Brivaracetam for the treatment of refractory epilepsy in patients with prior exposure to levetiracetam: A retrospective outcome analysis

Anniko Snoeren a,*, Marian H.J.M. Majoie b,c,d, Koen C.F.M. Fasen e,f, Dominique M. Ijff g

a Faculty of Health, Medicine & Life Sciences, Maastricht University, Maastricht, Netherlands
b Department of Neurology, Academic Centre for Epileptology, Epilepsy Centre Kempenhaeghe & Maastricht University Medical Centre, Netherlands
c MHeNS, School for Mental Health and Neuroscience, Department of Psychiatry and Neuropsychology, Maastricht University Medical Centre, Maastricht, Netherlands
d School of Health Professions Education, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands
e Department of Clinical Pharmacy, Academic Centre for Epileptology, Epilepsy Centre Kempenhaeghe, Netherlands
f Department of Clinical Pharmacy, Sint Anna Hospital, Netherlands
g Department of Medical Psychology, Academic Centre for Epileptology Kempenhaeghe, Heeze, Netherlands

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ABSTRACT

Purpose: To determine whether brivaracetam (BRV) provides an evident improvement in treatment efficacy and a reduction in treatment-emergent adverse events (TEAEs) in patients with refractory epilepsy, who previously failed treatment with levetiracetam (LEV).

Design: Retrospective analysis of data extracted from electronic patient files at Epilepsy Centre Kempenhaeghe (Heeze, the Netherlands) from the year 2000 until October 2020.

Methods: The inclusion criteria were met by 407 patients >18 years of age. During data collection, 26 patients were excluded due to too little follow-up information on the use of either LEV or BRV, and two more due to poor medication compliance, leaving a total of 379 patients for further analyses. All had used LEV before they started treatment with BRV. For every patient, data were collected including demographic information, efficacy (positive responder or non-responder) of LEV and BRV, and TEAEs occurring during LEV and BRV treatment.

Results: A total of 121 (29.8%) patients had discontinued BRV treatment before the end of data collection. At time of data collection the mean time since first seizure was 25.4 years. Of the 379 patients, 82.8% were diagnosed with focal epilepsy and 9.8% with generalized epilepsy. The median duration of treatment was 39 months for LEV and 20 months for BRV, the mean maximum dose was 1749.9 mg/day for LEV and 144.2 mg/day for BRV, and the mean number of concomitant AEDs was 1.4 at the start of LEV treatment and 2.0 at the start of BRV treatment. LEV was switched directly to BRV in 208 (54.9%) patients; 171 (45.1%) patients had an interval between discontinuation of LEV and the start of BRV. The mean duration of interval was 77.7 months. Of the patients who discontinued BRV, 30 (24.8%) switched back to LEV. Discontinuation of initial LEV treatment was due to TEAEs in 63.6% of patients, including 55.1% because of behavioural TEAEs. Discontinuation of BRV was due to inadequate efficacy in 24.0% of patients, to TEAEs in 47.1% and to both inadequate efficacy and TEAEs in 22.3%. Concerning efficacy, the analysis showed no significant difference between the positive responder rate of LEV and BRV (72.0% vs 69.1%, p<0.05). Of the patients who were positive responders to LEV treatment, 78.0% also had a positive response to BRV treatment. Of the non-responders to LEV treatment, 46.2% did have a positive response to BRV treatment. In comparison to LEV, patients reported significantly fewer TEAEs during BRV treatment (86.5% vs 61.7%, p<0.05). The most substantial difference was seen in the category ‘behaviour’ (55.1% vs 22.4%, p<0.05). Newly found behavioural TEAEs after switching from LEV to BRV were found in 7.1% of patients.

Conclusion: Overall BRV was better tolerated than LEV, especially regarding the behavioural TEAEs. Efficacy analyses showed that patients are likely to have a positive response to BRV when they had a positive response to LEV. However, this is not always guaranteed. Lack of response to LEV does not preclude a positive response to BRV. All in all, BRV seems to be an interesting treatment option in patients previously treated with LEV.

Abbreviations: AE, adverse event; AED, antiepileptic drug; BRV, brivaracetam; LEV, levetiracetam; TEAE, treatment emergent adverse events.

