as well as responder rate and discontinuation due to ineffectiveness or AEs, were similar between males and females in both the PER and BRV groups. In female patients, seizure freedom and ≥50% response were observed in 6/22 (27%) and 7/22 (32%) in the BRV group, and 9/27 (33.5%) and 9/27 (33.5%) in the PER group, respectively (*table 5*).

Considering the subgroup of PWE starting BRV, with or without previous LEV treatment, BRV was shown to be more effective in patients not previously treated with LEV compared to those previously treated with LEV.

In this retrospective observational analysis, patients affected by GGE were also included (*n*=21). Twelve patients were followed in Naples (six with PER and six with BRV), and nine patients were followed in Rome (six with PER and three with BRV). Based on comparison of these two small subgroups, no significant differences were observed, however, 2/9 (22.2%) patients treated with BRV were seizure-free after 12 months of follow-up compared to 5/12 (41.7%) treated with PER. Seizure reduction of ≥50% was observed in 3/9 (33.3%) patients with BRV and 4/12 (33.3%) with PER at the 12-month follow-up visit. Finally, no change in seizure frequency was observed for 3/9 (33.3%) patients with BRV and 3/12 (25%) with PER after 12 months of follow-up.

Tolerability

Based on the analysis of data obtained at 12 months, the rate of retention and discontinuation of treatment due to AEs or ineffectiveness was compared between patients with PER and BRV. Notably, at the 12-month follow-up visit, AEs leading to discontinuation of treatment were reported in two BRV patients and four PER patients. Moreover, three BRV patients and six PER patients discontinued the treatment due to ineffectiveness at the 12-month follow-up visit. Similar results were observed in the subgroups of patients aged ≥60 years and distributed for gender. No significant differences were observed in terms of tolerability between the subgroups of patients treated with BRV with or without previous LEV Finally, two patients affected by GGE discontinued ASMs (one with BRV and one with PER) at the 12-month follow-up visit.

Table 3. Effectiveness of BRV and PER when used as first or >second add-on treatment after 12 months of follow-up.

BRV add-on treatment	
First add-on (22)	Seizure-free: 9/22 (41%) Responders (≥ 50%): 8/22 (36%) Unchanged: 4/28 (18%) Discontinuation due to ineffectiveness: 0/22 Discontinuation due to AEs: 1/22 (5%)
≥ Second add-on (21)	Seizure-free: 4/21 (19%) Responders (≥ 50%): 6/21 (29%) Unchanged: 7/21 (33%) Discontinuation due to ineffectiveness: 3/21 (14%) Discontinuation due to AEs: 1/21 (5%)
PER add-on treatment	
First add-on (28)	Seizure-free: 14/28 (50%) Responders (≥ 50%): 7/28 (25%) Unchanged: 4/28 (14.5%) Discontinuation due to ineffectiveness: 2/28 (7%) Discontinuation due to AEs: 1/28 (3.5%)
≥ Second add-on (36)	Seizure-free: 6/36 (17.5%) Responders (≥ 50%): 15/36 (41.5%) Unchanged: 8/36 (22%) Discontinuation due to ineffectiveness: 3/36 (8%) Discontinuation due to AEs: 4/36 (11%)

BRV: brivaracetam; PER: perampanel; AE: adverse event.

Table 4. Effectiveness of BRV and PER in the subgroup of patients aged ≥60 years after 12 months of follow-up.

	BRV	PER
First add-on	*n*=6 Seizure-free: 4/6 (66.7%) Responders (≥ 50%): 2/6 (33.3%) Unchanged: 0/6 Discontinuation due to ineffectiveness: 0/6 Discontinuation due to AEs: 0/6	*n*=7 Seizure-free: 4/7 (57.1%) Responders (≥ 50%): 0/7 Unchanged: 1/7 (14.3%) Discontinuation due to ineffectiveness: 1/7 (14.3%) Discontinuation due to AEs: 1/7 (14.3%)
≥Second add-on	*n=2* Seizure-free: 1/2 (50%) Responders (≥ 50%): 0/2 Unchanged: 0/2 Discontinuation due to ineffectiveness: 0/2 Discontinuation due to AEs: 1/2 (50%)	*n=3* Seizure-free: 0/3 Responders (≥ 50%): 2/3 (66.7%) Unchanged: 0/3 Discontinuation due to ineffectiveness: 0/3 Discontinuation due to AEs: 1/3 (33.3%)

BRV: brivaracetam; PER: perampanel; AE: adverse event.

