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# Effect of brivaracetam on the anger levels of epilepsy patients. A prospective open-labelled controlled study

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ABSTRACT

*Purpose:* The rate of brivaracetam-related behavioural adverse events is a current focus of discussion. This study aims to assess the effect of brivaracetam on anger levels in patients with epilepsy, adjusted by mood symptoms, history of psychiatric disorders and seizure response.

*Method:* Prospective analysis of 37 patients assessed for anger levels (STAXI-2), depression-anxiety (HADS) and quality of life (QOLIE-10) before adjunctive brivaracetam treatment and reassessed 3–6 months later. A control group following the same protocol of assessment was used for 1:1 comparison. A high percentage of mood stabilisers were included in this control group.

*Results:* Brivaracetam was indicated for patients including focal onset (79%) and generalised epilepsies (21%). Nearly 60% of responders and no psychiatric adverse events were found. This was similar to controls. The overall results revealed that brivaracetam was assoiciated with better in anger levels, mood scores and quality of life at baseline. Prior use of levetiracetam or the presence of a psychiatric background did not influence the results. However, improvements in anger levels were seen in the brivaracetam responders.

*Conclusion:* This study shows that brivaracetam is not associated with an increased level of anger in patients with either focal or generalised epilepsies in the absence of psychiatric comorbidity. However, an improvement in anger levels is possibly influenced by a good seizure response.

## 1. Introduction

Anger and irritability are features of the aggressive behaviour described to be present in up to 7% of epilepsy patients [1]. History of psychiatric conditions, uncontrolled seizures and static encephalopathies have been the risk factors most commonly associated with aggressive behaviour [1]. However, medical treatment often results in behavioural changes in patients and some antiepileptic drugs (AEDs) have demonstrated a high risk of developing psychiatric adverse events [2]. The majority of AEDs may induce at some point positive or negative psycho-cognitive effects. For instance, some of the AEDs with a mechanism of action based on the blockage of sodium channels, such as carboxamides, lamotrigine and valproate, are associated with mood stabilising properties. Benzodiazepines also have anxiolytic properties [3,4]. Conversely, other AEDs, such as levetiracetam (LEV), are associated with psychiatric adverse effects in up to 20% of patients, which include irritability, anger, agitation, aggressive behaviour and depression [5,6].

Brivaracetam (BRV) is a new AED of the racetams family, approved for the treatment of focal onset epilepsy. Preclinical data showed that BRV has a higher affinity for the SV2 A binding site than LEV, which likely explains the more potent and complete seizure suppression provided by BRV in animal models of partial and generalised epilepsy [7,8]. In addition, the selective SV2 A binding mechanism of BRV does not involve α-amino-3-OH-5-methyl-4- isoxazolepropionic acid receptor (AMPA) antagonism, a characteristic that differentiates it from LEV [19]. Furthermore, a preclinical study showed that BRV is not likely to be associated with aggressive behaviour in rodents, in contrast with those exposed to LEV [10]. In summary, the preclinical reasoning suggests that BRV treatment in epilepsy patients must be effective and is less likely to be associated with adverse behavioural changes than LEV.

However, there is no definitive data on the better tolerability of BRV compared to LEV with regard to behavioural adverse events in humans.

*Abbreviations:* AEDs, antiepileptic drugs; BRV, brivaracetam; HADS, hospital anxiety and depression scale; LEV, levetiracetam; QOLIE-10, quality of life in epilepsy inventory-10; STAXI-2, state-trait anger expression inventory-2 STAXI-2