* Corresponding author at: Anniko Snoeren, Faculty of Health, Medicine & Life Sciences, Maastricht University, Maastricht, Netherlands.
E-mail addresses: a.snoeren@student.maastrichtuniversity.nl (A. Snoeren), majoien@kempenhaeghe.nl (M. H.J.M. Majoie), fasenk@kempenhaeghe.nl (K.C.F.M. Fasen), lijfd@kempenhaeghe.nl (D.M. Ijff).

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1. Introduction

Brivaracetam (BRV) is approved as an adjunctive therapy in the treatment of focal seizures, either with or without secondary generalisation, for patients from the age of four [1]. BRV is commercially available in the Netherlands since 2016. LEV and BRV share a similar mechanism of action in seizure reduction. Both target the transmembrane synaptic vesicle protein 2A (SV2A) [2]. However, BRV was found to have a 15- to 30-fold higher affinity and a higher selectivity for the SV2A receptor than LEV [3]. Also, whereas BRV does not have a modulatory effect on inhibitory and excitatory postsynaptic ligand-gated receptors, research suggests that LEV does. For example, LEV inhibits AMPA-gated currents, which has been suggested to be a factor in the induction of behavioural treatment-emergent adverse effects (TEAEs) in LEV [4,5]. These findings suggest that BRV might be a more advantageous AED than LEV in terms of efficacy and tolerability.

Efficacy and tolerability of BRV have been researched in six randomised controlled trials [6–11]. These trials found a significant effect associated with BRV at doses ranging from 5 to 200 mg/day, compared to placebo. The most reported treatment-emergent adverse events (TEAEs) for BRV throughout the trials were somnolence, dizziness, fatigue, headache, influenza, nasopharyngitis and nausea.

Over the last few years various clinical studies have been published which evaluate the use of BRV in the daily practice [12–18]. Four of these evaluated tolerability in patients who were previously exposed to LEV; all showed an improvement in (psycho-behavioural) AEs after switching from LEV to BRV [12, 14-16]. The aim of the current study is to evaluate the efficacy and TEAEs of BRV in patients who previously failed treatment with LEV, mostly due to tolerability issues.

2. Methods

2.1. Subject selection

This retrospective study analyses data extracted from electronic patient files at tertiary Epilepsy Centre Kempenhaeghe (Heeze, the Netherlands) from the year 2000, when LEV was first introduced, until October 2020. Inclusion criteria were the following: ≥18 years of age, treatment with BRV and a previous exposure to LEV, a clinical diagnosis of epilepsy, and signed informed consent. Note that all patients in this study had a reason to discontinue LEV. A large group of patients who were successfully treated with levetiracetam, and therefore did not need to switch to a different AED, were excluded. Patients who used BRV solely in combination with LEV were also excluded. In order to give an accurate representation of the patient population at the tertiary epilepsy centre, there were no exclusion criteria concerning demographic patient characteristics, epilepsy types, or comorbidities. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local medical ethical committee of Epilepsy Centre Kempenhaeghe, Heeze (ACE_2020_003).

2.2. Data collection

Data were collected using the electronic patient files. Firstly, demographic information was collected, such as gender, age, IQ (≤85 or >85), and the number of years since the first epileptic seizure. The IQ score was either based on a neuropsychological assessment or clinically estimated by a neurologist. The epilepsy type and aetiology were both classified using the ILEA classification of 2017 [19]. Information collected about the LEV and BRV treatment included the retention time, the maximum dose (mg/day), the number of concomitant AEDs at the start of treatment and the use of psychotropic medication during treatment. The reason for discontinuation was also noted, using the following classification: inadequate efficacy, TEAEs, both inadequate efficacy and TEAEs, or other reasons. In efficacy analyses, patients were classified as either positive responders or non-responders. A patient was classified as a positive responder if the medication reduced seizure frequency. For the non-responders, the medication had no effect or increased the seizure frequency. The information provided in the electronic files was too limited to provide quantitative data on this topic, such as a ≥50% responder rate. TEAEs were defined as effects related to the start of a treatment or to dose adjustment, or effects that disappeared after discontinuation of the treatment. These were assessed using the reports by patients and are therefore subjective. TEAEs were classified conform the categories in the SIdE-effect of the AntiEpileptic Drugs (SIDAED) questionnaire [20]: general CNS, behavioural, depressive symptoms, cognitive function, motor problems and coordination, visual complaints, headache, cosmetic and dermatological, gastrointestinal complaints, sexuality and menses. Based on the findings in the patient files, the two categories ‘psychotic symptoms’ and ‘other’ were added. Lastly, for each patient it was reported whether they switched directly from LEV to BRV or if there was interval (weeks/months/years) between LEV and BRV treatment. A direct switch from LEV to BRV was defined as either an overnight switch or gradually increasing the BRV dose while decreasing the LEV dose. If patients switched back to LEV, this was also noted.