Table 5. Effectiveness of BRV and PER relative to gender after 12 months of follow-up.

		Male	Female
BRV		***n*=21**	***n*=22**
	Seizure-free	7/21 (33.5%)	6/22 (27.25%)
	Responders (>50%)	7/21 (33.5%)	7/22 (32%)
	Unchanged	5/21 (23%)	6/22 (27.25%)
	Discontinuation due to ineffectiveness	1/21 (5%)	2/22 (9%)
	Discontinuation due to AEs	1/21 (5%) (ataxia)	1/22 (4.5%) (negative mood)
PER		***n*=37**	***n*=27**
	Seizure-free	11/37 (30%)	9/27 (33.5%)
	Responders (>50%)	13/37 (35%)	9/27 (33.5%)
	Unchanged	9/37 (25%)	3/27 (11%)
	Discontinuation due to ineffectiveness	2/37 (5%)	3/27 (11%)
	Discontinuation due to AEs	2/37 (5%) (ataxia)	3/27 irritability (11%)

BRV: brivaracetam; PER: perampanel; AE: adverse event.

Discussion

In several reports in the literature, the use of first- and second-generation ASMs is discussed, and recently more studies have been conducted on the effectiveness and tolerability of third-generation ASMs. However, there are currently no studies in the literature comparing third-generation ASMs, and their effectiveness, differences in MOA, administration, and tolerability have not been fully described. There has only been one meta-analysis study which indirectly compared third-generation ASMs, administered as an adjunctive treatment for epilepsy, which found no significant difference between lacosamide, eslicarbazepine, PER, and BRV for uncontrolled focal epilepsy. Nevertheless, BRV seemed to show better tolerability (Li-Na *et al*., 2018). Hence, based on the present retrospective double-centre study, we aimed to directly investigate and compare the effectiveness and tolerability between PER and BRV in PWE. We reviewed the clinical charts of PWE who were treated with PER or BRV and completed a follow-up of 12 months, in

order to compare the effectiveness and tolerability of these two drugs. Moreover, we distributed the sample considering:

– patients who started PER or BRV as first add-on treatment;
– patients over 60 years;
– patients' gender;
– patients taking BRV with or without previous treatment with LEV;
– and patients affected by GGE.

Overall, we found that the effectiveness of PER and BRV was similar in reducing the frequency of seizures after 12 months of follow-up, in terms of seizure freedom and >50% seizure reduction. Our data on effectiveness are in line with previous larger studies in the scientific literature documenting the beneficial effects of BRV or PER in PWE (Rohracher *et al*., 2018; Steinig *et al*., 2017). These results confirm a previous study in which a similar efficacy was found between these drugs when indirectly compared exclusively using RCTs (Li-Na *et al*., 2018). Regarding the gender analysis, we did not observe differences between men and women in either the BRV or PER group. This is consistent with the use of third-generation ASMs in women who require other therapeutic strategies for treating epilepsy, since valproic acid (VPA) is not recommended in women of childbearing potential (Tomson *et al*., 2015).

