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BRIVA-LIFE – a multicentre retrospective study of the long-term use of brivaracetam in clinical practice

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ABSTRACT

Objectives

Evaluate long-term effectiveness and tolerability of brivaracetam in clinical practice in patients with focal epilepsy.

Materials and Methods

This was a multicentre retrospective study. Patients aged ≥16 years were started on brivaracetam from November 2016 to June 2017 and followed over 1 year. Data were obtained from medical records at 3, 6 and 12 months after treatment initiation for evaluation of safety- and seizure-related outcomes.

Results

575 patients were included in analyses; most had been treated with ≥4 lifetime antiepileptic drugs. Target dosage was achieved by 30.6% of patients on the first day. Analysis of primary variables at 12 months revealed that mean reduction in seizure frequency was 36.0%, 39.7% of patients were ≥50% responders and 17.5% were seizure-free. Seizure-freedom was achieved by 37.5% of patients aged ≥65 years. Incidence of adverse events (AEs) and psychiatric AEs (PAEs) were 39.8% and 14.3%, respectively, and discontinuation due to these were 8.9% and 3.7%, respectively. Somnolence, irritability and dizziness were the most frequently reported AEs. At baseline, 228 (39.7%) patients were being treated with levetiracetam; most switched to brivaracetam (dose ratio 1:10–15). Among those who switched because of PAEs (n=52), 9 (17%) reported PAEs on brivaracetam, and 3 (3.7%) discontinued because of PAEs. Tolerability was not highly affected among patients with learning disability or psychiatric comorbidity.

Conclusions

In a large population of patients with predominantly drug-resistant epilepsy, brivaracetam was effective and well-tolerated; no unexpected AEs occurred over 1 year and the incidence of PAEs was lower compared with levetiracetam.

INTRODUCTION

Introduction of new antiepileptic drugs (AEDs) expands the pool of available options, increasing the potential for patients with drug-resistant epilepsy (DRE) to achieve seizure control. This group carries the major burden of epilepsy, with increased rates of cognitive and behavioural problems, comorbidities, and reduced quality of life.[1]

Brivaracetam (BRV), one of the most recent AEDs to become available, is a synaptic vesicle 2A (SV2A) ligand with a 10- to 30-fold increased affinity for SV2A compared with levetiracetam (LEV), the first AED to be shown to act via this mechanism.[2] The two AEDs bind to different sites on SV2A and at therapeutically relevant concentrations, BRV has no effect on ligand-gated receptors or voltage-gated potassium and calcium channels.[3–5] This mechanistic divergence between the two may explain the differences in outcomes observed in clinical trials.

In three Phase III, randomised controlled trials (RCTs), adjunctive therapy with BRV reduced focal seizure frequency and was associated with a favourable safety profile.[6–8] Full characterisation of the clinical profile of a new drug however, necessitates analysis of data from clinical practice, beyond the confines of clinical trials that stipulate strict inclusion/exclusion criteria. Several real-life BRV studies have been reported; however, most had small sample sizes and short follow-ups.[9–14]

The main objective of the study reported here was to evaluate the effectiveness and tolerability of BRV over a 1-year period in a large population of patients with focal epilepsies. Further objectives were to compare responses in particular patient subgroups, including those previously treated with LEV.

MATERIAL AND METHODS

BRIVA-LIFE (Brivaracetam in real-life setting) was a 1-year, retrospective study conducted across 18 centres. The study was approved by the ethics committee of La Fe University Hospital, Valencia, Spain, and following protocol, patients and/or their caregivers provided written informed consent for the use of anonymised data in their medical records. The study is reported according to STROBE guidelines.[15]

Study participants

Records of patients attending participating centres starting November 2016 were screened. Patients ≥16 years of age were included if they had focal epilepsy, and received treatment with BRV starting ≥1 year before database close (June 2018). Exclusion criteria included history of alcoholism or drug abuse in the previous year, and enrolment in other studies with AEDs or medical devices.