2.3. Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics Version 26.0. The collected data were processed using descriptive statistics including frequency, range, mean, median and standard deviation. Significance (p-values) of differences in efficacy and tolerability between LEV and BRV treatment was calculated using the McNemar test for paired data, since the use of LEV and the use of BRV were evaluated in the same patient population.

3. Results

3.1. Patient characteristics at baseline

The inclusion criteria were met by 407 patients. During data collection, 26 patients were excluded due to too little follow-up information on the use of either LEV or BRV, and two more due to poor medication compliance, leaving a total of 379 patients for further analyses. The study population had a mean age of 42.3 years (18–82, ±16.7), an almost equal distribution of male and female participants (48.5% vs 51.5%), and 49.3% had an IQ below 85. The most common epilepsy type in the population was focal epilepsy (82.8%); in most patients the aetiology was defined as either structural (33.0%) or unknown (52.0%). The majority of the patients switched directly from LEV to BRV (54.9%); in other patients there was an interval between LEV and BRV use (45.1%). For the second group the mean duration of the interval between the two treatments was 77.7 months. The average number of concomitant AEDs at the start of treatment was somewhat higher for BRV treatment than for LEV treatment (2.0 vs 1.4). The number of patients who used psychotropic drugs during treatment was similar for BRV and LEV (12.7% vs 14.0%). Details on the demographic characteristics of the population are stated in Table 1.

3.2. Reason for discontinuation

All patients had either discontinued LEV before treatment with BRV or switched to BRV by gradually decreasing the dose of LEV while increasing the dose of BRV. Discontinuation of LEV was due to inadequate efficacy in 80 patients (21.1%), to TEAEs in 241 patients (63.6%), to both inadequate efficacy and TEAEs in 43 patients (11.3%) and due to other reasons in 15 patients (4.0%). At the cut-off date, 121 patients had also discontinued BRV. Discontinuation of BRV was due to inadequate efficacy in 29 patients (24.0%), to TEAEs in 57 patients (47.1%), to both inadequate efficacy and TEAEs in 27 patients (22.3%) and due to other reasons in 8 patients (6.6%). Of the patients who discontinued BRV, 30 (24.8%) switched back to LEV.
Demographics, epilepsy characteristics and the specifications of LEV and BRV treatment at baseline.

Table 1

| Demographics                         | Baseline (N = 379) |
|--------------------------------------|--------------------|
| Age, M (range, SD)                   | 42.3 (18-82, ±16.7) |
| Sex, n (%)                           |                     |
| - Male                               | 184 (48.5)          |
| - Female                             | 195 (51.5)          |
| Intelligence, n (%)                  |                     |
| - IQ >85                             | 187 (49.3)          |
| - IQ ≤85                             | 192 (50.7)          |
| Epilepsy characteristics             |                     |
| Time since first seizure (years)a   | 25.4 (1-75, ±15.2)  |
| Epilepsy type, n (%)                 |                     |
| - Focal                              | 314 (82.8)          |
| - Generalized                        | 37 (9.8)            |
| - Combined generalized and focal     | 6 (1.6)             |
| - Unknown                            | 22 (5.8)            |
| Aetiology, n (%)                     |                     |
| - Structural                         | 125 (33.0)          |
| - Genetic                            | 32 (8.4)            |
| - Infectious                         | 23 (6.1)            |
| - Metabolic                          | 1 (0.3)             |
| - Immunological                      | 1 (0.3)             |
| - Unknown                            | 197 (52.0)          |