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Phase III studies of BRV showed that the likelihood to respond to BRV was greater in patients who had discontinued LEV due to adverse events rather than due to lack of efficacy [11]. The overall rate of psychiatric adverse events with BRV reported in the randomised blinded trials and in the long-term follow-up was lower than 8% [11,12]. Publications on clinical practice have constantly showed a trend for BRV to be less likely related to behavioural adverse events than LEV [13,14]. In populations at risk of developing behavioural adverse events, such as epileptic encephalopathies, BRV proved to be better tolerated than LEV [15,16]. According to real world evidence data, up to a quarter of patients who develop LEV-related behavioural adverse events may improve when switched to BRV [13,14]. Our group reported previously in a cross-sectional study that patients treated with BRV had lower levels of anger than those treated with LEV [16]. However, most of the human experience was drawn from open-label retrospective studies with lack of control groups. Published experience on the risk of BRV-related behavioural adverse events is still insufficient and needs supportive information to determine whether the psychiatric profile of BRV differs from other AEDs. To our knowledge, there are no prospective series that assess as the primary endpoint the irritability associated with the onset of treatment with BRV using a comparative group with other AEDs.

The primary aim of this study is to assess the levels of anger in epilepsy patients treated with BRV. The secondary endpoints are to study the performance in depression, anxiety and quality of life scores in the same population sample. Finally, we seek to find changes in anger levels in patients who switched from LEV to BRV.

## 2. Material and methods

Patients were prospectively recruited from the outpatient clinic visits of the epilepsy unit of a tertiary hospital (Vall d'Hebron Hospital, Barcelona, Spain) during the study period (May 2017 to June 2018). The patients selected had a clear diagnosis of epilepsy following ILAE criteria, the number of concomitant AEDs at baseline was limited to a maximum of 2, all patients were older than 17 and able to read and respond to the questionnaires. All patients signed a written informed consent form. The protocol was approved by the local ethics committee (PR(AG)163/2017). The reason for starting BRV or any other AED was based on the medical decision of the treating neurologist. Patients with progressive causes of epilepsy, history of non-epileptic seizures, major active psychiatric comorbidities, other neurological disorders, or any other condition that could influence the results of the assessments were excluded (i.e. family problems, work-related stress). The control group was obtained from patients that met inclusion and exclusion criteria using any other AED except LEV. The number of patients recruited for the control group during the same period was 99. For comparisons, we used an age-sex matched 1:1 group of patients. All patients were assessed with the following scales during the medical visit at baseline and in the follow-up between 3 and 6 months later: State-Trait Anger Expression Inventory–2 (STAXI–2), The Hospital Anxiety and Depression Scale (HADS) and The Quality of Life in Epilepsy Inventory (QOLIE-10). The mean seizure frequency per month during the three months prior to the assessments was calculated for the whole follow-up period for each patient with a quantifiable baseline and follow-up period. Active major psychiatric disorder was one of the exclusion criteria, and the psychiatric background was defined as the presence of a psychiatric disorder according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria or treatment-related psychiatric adverse events in the past. They were recorded by an active investigation during the patients' visits or by reviewing the medical history.

STAXI-2 is a 49-item inventory that measures the severity of anger as an emotional state (State of Anger), the disposition to experience angry feelings as a personality trait (Anger trait), and the feelings or actions that a subject can perform when they get angry (Anger Expression Index). Items consist of 4-point scales that evaluate the intensity of anger at a particular time and the frequency of the anger experience, expression and control. The subscales derived from this evaluation were converted to T scores corrected for age and gender (normalised scores with a mean value of 50 and standard deviation of ± 10). Lower scores indicated poorer performance. HADS is a 14-item scale that measures the levels of anxiety and depression of the patient. Each item consists of an ordinal variable with 4 categories. Seven of the items are related to the anxiety level score and the other 7 to the depression score. The QOLIE-10 is a 10-item scale to evaluate the overall quality of life of epileptic patients. This scale was standardised to take values from 0 to 100, in a way that a higher score means a better quality of life.

Descriptive and frequency statistical analyses were obtained and comparisons were made using the software SPSS Statistics 22.0. Categorical variables were reported as frequencies (percentages) and continuous variables as mean ± SD. Quantitative variables which were not normally distributed (checked with Q-Q plots) were expressed as median (interquartile range). Statistical significance for intergroup differences was assessed by Pearson's chi-square or Fisher's exact test for categorical variables and the Student's *t*-test or Mann-Whitney U test for quantitative variables. Paired-samples t-tests were used to analyse pre-post changes in the scores of the evaluated scales. General linear models for repeated measures were performed to assess differences between BRV and the control group in the evolution of the scores. A p-value $< 0.05$ was considered statistically significant.