Data collection

At baseline, physicians recorded demographics, seizure type, aetiology, previous/concomitant AEDs, presence of learning disability (LD), and medical/psychiatric comorbidities, and if applicable, the reason for switching from LEV to BRV. Classification was based on International League Against Epilepsy 1981 and 2017 terminology.[16,17]

At 3-, 6- and 12-month visits – standard practice when initiating a new AED – physicians recorded seizure frequency, BRV dose, and adverse events (AEs). Information was obtained from patients' seizure diaries (transcribed to clinical charts) and directly from patient/caregiver interviews. All patients had at least one blood test (complete blood count and biochemistry) over the 1-year observation period.

Study variables

Primary endpoints for evaluating effectiveness were seizure-freedom, patients with ≥50% reduction in seizure frequency from baseline (responders), and percentage seizure reduction from baseline at 12 months. Further analyses were conducted using data from the 3- and 6-month visits. Seizure-freedom at each time point was defined as no seizures since the previous visit – at 12 months, it was defined as no seizures during the preceding 6 months, and at 3 and 6 months defined as no seizures since baseline or the 3-month visit, respectively. Seizure reduction measures were based on monthly seizure frequency. Baseline seizure frequency was defined as the mean number of seizures/month during the 3-month period before BRV initiation. If no seizures were reported at this time, the baseline period was extended to the previous 12 months.

Safety end-points were incidences of, and discontinuations due to AEs as the main reason. Only AEs considered by participating physicians to be BRV-related were included in the analysis and were classified as mild, moderate or severe.

Exploratory analysis were performed to evaluate the impact of previous LEV exposure and the switch from LEV to BRV, as well as impact of age, LD or medical/psychiatric comorbidity on outcomes.

The safety set included all patients who received ≥1 BRV dosage; those who also had ≥1 seizure-related assessment during the 12 months after initiating BRV constituted the analysis set. Seizure-related outcomes were analysed using data from the analysis set, based on the last observation carried forward.

Statistical analysis

A descriptive analysis of all variables was conducted. Change in seizure frequency from baseline was analysed using the Wilcoxon test. For subgroup analyses, baseline characteristics were compared using the Mann-Whitney U test for quantitative and the chi-square test for qualitative variables. The Mann-Whitney U test was used to compare percentage reduction in seizure frequency, and the chi-square test to compare 100% (seizure-freedom) and 50% response rates. For safety analyses, AEs and their intensity were described by absolute frequencies and percentages. A binary logistic regression analysis was performed to identify factors predictive of seizure-freedom at the end of the observation period (methodology and results in supplementary material). The level of significance was set at 5%. SPSS version 19.0 was used for all analyses.

RESULTS

Of 636 patients, 575 (90.4%) met the inclusion criteria; most exclusions were due to follow-up <1 year (Figure S1). All included patients received ≥1 dose of BRV (safety set), and 572 had ≥1 seizure-related assessment (analysis set). Retention rate at 3, 6 and 12 months was 90.8%, 80.2% and 70.4%, respectively. Most frequent reasons for discontinuation were AEs (8.9%), lack of efficacy (12.3%), and a combination of both (7.5%). Most patients had been treated with ≥4 lifetime AEDs, indicating that a large proportion had DRE (Table 1).

Treatment profile

Mean retention time on BRV was estimated to be 11 months (95% confidence interval 10.6, 11.4) using the Kaplan-Meier approach. Mean (SD) BRV dose was 66.9±47 mg (median 50 mg, range 25–200 mg) on the first day, 131.6±54.8 mg (100 mg, 15–300 mg) at 3, 153.2 ± 60.7 mg (150 mg, 25–400 mg) at 6, and 160.9±59.9 mg (187.5 mg, 25–350 mg) at 12 months. Target dosage was achieved by 30.6% of patients on the first day; for the remainder, titration to full therapeutic dose lasted a mean of 18.9 days (range 3–70). Most frequent titration schedule was 25–50 mg/week (44.6%).

The main reasons for initiating BRV were inadequate seizure control (n=466, 81.1%), inadequate seizure control combined with poor tolerability (n=64, 11.1%), and poor tolerability (n=42, 7.3%). Patients were on a median of three concomitant AEDs at baseline and two at the 12-month visit (p<0.001; Figure S2). At the end of follow up, 21 patients (3.7%) were on monotherapy.

