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Brivaracetam versus Levetiracetam for Epilepsy: A Review of Comparative Clinical Safety

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Abbreviations

AED	antiepileptic drug
AE	adverse event
BAE	behavioral adverse events
BRV	Brivaracetam
I-GEBSE	Investigator Global Evaluation of Nonpsychotic Behavioral Side Effects
LEV	Levetiracetam
TEAE	treatment emergent adverse events

Context and Policy Issues

Epilepsy is a chronic neurological disorder characterized by spontaneous seizures and can be associated with genetic disorders, occur secondary to conditions affecting the central nervous system or can be due to unknown etiology.¹ In Canada, it has been estimated that around 300,000 people are living with epilepsy based on The Canadian Chronic Disease Surveillance System (September 2017).² Anti-epileptic drugs (AED) are the mainstay of pharmacological management of epilepsy.¹ Often, patients are treated with multiple AEDs, which are decided based on factors related to patients (e.g., age, type and frequency of seizures, comorbidities), and drugs (e.g., drug interactions, safety profile).¹

Brivaracetam (BRV) is an AED in the racetam group which was discovered as an analog to the related racetam drug levetiracetam (LEV).³ Both drugs have a similar mechanism of action with a selective and high affinity for binding to synaptic vesicle protein 2A, but they may differ in their pharmacological profiles.³ BRV is approved by Health Canada as adjunctive therapy in the management of partial-onset seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy.⁴ A CADTH Common Drug Review (CDR) assessment found that, based on evidence from four multicenter placebo controlled randomized trials, BRV demonstrated significantly greater reductions in seizure frequency compared to placebo.⁵ In the absence of head-to-head trials, evidence regarding comparative efficacy and safety of BRV versus LEV is limited.³ An indirect treatment comparison found no statistical differences between LEV and BRV with respect to efficacy and adverse events (AE) - overall and non-behavioral- except dizziness, which occurred at a significantly higher rate with high dose levels of BRV.⁶ Behavioral adverse events (BAE) appear to be less prevalent in BRV than with LEV based on evidence from pre-clinical studies⁷ and clinical studies.^{3,8,9}

The purpose of this report is to summarize the evidence regarding the comparative clinical safety of BRV compared to LEV among patients with epilepsy with mental health conditions as well as in patients with epilepsy who experienced psychiatric or behavioral adverse events with previous LEV treatment.

Research Questions

1. What is the clinical evidence regarding the comparative safety of brivaracetam versus levetiracetam in people with epilepsy with mental health conditions?
2. What is the clinical evidence regarding the safety of switching from levetiracetam to brivaracetam in people with epilepsy with mental health symptoms related to levetiracetam?

Key Findings

Ten nonrandomized studies were included in this report that provided low-to-moderate quality evidence regarding the safety of brivaracetam compared to levetiracetam in patients with epilepsy.

Descriptive findings from one study found that in patients with epilepsy with psychiatric comorbidities, treatment with brivaracetam was associated with an improvement in psychiatric and behavioral adverse events such as aggression and depressive symptoms compared to that with levetiracetam. Due to the descriptive nature of results and methodological limitations of the study, the evidence was of low quality.

In patients with epilepsy who had mental health symptoms related to treatment with levetiracetam, evidence from all included studies suggested that switching treatment to brivaracetam could improve the occurrences of such adverse events. Two studies found that significantly fewer patients reported behavioral symptoms during brivaracetam treatment compared to that during levetiracetam treatment. Among them one study was conducted in adult patients and the other study was conducted in children and adolescents. Descriptive results from seven other studies also found lower rates of occurrence of psychiatric or behavioral adverse events with brivaracetam than with previous levetiracetam treatment. Due to methodological limitations in the included studies (e.g., observational study design, concurrent treatment with other antiepileptic medications and subjective reporting of adverse events) the quality of evidence was low to moderate and findings should be interpreted with caution.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was brivaracetam. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and October 28, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed

for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q.1 a) People with epilepsy with current mental health conditions b) People with epilepsy with previous mental health conditions Q2. People with epilepsy with mental health symptoms related to Levetiracetam treatment.
Intervention	Q1, Q2: Brivaracetam
Comparator	Q1, Q2. Levetiracetam
Outcomes	Safety (i.e., any mental health or psychiatric outcome, such as: irritability, listlessness, delusions, hallucinations, unusual behavior, aggression, suicidal ideation)
Study Designs	Health technology assessments, systematic reviews, randomized controlled studies, non-randomized studies.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the Downs and Black checklist¹⁰ for randomized and non-randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 224 citations were identified in the literature search. Following screening of titles and abstracts, 193 citations were excluded and 31 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 21 publications were excluded for various reasons, and 10 publications met the inclusion criteria and were included in this report. These comprised ten non-randomized studies.^{8,9,11-18} Appendix 1 presents the PRISMA¹⁹ flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

The characteristics of the included studies that are relevant to the current report are summarized below. Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Ten single arm non-randomized studies were included in this report.^{8,9,11-18} One study was an open label, prospective interventional trial using a pre-post design.⁸ Among others, one¹² study was prospective observational and eight^{9,11,13-18} were retrospective observational in design.