## 3. Results

From an initial cohort of 44 patients included in the BRV group, 37 completed the study with follow-up assessments. The reasons for dropping out from the study were loss of follow-up (n = 4) or BRV withdrawn due to somnolence (n = 2) or lack of efficacy (n = 1). BRV was started in all patients at 50 mg daily, and the dose was adapted according to medical decisions. The median maintenance dose at the final visit was 100 mg with a range from 50 to 300 mg. The 37 patients in the BRV group had mean age of 43.8 and 43.2% were women. The responder rate was 59.5% for BRV and 73% for controls (Table 1). In the group of idiopathic generalised epilepsies, all controls (3 patients with juvenile myoclonic epilepsy) and 5 out of 8 BRV patients (5 juvenile myoclonic, 2 juvenile absence and 1 generalised tonic-clonic epilepsies) responded to treatment without statistical differences (Table 1).

**Table 1**
Patients' demographic and clinical characteristics.

| | Controls (n = 37) | Brivaracetam (n = 37) | p |
|---|---|---|---|
| Age | 43.8 ± 15.6 | 42.3 ± 15.5 | 0.666 |
| Sex (female) | 16 (43.2%) | 16 (43.2%) | 1.000 |
| Time with epilepsy, years | 6.1 (3.2–20.1) | 13.2 (4.4–34.7) | 0.076 |
| Previous AEDs. Median (range) | 1 [0–3] | 2 [1–4] | 0.072 |
| Epilepsy type | 29 (78.4%) | 26 (70.3%) | 0.073 |
| *Focal* | 3 (8.1%) | 8 (21.6%) | |
| *Idiopathic Generalised* | 5 (13.5%) | 3 (8.1%) | |
| *Unknown* | | | |
| Monotherapy | 22 (61.1%) | 15 (40.5%) | 0.079 |
| Previous LEV | 18 (48.6%) | 21 (56.8%) | 0.485 |
| Reason for treatment change | 5 (13.5%) | 0 (0%) | 0.073 |
| *First line* | 16 (43.2%) | 20 (54.1%) | |
| *Lack of efficacy* | 15 (40.5%) | 17 (45.9%) 0 (0%) | |
| *Adverse events* | 1 (2.7%) | | |
| *Lack of adherence* | | | |
| Past Psychiatric disorder | 12 (33.3%) | 18 (48.6%) | 0.184 |
| Seizures/month at baseline | 1 (0–3) | 1 (0.2–3) | 0.564 |
| Seizures/month at follow-up | 0 (0–2) | 0.3 (0–1) | 0.641 |
| Treatment efficacy (Seizure reduction > 50%) | 27 (73%) | 22 (59.5%) | 0.219 |

Previous psychiatric comorbidities encompassed in all patients' disorders were restricted to mood (anxiety and depression) and behavioural disorders. The control group had similar characteristics (Table 1), and the AEDs used in the analysis were lacosamide (n = 13), eslicarbazepine acetate (n = 8), lamotrigine (n = 4), valproate (n = 3), oxcarbazepine (2), clobazam (n = 2), zonisamide (n = 2), perampanel (n = 2) and carbamazepine (n = 1).

In the majority of patients, previous history of a psychiatric disorder did not influence the improvement observed in the STAXI-2. However, it had a negative impact on the evolution of the HADS-Depression (p = 0.007) and QOLIE-10 (p = 0.017) at the final follow-up.

Patients who were responders to treatment, considered as those in whom baseline seizure frequency reduced > 50%, improved STAXI-2 global scores (p = 0.002) as compared to the non-responders. In the evolution from baseline to final visit the seizure response was positively associated with a significant improvement in STAXI-2 (p = 0.002), HADS-Depression (p = 0.004), HADS-Anxiety (0.039) and QOLIE-10 (p = 0.004) scores.