Primary variables

Effectiveness

At 12 months, mean and median reduction in seizure frequency was 36.0% and 50.7%, respectively (p<0.001). Mean seizure reduction was 61.6% (median 100%) for simple partial seizures (focal with retained awareness), 37.9% (82.5%) for complex partial seizures (focal with impaired awareness), and 25.3% (88.7%) for secondary generalised seizures (focal to bilateral tonic-clonic). Seizure-freedom was observed in 17.5% of patients and 39.7% were responders; 12.6% reported worsening (Figure 1). Thirteen patients were seizure-free at baseline and 11/13 remained so over the follow-up. Better responses were observed in the early add-on setting – patients with fewer lifetime AEDs were more likely to achieve seizure-freedom, although some patients treated with 12 AEDs also responded (Figure 2).

Safety and tolerability

At 12 months, 39.8% of patients had reported ≥1 AE, and 14.3% ≥1 psychiatric AE (PAE); 8.9% and 3.7% had discontinued due to AEs and PAEs, respectively (Table 2). Most AEs were mild or moderate in intensity. Most frequent AEs were somnolence, irritability and dizziness (Table 3). The most frequent PAE was irritability (6.2%).

Exploratory analyses

Previous levetiracetam exposure

At baseline, 106 patients (20.2%) were LEV-naïve. Seizure-freedom was achieved by more LEV-naïve patients at 3 (26.0% vs 12.0%), 6 (23.6% vs 11.1%) and 12 months (17.9% vs 13.4%) than those with previous exposure (difference significant at 3 and 6 months; both p=0.001). Incidence of AEs at 12 months was similar; 40.6% in the LEV-naïve group and 39.4% in the group with previous exposure.

Among 347 (60.9%) patients not on LEV at baseline, 236 (73.3%) underwent BRV dose titration while 86 (26.7%) achieved target dosage on the first day (schedule unknown for 25 patients). At 3 months, the proportion of seizure-free patients was significantly greater in those reaching target dosage on first day than in the titration group (25.6% vs 15.7%; p=0.044), while the proportion of patients reporting AEs (32.6% vs 28.0%) was similar. Among patients starting BRV due to poor seizure control (n=315), 84 (26.7%) achieved target dosage on the first day, and 231 (73.3%) underwent dose

titration. At 3 months, the proportion of seizure-free patients was significantly greater in the non-titration than in the titration group (23.8% vs 14.3%; p=0.048).

Switch from LEV to BRV

Most patients (223/228) taking LEV at baseline switched to BRV; predominantly due to poor efficacy (n=145, 65%), followed by a combination of poor efficacy and AEs (41, 18.4%), and AEs only (33, 14.8%). Eighty-one (36.3%) patients transitioned overnight; 142 (63.7%) transitioned progressively over a mean of 21.5 days (median 21 days, range 3–70). Mean LEV dose at BRV initiation was 1904.7±823.6 mg/day (median 2000, range 250–4000mg/day). At the end of follow-up, mean BRV dose was 173.2±823.6 mg/day (median 200, range 25–300mg/day). At 3 months, patients who transitioned progressively achieved numerically higher seizure-freedom (21.5% vs 18.9%) and responder (45.4% vs 35.1%) rates and reported less seizure worsening (6.9% vs 8.1%) compared with those who transitioned overnight; they also reported more AEs (28.2% vs 24.7%) and AEs that led to discontinuation (5.6% vs 1.2%).

The improvement in seizure control among patients who switched because of poor efficacy was less than that observed in the overall population, while patients who switched because of poor tolerability, had similar results to the overall population in terms of tolerability. It should be emphasized that among the 53 patients who switched due to PAEs, 9 (17.0%) reported PAEs at 12 months, and 3 (5.7%) discontinued because of PAEs; most (5/9) had previous psychiatric comorbidity. The most frequently reported PAEs were depression and irritability (both n=2, 3.8%). Outcomes are summarised in Table 4.

Subgroup comparisons

Full details of the subgroups and their treatment outcomes are summarised in Supplementary Material. Overall, effectiveness appeared to be better in patients with, than those without medical comorbidities. In contrast, outcomes were worse among patients with than those without LD. Brivaracetam tolerability was not highly impacted among patients with LD or psychiatric comorbidity, but was less well-tolerated by those with medical comorbidity.