Among the included studies, one study was published in 2020,¹¹ two in 2019,^{12,13} five in 2018,¹⁴⁻¹⁸ and one each in 2017⁹ and 2015.⁸

Country of Origin

The authors of the included studies were from Germany,^{9,14-18} Spain,^{11,13} UK¹² and the US.⁸

There were six multi-center studies.^{8,9,13,15,16,18} Among them, one study⁸ enrolled patients from the US, France, Germany and Spain and others enrolled patients from multiple clinics in Spain¹³ and Germany.^{9,15,16,18} Four studies were single center studies.^{11,12,14,17}

Patient Population

Patient population in all included studies comprised of patients with epilepsy. The population from each study relevant to the current report are described below.

In the pre-post trial by Yates et al.,⁸ patients who were at least 16 years of age with partial onset seizure or primary generalized epilepsy and treated with LEV were considered eligible if they were experiencing behavioral adverse events on LEV treatment. Other inclusion criteria were, discontinuation of LEV treatment within 16 weeks of initiation (due to behavioral AE), concomitant treatment with 2 to 3 AEDs (including LEV) in doses which were stable for at least 4 weeks. Patients who were treated with LEV for greater than 16 weeks were excluded. Other exclusion criteria were: cluster of flurry seizures, history of psychogenic non-epileptic seizures or status epilepticus in the year prior, rapidly progressing brain disorder, brain tumor or other serious uncontrolled diseases. Based on these criteria, 29 patients were enrolled, all of whom were relevant to the current report. The number of patients with pre-existing mental health conditions were not reported

In the study by Fonesca et al.,¹¹ 37 patients with genetic generalized epilepsy from a single center, for whom at least 6 months follow up data was available, were enrolled to the study. Patients without a definite diagnosis or those with other conditions that could mask the results of the study were excluded. Relevant to the current report, 31 patients had previous exposure to LEV. Mental health conditions present at the baseline were not reported.

In the study by Foo et al.,¹² patients with drug resistant focal or generalized epilepsy who were 16 years or older were enrolled from a single center (n = 134). All patients were exposed to LEV such as switched from LEV to BRV at the study start (n = 63) or with previous LEV treatment (n = 71). More than half of the study participants had a psychiatric or behavioral disorder (54%).

In the study by Villanueva et al.,¹³ patients with focal epilepsy who were 16 years or older were enrolled from multiple centers (n = 575). Patients with a history of alcoholism or drug abuse (within a year prior to the study) were excluded. Relevant to the current report, 223 patients were switched from LEV to BRV during the study, and 419 patients were previously exposed to LEV. Among whose data was available, 244 (44.2%) patients had a previous psychiatric comorbidity.

In the study by Hirsch and colleagues¹⁴ patients with epilepsy (type not specified) who were between 11 and 70 years of age (n = 102) were enrolled. The study only included patients for whom clinical information was available for a period 3 months before BRV initiation and 6 months after. All patients had a history of treatment with LEV : they either switched from LEV to BRV at the study start (n = 62) or had previous LEV treatment (n = 40). Among them, 49 patients (48%) had a psychiatric comorbidity.

In the study by Schubert-Bast et al.,¹⁸ children and adolescents (≤ 17 years) with focal epilepsy were enrolled from four clinics. (n = 34). Among them 20 patients switched from LEV to BRV at the start of the study, and 6 patients had previous LEV treatment. The number of patients with pre-existing mental health conditions were not reported.

In the study by Strzelczyk et al.,¹⁵ patients (n = 61) with genetic generalized epilepsy irrespective of age were enrolled included from multiple centers in Germany. 12 patients were under the age of 18. A little over half of the included patients were switched from LEV to BRV during the study (n = 31). Number of patients with pre-existing mental health conditions were not reported.

In the study by Willems and colleagues,¹⁶ patients (n = 44) with epileptic encephalopathies irrespective of age were included from multiple centers in Germany. Nine participants were under the age of 18. Relevant to the current report, 24 patients were switched from LEV to BRV during the study, and 13 patients were previously exposed to LEV. Seven patients were never exposed to LEV during their lifetime. Number of patients with pre-existing mental health conditions were not reported.