Specifications LEV treatment

| Duration of LEV treatment in months, Mdn (range, IQR) | 39.00 (1-233, 95) |
| Maximum dose LEV, M (range, SD) | 1749.9 (250-6000, 880.9) |
| Concomitant AEDs at start of LEV treatment, M (range, SD) | 1.4 (0-4, ±1.0) |

Specifications BRV treatment

| Duration of BRV treatment in months, Mdn (range, IQR) | 20.00 (1-75, 25) |
| Maximum dose BRV, M (range, SD) | 144.2 (20-400, 66.4) |
| Concomitant AEDs at start of BRV treatment, M (range, SD) | 2.0 (0-7, ±1.1) |
| Direct switch LEV to BRV, n (%) | 208 (54.9) |
| Interval between LEV and BRV treatment, n (%) | 171 (45.1) |
| Duration of interval in months, M (range, SD) | 77.7 (1-364, 61.7) |

M = Mean, SD = Standard Deviation, Mdn = Median, IQR = Interquartile Range.
a The age at first seizure was not reported in the electronic files of 31 patients. Hence, for these patients, the time since the first seizure could not be calculated.
b The median value was used for the duration of treatment, because there was no normal distribution.

In the population there was a group of 30 patients who discontinued LEV or BRV, or both, as a result of prominent TEAEs, before they had reached the therapeutic dose. A modified efficacy analysis was, therefore, performed, excluding these patients. In the remaining population (n = 349) 75.6% of the patients were positive responders to LEV. For BRV 72.8% of the patients were positive responders. Neither analysis showed significant difference between the efficacy of LEV and BRV in the population (p>0.05).

In the group of patients with uncontrolled seizures on LEV (n = 34) who switched directly to BRV, 29.4% did have a positive response to BRV.

3.4. TEAEs

Table 2 shows the number of patients who reported TEAEs during LEV and BRV treatment. For both treatments, the most reported TEAEs were in the categories ‘general CNS’, ‘behaviour’ and ‘depressive symptoms’.

Significantly fewer patients reported TEAEs during BRV treatment than in prior treatment with LEV (61.7% vs 86.5%, p<0.05). In particular, behavioural TEAEs occurred less often during BRV treatment than during prior LEV treatment (22.4% vs 55.1%, p<0.05). Of the 209 patients who had behavioural TEAEs during the LEV treatment, 73 (34.9%) reported similar TEAEs during the BRV treatment. Of the 170 patients without behavioural TEAEs during the LEV treatment, 12 (7.1%) patients did have behavioural TEAEs on BRV treatment.

Patients reported significantly more TEAEs in the category ‘motor problems and coordination’ for BRV compared with LEV (8.7% vs 12.9%, p<0.05)

Table 3 shows how many patients experienced similar TEAEs on both treatments. Patients treated with LEV experiencing TEAEs in the categories ‘General CNS’, ‘Motor problems & coordination’ and ‘Depressive symptoms’, were most likely to experience similar TEAEs during BRV treatment.

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In the group of patients with uncontrolled seizures on LEV (n = 34) who switched directly to BRV, 29.4% did have a positive response to BRV.

3.3. Efficacy

The efficacy analysis (n = 379) showed that 72.0% of patients were positive responders to LEV, and 69.1% were positive responders to BRV. Of the positive responders to LEV treatment (n = 273) 78.0% also had a positive response to BRV treatment. Of the non-responders to LEV treatment (n = 106) 46.2% did have a positive response to BRV treatment.

Twelve patients on LEV and eight on BRV discontinued treatment for other reasons than the ones stated above. One patient in each treatment group (LEV and BRV) discontinued treatment because of pregnancy. Four patients using LEV and three patients using BRV discontinued treatment to evaluate whether adverse events were indeed treatment emergent, which proved not to be the case. Two patients using LEV discontinued treatment, aiming for monotherapy.

Four patients discontinued LEV treatment because of long-term seizure-freedom, aiming for a life without anti-seizure medication. One patient using BRV discontinued treatment because they achieved seizure-freedom after epilepsy surgery. Lastly, for one patient using LEV and three patients using BRV the reason for discontinuation was not provided in the electronic patient file.