Outcomes of patients who had experienced a stroke (n=22) were compared with those of the 483 patients who did not. A significantly greater proportion of patients in the stroke group were seizure-free at 12 months compared with other patients (40.9% vs 17.5%; p=0.006). The proportion of patients reporting AEs was numerically higher in the group with stroke (50.5% vs 38.6%), but not those who discontinued due to AEs (4.5% vs 9.1%).

Subgroup analysis according to age showed that 57/575 (9.9%) patients were aged ≥65 years and 27 switched treatment from LEV to BRV. Among patients aged ≥65 years, a significantly greater proportion were seizure-free (37.5% vs 15.3%; p<0.001) and responders (60.7% vs 37.4%; p<0.001) at 12 months compared with younger patients; incidences of AEs (42.1% vs 39.6%), and discontinuation due to AEs (14.0% vs 8.3) were numerically higher. Final BRV dosage was significantly lower among older than younger patients (median 100 vs 150 mg/day; p=0.003).

DISCUSSION

BRIVA-life was a retrospective analysis of data from 575 patients with focal epilepsy treated with BRV over 12 months. Most patients had DRE, as 89.3% had tried≥3 AEDs in the past. Brivaracetam was found to be effective in this large, difficult-to-treat population, with 40.0% of patients being responders and 17.2% seizure-free at 6 months and 39.7% and 17.5% at 12 months.

These findings are generally consistent with those of other retrospective series. Three studies in particular were similar to the current study in terms of patient population.[9–11] In two, 101 and 93 patients with focal epilepsy (both 97%), who had failed 10 (median) and 6.3 (mean) previous AEDs, respectively, were included.[10,11] At 6 months, responder and seizure-freedom rates were 27.8% and 7.0% in one,[10] and 35.1% and 8.8% in the other study.[11] In a larger study (N=262), 87% of patients had focal epilepsy and had failed a mean of 4.4 AEDs (vs 7.9 in the current study); responder and seizure-freedom rates at 6 months were 40.5% and 15.3%, respectively.[9] As with other AEDs, an inverse relationship between response and the number of lifetime AEDs was observed.[18,19] Responder rates in the current study were also consistent with those in the BRV RCTs. In an analysis of data pooled from three RCTs, responder rates were 34.2%, 39.5% and 37.8% for patients treated with 50, 100, or 200 mg/day,respectively.[20] Seizure-freedom rates were considerably lower in the RCTs than in the current study; the highest, 5.1%, was observed in the 100 mg/day group.[20] However, any comparison of the results between the current study and the RCTs must be done with caution given the major differences in design and patient populations.

Retention rate was 80.2% at 6 months, and 70.4% at 1 year. The 6-month retention rate was similar in the study by Steinert et al (78.5%),[9] but lower in the study by Steinhoff et al (51.5%),[10] most probably due to the inclusion of patients with more severe disease. One-year retention rates for other newer AEDs are similar to that obtained in this study, including eslicarbazepine (73.4%), perampanel (60.6%) and lacosamide (70%).[21–23] These first long-term data for BRV obtained in a large series of patients in clinical practice emphasize the lack of a high rate of early withdrawal.

At 12 months, 39.8% of patients reported AEs, with 8.9% discontinuing due to AEs. These results are in keeping with findings of the three aforementioned retrospective series,[9–11] and with those of a meta-analysis, which found BRV, LEV and gabapentin to have the best tolerability profiles among newer AEDs.[24] Adverse events reported by ≥5% of patients were somnolence, dizziness, headache, and fatigue in the BRV pivotal trials[18] and somnolence, irritability, dizziness and fatigue in the current study. Importantly, no unexpected AEs, such as laboratory test and cardiac abnormalities, or DRESS syndrome, were observed.