This observational study is novel in that we compared PWE who started both drugs as first adjunctive treatment. This novel aspect merits further attention since the use of the newer ASMs in less challenging conditions (*e.g*. as first adjunctive treatment) clashes with cost, and there are difficulties in prescribing third-generation ASMs with respect to older ASMs. However, the short- and long-term AEs associated with first- and second-generation ASMs should encourage the use of better tolerated ASMs, such as third-generation ASMs. We did not find differences in the effectiveness or tolerability between PER and BRV when used as first add-on treatment, and both drugs showed compelling evidence in terms of effectiveness in reducing seizures and achieving seizure freedom at 12 months. Additionally, the tolerability of these drugs may be further improved as the dose necessary to achieve seizure control when administered as first add-on treatment can be lower than that reached in more refractory PWE who have already been treated with concomitant multiple ASMs for very drug-resistant epilepsy (Coyle *et al*., 2014; Margiolis *et al*., 2014; Brodie and Stephen, 2016; Shah *et al*., 2016; Liguori *et al*., 2018; Li-Na *et al*., 2018, Feyissa, 2019; Villanueva *et al*., 2019). The retention rate of the two drugs was also similar in the population of PWE analysed, with only a few patients discontinuing treatment due to AEs. This result is concordant with previous studies, considering that the dose administered was lower than that in the RCTs for both drugs (Margiolis *et al*., 2014). Although PER is approved for both focal and generalized seizures, BRV has received approval as an indication exclusively for focal epilepsies (Klein *et al*., 2015; Strzelczyk *et al*., 2015). Considering that BRV acts with the same mechanism of action as that of LEV, but with a higher affinity for synaptic vesicle glycoprotein 2A (Wood and Gillard, 2017), interest towards its use for genetic generalized epilepsy (GGE) has recently increased (Strzelczyk *et al*., 2018; Fonseca *et al*., 2020). Accordingly, the clinical potential of BRV for GGE has been proven in preclinical studies and thereafter confirmed in clinical trials and real-world studies (Strzelczyk *et al*., 2018; Fonseca *et al*., 2020). Considering the limited number of ASMs approved for treating GGE and the recent concerns about the use of VPA in women of childbearing potential, the lack of alternatives in cases of refractory GGE has driven clinicians to use BRV, as in this retrospective observational study. In this report, we also compared patients affected by GGE, treated with PER or BRV. However, considering the small subgroups of patients analysed, we did not find significant results and therefore invite further analysis considering more subjects in the future.

Finally, we also analysed the effectiveness of BRV in patients with or without previous treatment with LEV. BRV shares a similar MOA with LEV, but has been documented to have a safer profile in terms of AEs (Steinhoff and Staack, 2019). We found significant differences in effectiveness, but not tolerability, between the two groups (with or without previous LEV); better seizure control was reported in patients who were not previously treated with LEV. This finding confirms the previous evidence documenting that BRV is more effective in patients not previously treated with LEV (Steinig *et al*., 2017; Villanueva *et al*., 2019).

We are aware that this study has several limitations:

– PER and BRV effectiveness and tolerability were not prospectively assessed, but retrospectively analysed;
– the number of patients in the BRV group was lower than that in the PER group (PER was licensed for epilepsy before BRV);
– and data were not systematically collected, but based on routine clinical records.

However, this study also has some strengths:

– the follow-up of 12 months may provide more information on the clinical potential of both drugs;
– the study provides an analysis of patients who started PER or BRV as first add-on treatment;
– the analysis based on gender distribution provides information on possible use in women of childbearing potential regarding tolerability and reduction of risk associated with fertility, conception and pregnancy;

– the sample of patients included was relatively large and included two outpatient epilepsy centres, situated in two different cities.
Hence, this first clinical retrospective investigation to compare PER and BRV, also as first adjunctive therapy, in PWE provides a basis for future prospective studies aimed at comparing the effectiveness and tolerability profiles of BRV and PER.

Conclusion

Our study documents similar effectiveness between PER and BRV, also as first add-on treatment, in PWE in a real-life setting. Notably, early prescription of third-generation ASMs as add-on treatment may potentially become a new strategy in PWE, to increase tolerability of the drugs used, as well as effectiveness. Accordingly, we documented similar tolerability in patients starting PER or BRV in both genders. Moreover, the retention rate was higher than that in RCTs, possibly due to the fact that the dose of PER or BRV required to achieve seizure control is lower when the drug is used as first adjunctive therapy. Although the literature suggests the use of rational ASM polytherapy for achieving greater efficacy in patients with drug-resistant epilepsy (Margiolis *et al*., 2014), we suggest earlier administration of third-generation ASMs. We also recommend administration of third-generation ASMs as first add-on treatment in PWE, when monotherapy fails, considering the clinical potential of administration of PER over a single day and the improved effectiveness of BRV in patients not previously treated with LEV. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) How did brivaracetam and perampanel, both third-generation anti-seizure medications, compare in terms of effectiveness in the present study?

(2) Considering the present study, do the data suggest early use of third-generation anti-seizure medication (such as perampanel and brivaracetam) in patients with epilepsy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".