The baseline characteristics of the BRV patients compared to controls showed longer duration of epilepsy (p = 0.076) and a substantially higher number of idiopathic generalised epilepsies (p = 0.073) (Table 1). The control group was more likely to use monotherapy than BRV patients (p = 0.079), probably related to the 13.5% of first-line AEDs prescribed in the control group and the absence of first-line BRV therapies (Table 1). Overall, the efficacy and safety were probably the same for both groups (Table 1).

## 4. Anger levels, depression, anxiety and quality of life assessments

BRV patients had worse baseline performances in the 'State of anger' (p = 0.030) and 'Anger trait' (p = 0.033). In the follow-up, the 'Anger trait' showed improvements in BRV (p < 0.001) and controls (p = 0.004). The 'State of anger' was likely to improve in the BRV group (p = 0.035) (Fig. 1). Baseline anxiety (HADS-A) (p = 0.004) and quality of life (QOLIE-10) (p = 0.010) assessments showed poorer results in the BRV group. In the final follow-up, BRV improved anxiety (p = 0.010), depression (p = 0.010) and quality of life (p = 0.001), whereas in the control group a trend to improve was observed only in anxiety (p = 0.090). A better evolution in the QOLIE-10 was observed in BRV compared to controls (p = 0.015) (Fig. 2).

Within BRV patients, those who responded to treatment had significant improvement in the STAXI-2 global (p = 0.001), anger trait (p = 0.006) and QOLIE-10 (p = 0.006); as in the control group the seizure response had no influence in the STAXI-2, HADS and QOLIE-10 scores. The history of psychiatric disorders in the past did not influence the scores during the evolution for STAXI-2, HADS or QOLIE-10 both in BRV and control patients.

## 5. Subgroup analysis of patients previously taking LEV at baseline

We performed a subgroup analysis on those patients who had been treated with LEV at the baseline visit and stopped the treatment. We compared 21 BRV patients with a sex-aged matched control group of 18 patients, who were started on lacosamide (n = 10), eslicarbazepine acetate (n = 8), lamotrigine (n = 1), valproate (n = 1) and clobazam (n = 1)). Clinical characteristics were similar in both groups, except for the reason for starting BRV, which was more likely associated with the presence of baseline adverse events rather than the lack of efficacy, which was the case for the control group (p = 0.07). The LEV-related adverse events at baseline that led to drug discontinuation were mild to moderate irritability and depressive symptoms in more than 90% of the cases in both groups. In the baseline assessments, the 37 patients taking LEV had a higher score in HADS-Depression (p = 0.008) than those 34 patients taking other AEDs and no differences in STAXI-2, HADS-anxiety or quality of life. In the follow-up, both BRV and controls showed similar efficacy and safety parameters (Table 2).

In the follow-up, an improvement in Anger trait (p = 0.037) and state was observed in the BRV patients (p = 0.001). Likewise, significant improvements were seen in anxiety (p = 0.015), depression (p = 0.001) and quality of life (p = 0.004) for BRV patients, whereas only a trend to improve the depression symptoms was observed in the control group (p = 0.089 (Fig. 3). The differences observed in the evolution of the anger state were significantly higher in patients with BRV (p = 0.027).

None of the patient-related demographic or clinical variables were associated with greater irritability, with the exception of epilepsy duration and the presence of psychiatric disorders. Patients with a history of psychiatric disorders, including AED-related behavioural adverse events, showed worse baseline performances in STAXI-2 anger expression (p = 0.011), HADS (p = 0.087) and QOLIE-10 (p = 0.014) in both groups.