Psychiatric/behavioral AEs have been reported as one of the disadvantages of using LEV;[25] therefore, PAEs were monitored closely in this study. At 12 months, 14.3% of patients reported PAEs; 0.7% cases were considered severe and 3.7% led to discontinuation. The most common PAE in the current report and in BRV RCTs was irritability; 6.6% and 3.2%, respectively.[18] The higher incidence in this study is likely due to the large proportion of patients with psychiatric comorbidity (44.2%) – such patients are typically excluded from RCTs.[26] Among 52 patients who switched from LEV because of PAEs, nine (17%) reported PAEs, and three (3.7%) discontinued because of PAEs. Reduction in PAEs among patients switching from LEV to BRV has been reported in an exploratory prospective study;[27] Hirsch et al also reported improved tolerability among patients who switched from LEV because of PAEs,[14] while Steining et al reported improvement regardless of the switch reason. Differences in BRV and LEV PAE profiles could potentially be explained by the lack of interaction between BRV and inhibitory (GABA, glycine) or excitatory (glutamate) postsynaptic ligand-gated receptors, unlike LEV.[5]

Median BRV dosage on the first day was 50 mg. Among patients not transitioning from LEV, seizure-freedom at 3 months was significantly greater among those (26.7%) who reached target dosage on the first day than those who did not, while incidences of AEs and discontinuations due to AEs were similar. Titration, therefore, could be avoided for patients at high risk of breakthrough seizures and accidents, or those experiencing severe AEs requiring rapid AED replacement.[28,29]

For patients who transitioned from LEV to BRV, a 1:10 ratio was used for those on a median LEV dosage ≤2000 mg/day; for those on >2000 mg/day, equivalence was not clear and a higher ratio (1:15) was used, as observed in other studies.[9,14] More patients who switched overnight experienced seizure worsening than those who transitioned progressively (8.1% vs 6.9%). In contrast, those who transitioned progressively reported more AEs that led to discontinuation (7.7% vs 2.5%). This increase is likely due to overlapping of two AEDs (LEV and BRV) that share a similar mechanism of action,[30] and an increase in the total drug load over the transition period (mean duration 21.5 days).[31] Therefore, overnight transition could be recommended for patients more susceptible to AEs, and progressive transition for those at risk of worsening. Seizure-freedom was also lower among

patients who had previous LEV exposure compared with LEV-naïve patients (13.4% vs 17.9%). Overall, these observations confirm that although previous LEV failure can affect response to BRV, treatment with BRV could still be of benefit for these patients. Predictors of seizure-freedom with BRV were absence of complex partial seizures at baseline, longer epilepsy duration, and fewer lifetime AEDs in a logistic regression analysis.

Brivaracetam was less effective, but better tolerated by patients with than those without LD. These findings are similar to those of smaller studies that included patients with epileptic encephalopathies or LD.[32,33] While classifying seizures in such patients may be challenging, results from the current and other studies (including genetic generalized epilepsy) justify further exploration of the role of BRV in their treatment.[12,30] The number of elderly patients and those with late-onset epilepsy continue to increase; therefore, data from these groups, frequently excluded from RCTs, are needed.[34] Brivaracetam showed promise in the treatment of elderly patients, as well as those who had experienced a stroke, the most frequent cause of late-onset epilepsy.[35]

BRIVA-LIFE has limitations associated with its retrospective design; notably, the risk of missing relevant information from records, and lack of randomization and blinding, which may introduce bias. Its strength lies in its large sample size and long follow-up. Results showed that treatment with BRV was effective and well-tolerated, with no unexpected AEs over 12 months; PAEs were less frequent than with LEV. Treatment initiation without titration was feasible in some patients, as was a switch from LEV at a dose ratio of 1:10–15. Tolerability was not highly affected among patients with LD or psychiatric comorbidity.

DISCLOSURE

V Villanueva has participated in advisory boards and industry-sponsored symposia for Eisai, UCB Pharma, Bial, GSK, Esteve, Novartis, and GW Pharmaceuticals. FJ López-González has participated in advisory boards and industry-sponsored symposia for EISAI, UCB Pharma, Bial, Esteve, Novartis and Livanov. JA Mauri has participated in advisory boards and industry-sponsored symposia for Eisai, UCB Pharma, Bial, GSK and Esteve. J Rodriguez-Uranga has participated in advisory boards for UCB Pharma, Eisai, Bial, and Pfizer. J Zurita has participated in industry-sponsored symposia or received congress travel bursaries from Bial, UCB Pharma, Eisai and Esteve. M Olivé-Gadea, J Montoya and J Ruiz-Giménez have no conflict of interest to disclose.