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3.5. Retention rate

The retention rate at three months was 91.0% for LEV and 88.1% for BRV; at six months 80.2% for LEV and 79.1% for BRV; and at 12 months 70.2% for LEV and 70.5% for BRV. Patients with a retention time of less than six or 12 months, who were still using the medication at the cut-off point were not included in the rates at six and 12 months. No patients with a retention time of less than three months were still using the medication at the cut-off date.

3.6. BRV in generalized epilepsy

In the population, 37 patients had generalized onset seizures only. The majority of these patients had seizures of the tonic-clonic type (83.8%), 32.4% of the absence type, 32.4% of the myoclonic type, and 18.9% of the tonic type. Out of the patients with generalized onset seizures 37.8% exclusively had seizures of one type, the others suffered from two or more of the above mentioned seizure types.

In twelve patients the generalized onset seizures were due to a syndrome, including Lennox-Gastaut Syndrome, Angelman Syndrome, juvenile myoclonic epilepsy and juvenile absence epilepsy. Eight patients had a genetic mutation as cause for their epilepsy, including a partial X trisomy, GABRA1 mutation and a CACNA1A mutation. The general onset seizures in the other patients were either caused by meningitis/encephalitis (n = 2), a structural abnormality (n = 1), or an unknown cause (n = 14). BRV is not registered for generalized epilepsy, and so the BRV treatment these patients received was off-label.

Retention rates for LEV and BRV in this group were, respectively, 89.2% and 86.5% at 3 months, 83.7% and 83.7% at 6 months, and 81.1% and 73.0% at 12 months.

The efficacy analysis showed 75.7% of patients with generalized epilepsy were positive responders to LEV, and 73.0% were positive responders to BRV (p > 0.05). Out of the positive responders to LEV (n = 28), 78.6% were also positive responders to BRV. Out of the non-responders to LEV (n = 62), 65.2% were positive responders to BRV.

In the modified efficacy analysis, excluding three patients who discontinued LEV or BRV before reaching the therapeutic dose, 82.4% were positive responders to LEV, compared with 76.5% for BRV (p > 0.05). An overview of the TEAEs on LEV and BRV in patients with generalized epilepsy, and a comparison with patients with focal epilepsy, can be found in table 4. Similar to the overall patient population in this study, significantly fewer patients reported TEAEs during BRV treatment in comparison to LEV treatment (56.8% vs 89.2%, p < 0.05), especially in the category ‘behaviour’ (18.9% vs 59.5%, p < 0.05).

4. Discussion

This retrospective study evaluated the efficacy and TEAEs of BRV in a population of 379 patients with a clinical diagnosis of epilepsy, who previously failed LEV treatment. The population in this study was drug-resistant; 97.6% of the patients had been prescribed more than two AEDs prior to starting treatment with BRV.

Whereas most of the available clinical studies evaluating BRV are limited by their relatively small number of participants with prior LEV use and/or the short follow-up period [12, 13, 15-18], the current study consists of a large patient group with, on average, a long follow-up period.

As both the LEV and the BRV groups consist of the same set of patients, the patient characteristics are the same in both treatments.

We found no significant difference in positive responder rates between LEV and BRV in either the efficacy analysis (72.0% vs. 69.1%) or the modified efficacy analysis (75.6% vs. 72.8%). Idem, the open label, prospective, exploratory study by Yates et al. [12] indicated no substantial difference in the frequency of focal onset seizures while on BRV treatment, compared with the four weeks prior to baseline when they were still being treated with LEV. The responder rate of BRV in the current study is high compared to the responder rates of pivotal trials and RCTs researching BRV efficacy. These studies show ≥50% responder rates with a range of 21.9–55.8% [6-11] amongst various doses. The most likely explanation of this difference is the fact that the current study had no quantitative information on seizure frequency and relied on the patients and the neurologists to define whether or not there was a positive response. Therefore, responses below 50% were also included in the responder rate.