When comparing the evolution of STAXI-2, HADS and QOLIE-10 according to the presence of psychiatric background and seizure response, we noticed a trend of improvement in the STAXI-2 scores in those patients who responded to treatment (p = 0.099) in the overall

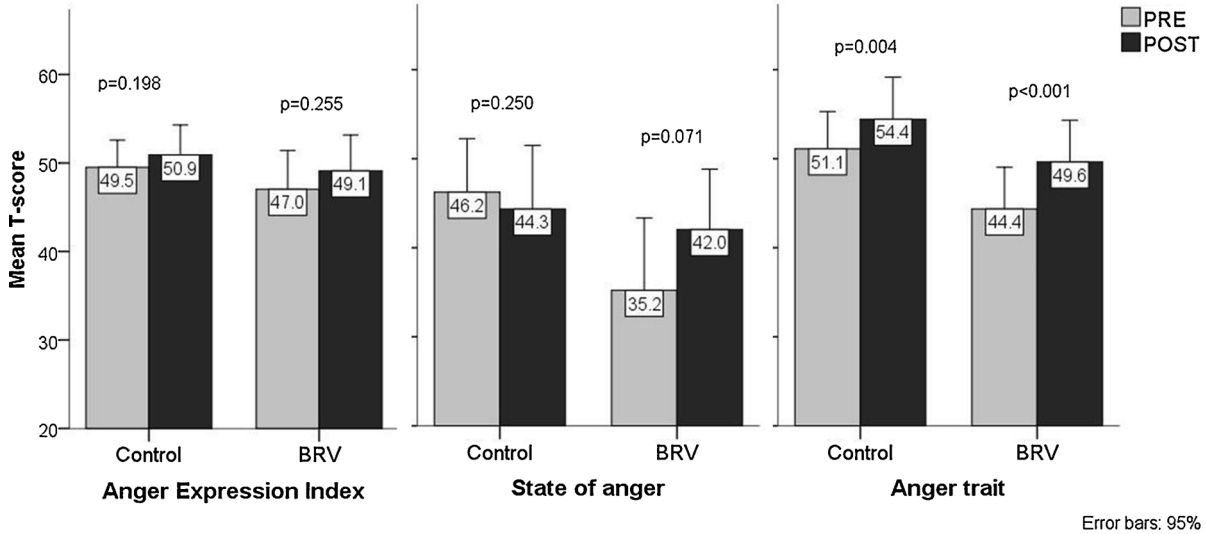


**Fig. 1.** Evolution of irritability (STAXI-2) during follow-up in BRV (n = 37) and control patients (n = 37). Both the control and BRV groups improved with regard to the anger trait. (BRV: Brivaracetam; PRE: Assessments at baseline visit, no BRV administration. POST: Assessment in the final visit with active BRV).