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BRIVA-LIFE study group

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Table 1

Demographics and baseline disease characteristics of the study population (all values are based on the safety set, unless specified otherwise) .

Characteristic	Safety set N=575
Sex, n (%) Female | Male	 285 (49.6) |290 (50.4)
Age at baseline, mean (range), years	41.9 (16–88)
Age at baseline, n (%) <65 years | ≥65 years	 518 (90.1%) | 57 (9.9%)
Age at epilepsy onset, median (IQR), years	20 (10.0–34.8)
Duration of epilepsy, median (IQR), years	14 (5.0–27.0)
Number of monthly seizures Mean (SD) | Median (IQR)	 17.5 (45.7) | 5 (1.7–15.0)
Type of seizures at baseline, n (%)[a] SP | CPS | Secondary generalised	N=560 132 (23.6) | 391 (69.8) | 181 (32.3)
Aetiology, n (%) Cryptogenic | Cortical developmental malformation Mesial temporal sclerosis | Perinatal hypoxia Tumour | Vascular Trauma | Cavernoma Other	 215 (37.4) | 89 (15.5) 58 (10.1) | 43 (7.5) 35 (6.1) | 25 (4.3) 18 (3.1) | 13 (2.3) 79 (13.7)
Number of previous AEDs Mean (range) | Median (IQR)	N=525 7.9 (1–19) | 8 (5–10)
Number of concomitant AEDs Mean (range) | Median (IQR) Most frequently used concomitant AEDs, n (%)[b] Levetiracetam | Lacosamide Carbamazepine | Eslicarbazepine Lamotrigine | Perampanel	N=574 3 (0–6) | 3 (2–3) 228 (39.7) | 178 (31.0) 142 (24.7) | 138 (24.0) 135 (23.5) | 131 (22.8)
Number of previous AEDs Mean (range) | Median (IQR) Number of previous AEDs, n (%) 1–3 | 4–6 7–9 | 10–12 ≥13	N=525 7.9 (1–19) | 8 (5–10) 56 (10.7) | 153 (29.1) 157 (29.9) | 100 (19.0) 59 (11.2)
Levetiracetam treatment status, n (%) Prescribed at baseline|Previous exposure[c]|Naïve	 228 (39.7) | 419 (79.8) | 106 (20.2)
Previous medical comorbidity, n (%) Hypertension | Obesity Migraine | Stroke | Diabetes	N=483 |127 (26.3) 59 (12.2) | 36 (7.5) 28 (5.8) | 22 (4.6) | 14 (2.9)
Previous psychiatric comorbidity, n (%) Depression | Anxiety Personality disorder | Hyperactivity Psychosis | Other	N=522 | 244 (44.2) 112 (20.3) | 97 (17.6) 32 (5.8) | 29 (5.3) 18 (3.3) | 35 (6.3)
Learning disability, n (%)	N=570 | 182 (31.9)

[a]Patients could report >1 seizure type; [b] Patients could be on >1 concomitant AED; [c] Before or at baseline

AED=antiepileptic drug; CPS=Complex partial; IQR=interquartile range; SD=standard deviation, SP=simple partial

Table 2

Summary of safety outcomes (safety set, N=575).

	3 months	6 months	12 months
Adverse events, n (%)			
Any AE	160 (27.8)	210 (36.5)	229 (39.8)
Mild	64 (11.1)	84 (14.6)	86 (15.0)
Moderate	69 (12.0)	94 (16.3)	110 (19.1)
Severe	11 (1.9)	12 (2.1)	14(2.4)
Not classified	16 (2.8)	20 (3.5)	19 (3.3)
AEs leading to discontinuation	27 (4.7)	44 (7.7)	51 (8.9)
Psychiatric adverse events, n (%)			
Any AE	52 (9.0)	73 (12.7)	82 (14.3)
Mild	19 (3.3)	30 (5.2)	35 (6.1)
Moderate	25 (4.3)	33 (5.7)	36 (6.3)
Severe	4 (0.7)	4 (0.7)	4 (0.7)
Not classified	4 (0.7)	6 (1.0)	7 (1.2)
AEs leading to discontinuation	10 (1.7)	17 (3.0)	21 (3.7)

Table 3

Frequently-reported adverse events (reported by ≥1% of patients).