What may give a more realistic view of the efficacy of BRV in the current study, is isolating the patients with uncontrolled seizures on LEV who switched to BRV directly. The analysis shows that 29.4% of this group of patients had a positive response to BRV, a number more in

| Table 4 |
| --- |
| **Comparison of efficacy and TEAEs in patients with focal epilepsy (n = 314) and generalized epilepsy (n = 37).** |
| | Focal epilepsy | Generalized epilepsy |
| | LEV | BRV | LEV | BRV |
| Positive effect | (222) | (214) | n.s. | (28) | (27) |
| Positive effect (modified) | (70.7) | (68.2) | n.s. | (75.7) | (73.0) |
| Any TEAEs | (272) | (197) | p < 0.05 | (33) | (21) |
| General CNS, n (%) | (107) | (86) | p < 0.05 | (14) | (11) |
| Behaviour, n (%) | (171) | (73) | p < 0.05 | (22) | (7) |
| Depressive symptoms, n (%) | (51) | (45) | n.s. | (11) | (8) |
| Cognitive function, n (%) | (19) | (12) | n.s. | (3) | (2) |
| Motor problems & coordination, n (%) | (29) | (38) | n.s. | (3) | (5) |
| Visual complaints, n (%) | (9.2) | (12.1) | n.s. | (8.1) | (13.5) |
| Headache, n (%) | (7) | (2.2) | 1 (1.6) | n.s. | 0 |
| Cosmetic and dermatological, n (%) | (17) | (16) | 2 (3) | n.s. | 3 |
| Gastrointestinal complaints, n (%) | (31) | (32) | 2 (6) | n.s. | 6 |
| Sexual complaints, n (%) | (9.9) | (10.2) | 2 (5.4) | n.s. | 16.2 |
| Psychotic symptoms, n (%) | (7) | (2.2) | 1 (1.6) | n.s. | 0 |
| Other, n (%) | (4) | (1.3) | n.s. | 2 (0.6) | 4 |

Table 3

Patients experiencing similar TEAEs during BRV treatment as during LEV treatment (N = 379).

| Similar TEAEs on BRV as on LEV (%) |
| --- |
| Any TEAEs | 67.7 |
| General CNS | 46.1 |
| Behaviour | 24.9 |
| Depressive symptoms | 42.3 |
| Cognitive function | 28.0 |
| Motor problems & coordination | 42.4 |
| Visual complaints | 0 |
| Headache | 28.6 |
| Cosmetic and dermatological | 29.8 |
| Gastrointestinal complaints | 18.9 |
| Sexual complaints | 28.6 |
| Psychotic symptoms | 25.0 |

\( a \) Modified efficacy analysis: excluding patients who discontinued LEV or BRV, or both, as a result of prominent TEAEs, before they had reached the therapeutic dose, leaving n = 289 for focal epilepsy and n = 34 for generalized epilepsy.
accompany with the responder rates of the pivotal trials and RCTs.

The study by Gillard et al. [3] found BRV to have a higher affinity and a higher selectivity for the SV2A receptor than LEV and that therefore, BRV may be more effective in seizure reduction. However, in the current study there was no significant difference between LEV and BRV in terms of efficacy. Not even all patients with a positive response to LEV had the same response to BRV (78.0%). This is an unsuspected finding which might suggest that a higher affinity for the SV2A receptor does not increase the efficacy of BRV. Additional research, with head to head comparison between LEV and BRV, is needed before a definitive statement about this can be made.

LEV and BRV share a mechanism of action through the SV2A protein, but a study by Wood and Gillard [21] found evidence that LEV and BRV may act at different binding sites of that protein. Hirsch et al. [16] suggested that this could explain the seizure reduction during BRV treatment even when prior LEV treatment proved ineffective. This may explain the fact that nearly half of the non-responders to LEV did have a positive response to BRV, similar to results found in the multicentre retrospective study by Villanueva et al. [14], where seizure control improved in 55.8% of the patients who switched from LEV to BRV due to lack of efficacy.

Pivotal trials and RCTs found that of 52.0–79.0% of the patients reported ≥1 TEAEs during BRV use [6–11], which is comparable to the results found in the current study (61.7%). In other retrospective clinical studies, the occurrence of TEAEs on BRV in patients with a history of LEV in other is much lower (Villanueva et al.: 39.4%, Hirsch et al.: 29.4%) [14, 16]. This difference could not be explained using the information available in the publications. Missing information (e.g. drug concentration ranges or comorbidities) might play a role in the difference between the outcomes of these clinical studies and the current study.