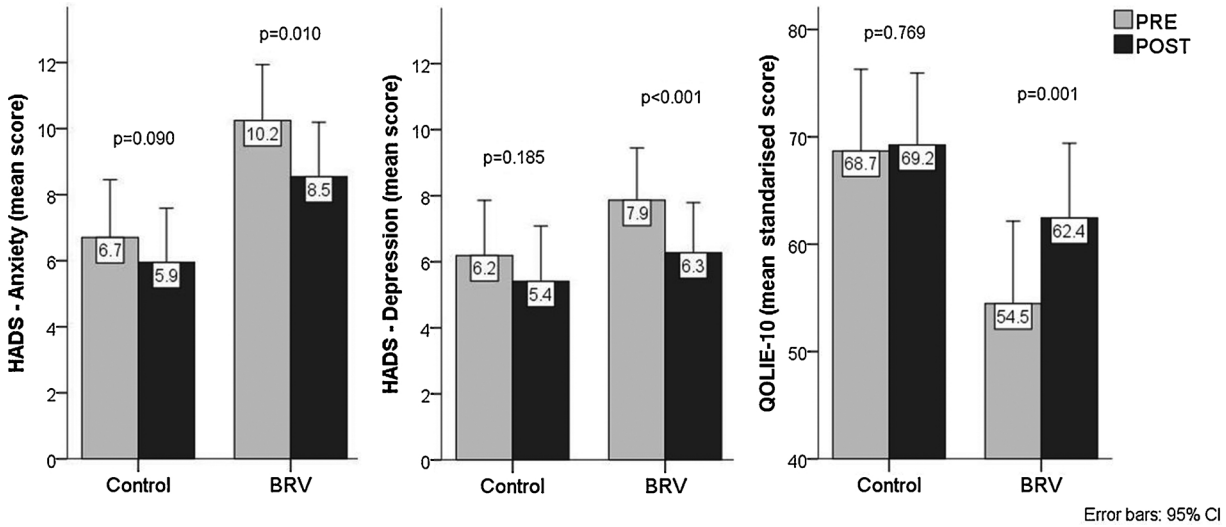


**Fig. 2.** HADS and QOLIE-10 comparing BRV (n = 37) vs control patients (n = 37). BRV patients were those who showed significant improvements in anxiety, depression and quality of life, which was not observed in the control group. (BRV: Brivaracetam; PRE: Assessments at baseline visit, no BRV administration. POST: Assessment at the final visit with active BRV).

**Table 2**
Characteristics of patients with previous use of levetiracetam.

| | Controls (n = 18) | Brivaracetam (n = 21) | p |
|---|---|---|---|
| Age | 43.6 ± 15.9 | 46.5 ± 16.9 | 0.578 |
| Sex (female) | 6 (33.3%) | 8 (38.1%) | 0.757 |
| Previous AEDs. Median (range) | 1 [0-3] | 2 [1–4] | 0.091 |
| Epilepsy type | 16 (88.9%) | 16 (76.2%) | 0.418 |
| *Focal* | 2 (11.1%) | 5 (23.8%) | |
| *Generalised (Idiopathic)* | | | |
| Aetiology | 7(38.9%) | 11 (52.4%) | 0.060 |
| *Structural* | 2(11.1%) | 5 (23.8%) | |
| *Genetic (Idiopathic)* | 9(50%) | 4 (19.1%) | |
| *Unknown* | | | |
| Monotherapy | 13 (72.2%) | 12 (57.1%) | 0.328 |
| Reason for treatment change | 3 (16.7%) | 0 (0%) | 0.070 |
| *First line* | 4 (22.2%) | 10 (47.6%) | |
| *Lack of efficacy* | 11 (61.1%) | 11 (52.4%) | |
| *Adverse events* | | | |
| Psychiatric history | 9 (52.9%) | 10 (47.6%) | 0.744 |
| Seizures/month at baseline | 1 (0–4) | 1 (0–1.7) | 0.696 |
| Seizures/month at follow-up | 0 (0–2.5) | 0 (0–1) | 0.831 |
| Treatment efficacy (Seizure reduction > 50%) | 14 (77.8%) | 14 (66.7%) | 0.442 |

group of patients who were taking LEV in the baseline visit and switched to BRV. In the same set of patients, the seizure response had a significant impact, improving the evolution of the STAXI-2 (p = 0.013) and HADS-depression (p = 0.045) for BRV, whereas it had no influence in the control group.

## 6. Discussion

This is an open-label study that assesses the level of anger in patients with epilepsy comparing BRV with other AEDs in similar clinical conditions. The prospective design and objective evaluation of the anger levels are the main differential factors of this research. In line with previous literature, the results basically show that in an overall group of patients, which includes focal onset and idiopathic generalized epilepsies, BRV can be well tolerated with regard to drug-related irritability [13,15–17]. However, seizure control in patients treated with BRV seems to be relevant to improve anger levels.

According to previous publications, BRV is a drug that can be effective and well-tolerated with regard to behavioural adverse events [14–16]. Even in the presence of a psychiatric background or history of LEV-related adverse events, BRV can be safely used and is an effective AED alternative [13,20]. In a previous publication by our group independent from this study, we observed similar anger levels in BRV patients to other AEDs, and lower than those exposed to LEV [17]. Unlike some previous studies, we did not include patients with active psychiatric comorbidities and, therefore, we could not assess the anti-aggression or mood stabiliser effects of BRV in that population setting [13]. The 87% retention rates in our patients are higher than the 60%–80% reported, probably as a consequence of the short-term evaluation and the absence of active psychiatric disorders in the selected population [20]. Overall, both BRV and the other AEDs showed better performances at the final evaluation with regard to anger levels, mood scores, and definitively in the overall quality of life, which are the expected observations in a population with a low rate of adverse events, no psychiatric comorbidities and responders to treatment [21].