Adverse event, n (%)	Safety population N=575
Somnolence	65 (11.3)
Irritability	38 (6.6)
Dizziness	36 (6.3)
Fatigue	35 (6.1)
Memory disturbances	27 (4.7)
Verbal aggressiveness	19 (3.3)
Anxiety	16 (2.8)
Headache	14 (2.4)
Insomnia	14 (2.4)
Depression	13 (2.3)
Physical aggressiveness	10 (1.7)
Nausea and vomiting	6 (1.0)

AEs reported by <1% pf patients: weight increase (n=4, 0.7%), hyporexia (n=3, 0.5%), ataxia, mouth disturbances, attention disturbances, tongue paresthesia, suicidal ideation, erectile disfunction, behavioral disturbances, myalgias, myoclonic jerks (all n=2, 0.3%), allopecia, visual hallucinations, anorexia, appetite increase, tics, falls, cold, renal colic, confusion, respiratory depression, urninary disturbances, skin disturbances, psychosis, dysgeusia, stomach pain, constipation, gingivorrhagia, hypersalivation, restlessness, nervoussness, libido disturbances, weight loss, influenza, phonophobia, cough and blurred vision (all n=1, 0.2%).

Table 4

Seizure-related and safety outcomes among patients who switched treatment from levetiracetam to brivaracetam and according to reason for switch.

	3 months	6 months	12 months
Switch overall, n (%)			
Seizure-related outcomes	**n=204**	**n=220**	**n=221**
Seizure-free	42 (20.6)	44 (20.0)	50 (22.6)
Responders	85 (41.7)	87 (39.5)	99 (44.8)
Improvement	119 (58.3)	127 (57.7)	121 (54.8)
Worsening	15 (7.4)	23 (10.5)	25 (11.3)
Safety outcomes	**n=223**	**n=223**	**n=223**
Any AE	60 (26.9)	79 (35.4)	86 (38.6)
Discontinuation due to AEs	9 (4.0)	16 (7.2)	19 (8.5)
Switch due to lack of efficacy, n (%)			
Seizure outcomes	**n=171**	**n=185**	**n=185**
Seizure-free	20 (11.7)	21 (11.4)	24 (13.0)
Responders	61 (35.7)	61 (33.0)	70 (37.8)
Improvement	95 (55.6)	100 (51.4)	92 (49.7)
Worsening	14 (8.2)	21 (11.4)	24 (13.0)
Safety outcomes	**n=186**	**n=186**	**n=186**
Any AE	44 (23.7)	62 (33.3)	68 (36.6)
Discontinuation due to AEs	4 (2.2)	7 (3.8)	9 (4.8)
Switch due to adverse events, n (%)			
Seizure outcomes	**n=70**	**n=71**	**n=72**
Seizure-free	27 (38.6)	29 (40.8)	31 (43.1)
Responders	37 (52.9)	36 (50.7)	42 (58.3)
Improvement	49 (70.0)	47 (66.2)	47 (65.3)
Worsening	3 (4.3)	7 (9.9)	9 (12.5)
Safety outcomes	**n=74**	**n=74**	**n=74**
Any AE	33 (44.6)	36 (48.6)	37 (50.0)
Discontinuation due to AEs	7 (9.5)	10 (13.5)	12 (16.2)
Switch due to psychiatric adverse events, n (%)			
Seizure outcomes	**n=51**	**n=51**	**n=52**
Seizure-free	25 (49.0)	26 (51.0)	29 (55.8)
Responders	33 (64.7)	32 (62.7)	36 (69.2)
Improvement	40 (78.4)	39 (76.5)	38 (73.1)
Worsening	1 (2)	4 (7.8)	6 (11.5)
Safety outcomes	**n=53**	**n=53**	**n=53**
Any AE	20 (37.7)	21 (39.6)	22 (41.5)
Discontinuation due to AEs	3 (5.7)	4 (7.5)	5 (9.4)
Any psychiatric AE	7 (13.3)	8 (15.1)	9 (17.0)
Mild	3 (5.7)	3 (5.7)	4 (7.5)
Moderate	3 (5.7)	4 (7.5)	4 (7.5)
Severe	1 (1.9)	1 (1.9)	1 (1.9)
Discontinuation due to psychiatric AEs	2 (3.8)	2 (3.8)	3 (5.7)