We found a significant decrease in TEAEs after switching from LEV to BRV (86.5% vs 61.7%). The clinical trial with a similar design by Hirsch et al. showed an even greater decrease (LEV: 77.5%, BRV: 29.4%)[16]. As also seen in other studies, the significant difference in occurrence of behavioural TEAEs between LEV (55.1%) and BRV treatment (22.4%) stood out most. Behavioural TEAEs included aggression, agitation, restlessness, and increased irritability. The occurrence of behavioural TEAEs during BRV treatment in the current study is higher than that found in pivotal trials and RCTs (3.7–6.0%) [7,8,10]. We think this difference is caused by the fact that the majority of the patients in the current study had prior behavioural TEAEs during LEV use and were, therefore, more prone to having similar TEAEs on BRV. This is supported by the outcome that in the patients who previously reported behavioural TEAEs on LEV, 24.9% reported similar TEAEs on BRV, versus 7.1% of patients with no behavioural TEAEs during prior LEV use.

Nonetheless, the results of the current study and other clinical studies suggest that switching to BRV can be beneficial when behavioural symptoms occur during LEV treatment. In the current study behavioural TEAEs vanished in 75.1% of patients after switching from LEV to BRV, which is consistent with clinical studies by Yates et al. (65.5%) [12] and Steinig et al. (77.3%) [15].

Interestingly, in the current study, patients reported significantly more TEAEs in the category ‘motor problems and coordination’ during BRV treatment (12.9%) than during LEV treatment (8.7%). Dizziness was the symptom that was almost exclusively reported in this category. Consistent with our results, the prevalence of dizziness during BRV use in many pivotal trials, RCTs, and other clinical studies ranges from 4% to 17% [6–18]. Meta-analysis of RCTs by Zhu et al. [22] found dizziness to be one of the three TEAEs distinctly associated with BRV, the other two being fatigue and back pain. None of the available studies made the comparison between the occurrence of dizziness during BRV treatment and the occurrence of dizziness during prior treatment with LEV.

Table 4 shows that TEAEs in the categories ‘General CNS’, ‘Depressive symptoms’, and ‘Motor problems & coordination’ are most likely to ‘breed true’, as it were, when switching from LEV to BRV.

This information is useful for clinicians who consider starting BRV in patients with previous exposure to LEV.

Although BRV treatment induced fewer TEAEs than prior LEV treatment, retention rates for LEV and BRV at three (91.0% vs 88.1%), six (80.2% vs 79.1%), and 12 months (70.2% vs 70.5%) did not show major differences. The retention rates for BRV at three and six months were comparable to pivotal trials and RCTs (3 months: 90.6–92.2%) [8, 10, 11], and at the high end of the range found in other clinical studies (3 months: 74.4%–90.8%, 6 months: 51.5%–80.4%) [15–19]. The retention rate at 12 months was comparable to that found in the clinical study by Villanueva et al. (70.4%)[15].

Currently, LEV is registered as a treatment for generalized epilepsy, but BRV is not. Some research has been carried out on the use of BRV in generalized epilepsy. The randomized controlled trial by Kwan et al. [8] found a higher ≥50% responder rate for BRV (44.4%) compared to a placebo (14.4%) and found it to be well tolerated. The efficacy analysis of the current study showed no significant differences in the numbers of positive responders between BRV (73.0%) and LEV (75.7%) in patients with generalized epilepsy. Nor did the modified efficacy analysis. Patients with generalized epilepsy reported significantly fewer TEAEs during BRV treatment (56.8%) than during prior LEV treatment (89.2%), especially regarding the behavioural TEAEs, which is comparable to the results of the multicentre, retrospective cohort study by Strzelczyk et al. [23] Additionally, there seemed to be a higher positive responder rate and a greater reduction in (behavioural) TEAEs for BRV in the patients with generalized epilepsy compared to the patients with focal epilepsy, which was also found in the multicentre, retrospective cohort study by Steinig et al. [14] The positive responder rate for BRV in the current study is higher than the rates reported in other studies (range 36.0%–52.2%) [9, 15, 23]. As explained earlier, this is most likely due to the fact that other studies reported ≥50% responder rates, whereas the current study could not quantify the positive response of patients and therefore also classified patients with a response lower than 50% as positive responders.