One of the most striking results was the improvement both in anger levels and mood scores in the BRV patients conditioned by the response to seizure frequency. In the control group, the improvements in anger, mood and quality of life were not significant probably due to patients' profile; however, they were independent from the seizure response. Interestingly, most patients in the control group were using AEDs reported to have beneficial psychotropic effects, such as sodium channel blockers, valproate or lamotrigine [3,4]. Anti-aggression effects have been demonstrated for some of them, a fact that may explain the overall anger, mood and quality of life variations independent from seizure control in the control group. In the subgroup of patients who had used LEV in the past the results were reproducible. Limited information is available to compare regarding this finding since, to our knowledge, this is the first series which specifically assesses behaviour prospectively using a control group. Witt et al., performed a cognitive evaluation of exclusively focal epilepsies treated with BRV for the first time with a more refractory profile than our population and they observed unchanged mood and aggression scores, as there was an improvement in the executive functions [22]. Full neuropsychological assessments were not performed in our study and cognitive risk factors for anger changes could not be found [22]. In the BRV double blind randomised, controlled studies, patients who had abandoned LEV in the past due to adverse events were more likely to respond, supporting the notion that BRV can be better tolerated than LEV with regard to behavioural adverse events [11,23]. Results from real world evidence data mostly conclude that the responders to BRV are up to half of