Subgroup comparisons

Of 570 patients, 182 (31.9%) reported learning disability (LD). Data on presence of medical comorbidities were available for 483 patients, with 127 (26.3%) reporting comorbidities. Similarly, data on presence of psychiatric comorbidities were available for 483 patients, with 244(44.2%) reporting comorbidities. A comparison of baseline characteristics and study outcomes between the groups of patients with and without comorbidities are presented in Table S1.

Predictive factors for seizure freedom

A binary logistic regression analysis was performed to determine factors predictive of seizure-freedom at the end of the 12-month observation period.

Baseline characteristics of the population were analysed according to seizure- and safety-related results. The Student t test (or the Mann-Whitney U test) and the chi-square test (or Fisher's exact test) were used depending on the nature of the variables. Once potential relationships between the baseline variables with the response/adverse effects was determined, those with $p<0.10$ were selected to construct the model.

The following variables were selected for inclusion in the model to predict seizure-freedom: patient age ($p<0.001$), age of onset of epilepsy ($p<0.001$), epilepsy duration ($p<0.001$), vascular etiology ($p<0.001$), mesial temporal sclerosis etiology ($p=0.027$), cortical developmental malformation etiology ($p = 0.024$), learning disability ($p=0.001$), presence of any medical comorbidity ($p=0.009$), number of medical comorbidities ($p=0.002$), hypertension ($p<0.001$), stroke ($p=0.006$), diabetes ($p=0.002$), concern about the disease ($p=0.002$), presence of seizures at onset ($p <0.001$), seizure frequency at baseline ($p<0.001$), simple partial seizure frequency at baseline ($p<0.001$),complex partial seizures (CPS) at baseline ($p<0.001$), CPS frequency at baseline ($p<0.001$), secondary generalised seizure frequency at baseline ($p<0.001$), number of previous AEDs ($p<0.001$), number of concomitant AEDs at baseline ($p<0.001$).

The best resulting model contained three variables: duration of epilepsy, CPS at baseline, and number of previous AEDs (Table S2). In terms of epilepsy duration, the longer the duration, the greater the likelihood of seizure-freedom. The presence of CPS seizures at baseline was also found to influence seizure freedom – patients not reporting CPS baseline had a greater chance of seizure-freedom at follow-up. Finally, the fewer lifetime AEDs the patients had taken, the greater the likelihood of seizure-freedom. A valid multivariate binary logistic regression model with variables based on adverse effects could not be performed.

Figure 1
Seizure-related outcomes at the 3-, 6- and 12-month follow-up visits.

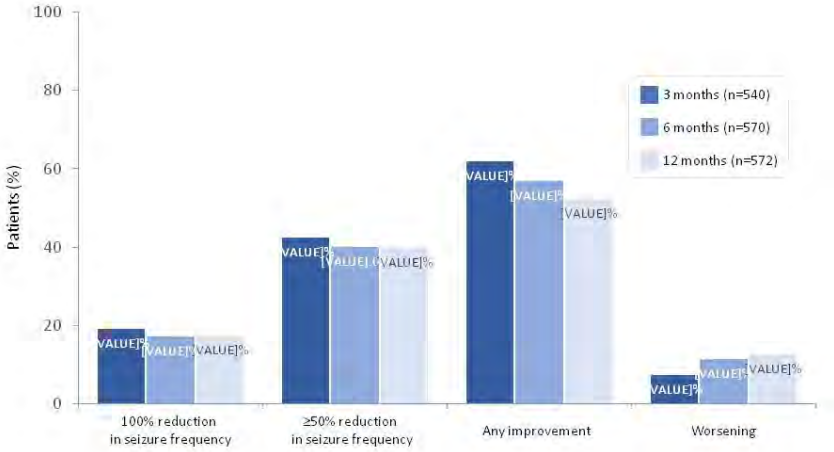

Figure 2
Impact of the number of lifetime antiepileptic drugs on achieving seizure-freedom.