The outcomes of the current study and studies mentioned above underline the need for additional research into the treatment of generalized epilepsy with BRV in larger populations.

As with any clinical study, there are limiting factors. The first and foremost limitation is the retrospective nature of the study. The outcomes are dependant on the information provided in the electronic patient files at the tertiary epilepsy centre on account of which the data may not be complete. Also, since the study was not blinded nor controlled, the reports by the neurologists may have been skewed to TEAE changes rather than seizure control, given the general view that LEV causes behavioural problems.

Due to the retrospective design, we could not retrieve quantitative data on seizure frequency and treatment-emergent adverse events and had to rely on the qualitative data provided by the neurologists in patient files. Hence, we could not clearly abstract the exact seizure response for patients, such as a ≥50% responder rate. This poses the question whether all patients classified as positive responders had a clinically relevant reduction in seizure frequency. However, the patients and the neurologists determined together whether or not there was a positive response to the medication. If both the patient and the neurologist agree about a positive response, one could argue that this equals a clinically relevant reduction in seizure frequency.

In a group of patients there was an interval of multiple years between LEV and BRV treatments. Therefore they were treated with LEV in a different time period with different intervening therapies than when they were treated with BRV. Patients may have been more drug resistant when starting treatment with BRV after failing other AEDs or surgical treatment. This limits the quality of the comparison between the LEV and BRV treatments in the results.

As the only source of information on patients in the study was their electronic patient file from the epilepsy centre, we did not have access to a complete medication list. Therefore, it is theoretically possible that
patients were prescribed comedication during the initiation period of LEV or BRV, which would make it hard to distinguish between the TEAEs of different medications. However, in practice, this happens rarely to never, because the neurologists at the epilepsy centre adhere to protocol, which states that AEDs should be altered one at a time.

The majority of patients had not yet completed BRV treatment at the cut-off date. Therefore, the study might have missed information about efficacy or missed the onset of TEAEs, as they had not occurred by the cut-off date. However, a study by Meador et al. [24] reported that both prevalence and incidence of various TEAEs declined in the course of the first 12 weeks of BRV treatment until no new TEAEs were reported at week 12. Since all the patients in the current study did complete at least three months of BRV treatment, we expect to have included the onset of the majority of TEAEs.

The outcomes of the group with primary generalized epilepsy are limited by the fact that it consists of only 37 patients, which is less than 10% of all patients in this study. This does, however, reflect the proportions in the patient population at the tertiary epilepsy centre where the study took place.

Lastly, one should be aware that this study only provides information on BRV use in patients who have previously discontinued LEV treatment, due to various reasons. This may cause an order effect of switching from LEV to BRV, without any comparison to patients switching from BRV to LEV. Note that this study does not provide any information on possible superiority of one of these medications over the other. For this, studies are needed which are designed to compare LEV and BRV directly.

5. Conclusion

This retrospective outcome analysis shows the majority of patients with TEAEs during LEV treatment benefit from a switch to BRV, especially regarding the behavioural TEAEs. A small group of patients without behavioural TEAEs on LEV did, however, develop newly found behavioural TEAEs on BRV. Also, switching from LEV to BRV might cause patients to experience more dizziness. The efficacy analyses showed that having no response to LEV does not preclude a positive response to BRV. Even though most positive responders to LEV also had a positive response to BRV, a positive response to BRV cannot be guaranteed after switching. All in all, BRV seems to be an interesting treatment option in patients previously exposed to LEV, especially in the attempt to improve tolerability. The percentage of positive responders of patients with generalized epilepsy was not significantly lower for BRV than for LEV; tolerability improved after the switch to BRV consistent with other results. This suggests BRV has potential as a treatment option for patients with generalized epilepsy for whom LEV treatment has failed. Additional comparative research in larger populations is, however, required.

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