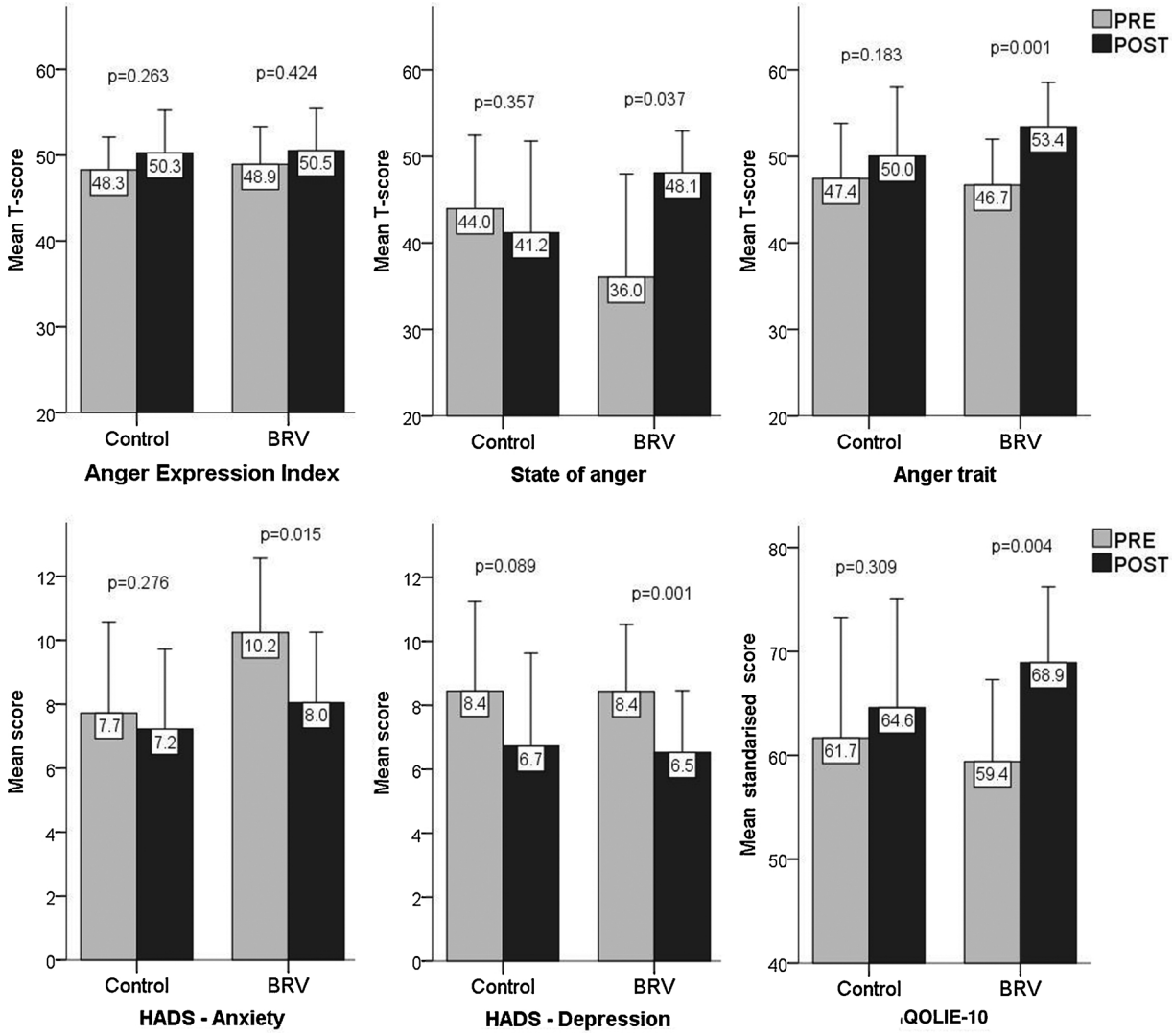


**Fig. 3.** Baseline and follow-up STAXI-2 (Anger expression index, state of anger and anger trait), HADS and QOLIE-10 scores in patients with previous use of LEV [Controls (n = 18); BRV (n = 21)]. In this subgroup analysis, significant improvements were seen only in the BRV patients for the anger trait, HADS-anxiety, HADS-depression and QOLIE-10. (BRV: Brivaracetam; PRE: Assessments at baseline visit, no BRV administration. POST: Assessment at the final visit with active BRV).

patients in the long-term follow-up and a quarter of patients with a history of LEV-related behavioural adverse events may improve when treated with BRV [13,18]. Even when the irritability scores were not specifically assessed in those publications, their results suggest that the seizure control may have influenced the behavioural improvements.

Seizure frequency at baseline in our population set was not high enough to really notice differences according to the degree of seizure control, specifically seizure-freedom or seizure-responder. Moreover, in a significant number of patients, the reason for starting the treatment was not insufficient seizure control, but side effects of the baseline treatment. Although numbers are not significantly different, the numbers of first-line treatments, monotherapies and the short duration of epilepsy were higher in the control group than in BRV patients, which are factors related to a better outcome. [1]

Finally, in our series, there is a significant frequency of patients with idiopathic generalised epilepsy within the BRV patients. Seizure response and safety parameters were similar in focal onset seizures and idiopathic generalised epilepsies which are expected results according to preclinical data and previous publications on idiopathic generalised epilepsies [19]. Herein, in the group of idiopathic generalised epilepsies, the better performance of anger levels, mood status and quality of life was conditioned by the response to seizure.

The open-label design and the exclusion of psychiatric disorders and cognitively impaired patients, which are major risk factors for developing psychiatric adverse events [1,4], are some of the major limitations of this study in drawing robust conclusions on the potential psychiatric side effects of BRV. However, the detailed clinical information obtained using objective scales to assess prospectively the psychiatric status of the patients may give reliable information, which is useful for daily clinical practice.

## 7. Conclusion

Brivaracetam does not increase levels of anger, depression or anxiety in patients with focal or idiopathic generalised epilepsies in the absence of psychiatric comorbidity. However, the improvement in the psychiatric assessments is conditioned by the seizure response.

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## Conflicts of interest

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