In the study by Zahnert et al.,¹⁷ patients (n = 93) with epilepsy irrespective of age were included from a single German clinic. Among them, 47 patients were switched from LEV to BRV during the study, and 87 patients were previously exposed to LEV. Six patients were naïve to LEV treatment. Psychiatric comorbidities were present in 42 patients (45.2%).

In the multicenter study by Steinig et al.,⁹ all patients with epilepsy without any age restriction were considered eligible if follow up data was available (n = 262). Nine patients included in the study were less than 18 years old. All but 26 study participants were exposed to LEV as follows: switched from LEV to BRV at the study baseline, n = 133; previous treatment with LEV, n = 103. Number of patients with pre-existing mental health conditions were not reported.

Interventions and Comparators

The intervention in all the studies included in this report was BRV, given in varying doses across the studies. The occurrences of study outcomes during BRV treatment was compared to that during LEV treatment, which was either just before starting treatment with BRV (indicated as direct switch from LEV to BRV) or a previous treatment anytime in the patient's life (indicated as previous treatment with LEV). Other concurrent AEDs were prescribed to patients in all studies.

In the pre-post trial by Yates et al.,⁸ BRV (initial dose 100 mg twice daily, no titration) was compared to LEV with outcomes measured before and after switching from LEV to BRV. Prior to switching, all patients were on LEV treatment (1-3g/day) for up to 16 weeks which was considered as a baseline period. All patients were switched from LEV to BRV after their last morning dose of LEV, without an overlapping period. There were 2 to 3 concomitant AEDs received by each patient in stable doses for at least 4 weeks.

In the study by Fonesca et al.,¹¹ the mean daily dose of BRV was 135.1 mg and the duration of treatment was 10.4 months. The comparator was previous treatment with LEV. More than two thirds of the patients (n =25,67.5%) received concomitant treatment with other AEDs such as lamotrigine, clobazam and valproate. In the Foo et al.¹² study, BRV (median dose 200 mg, range 50 to 200 mg) was compared to LEV (previous treatment as well as a gradual switch to BRV). All patients received concomitant treatment with at least one other AED. In the study by Villanueva and colleagues,¹³ the safety BRV (mean dose 66.9 mg, SD: 47) was compared to that with previous LEV treatment as well as switching from LEV to BRV. Among the patients who switched from LEV to BRV (n= 223), 81 (36.3%) patients switched overnight and 142 patients (67.3%) did so gradually with a mean overlapping transition period of 21.5 days. All patients received concomitant treatment with other AEDs (median 3). In the Hirsch et al.¹⁴ study BRV (mean dose 153.2 mg /day) was compared to LEV prior to an overnight switch (mean dose 2161 mg/day) to BRV as well as previous LEV treatment. Mean number of concomitant AEDs was 1.6. In the study by Schubert-Bast et al.,¹⁸ the clinical safety of BRV was compared to LEV (previous LEV treatment as well as direct switch to BRV). Median titration ratio of switch to BRV was 10:1. All patients received concomitant treatment with other AEDs (median 1).

As for the study by Strzelczyk et al.,¹⁵ BRV (target dose, mean 134.2mg/day) was compared to LEV (direct switch). The median titration of switch was 10:1; 26 patients underwent overnight switch and five underwent overlapping transition. Patients also received concurrent treatment with other AEDs at the study baseline (median 2 AEDs). Willems and colleagues¹⁶ examined the safety of BRV (target median dose 138.5mg) compared to that with LEV (direct switch, median ratio of switch 15:1) as well as with previous LEV treatment. Among the patients who switched from LEV to BRV (n= 24), 21 patients switched overnight, and 3 patients did so with an overlapping transition period. The median number of concomitant AEDs at baseline was 2 (range 1 to 4). In the study by Zahnert et al.,¹⁷ BRV was compared to LEV (direct switch to BRV as well as previous LEV). The dose ratio of switch from LEV to BRV was not reported. Concurrent use of other AEDs was present in 81 patients at baseline, with a mean of 1.7 AEDs (SD: 1.7). Among the patients who switched from LEV to BRV (n= 47), 43 patients switched overnight, and 4 patients underwent a gradual switch. Steinig and colleagues⁹ examined the safety of BRV compared to that with LEV (direct switch to BRV and previous treatment). There was an overnight switch in 105 patients, out of 133 patients who underwent a switch. All patients received concomitant treatment with other AEDs at baseline (median 2).

Outcomes

All included studies examined efficacy and safety outcomes. The safety outcomes which are relevant to the current report evaluated by the included studies are described below.

In the experimental pre-post study by Yates et al.,⁸ the primary safety outcome of interest was a clinically meaningful reduction of BAE. This was assessed by the study investigator by answering yes or no to the question: “Has there been a clinically meaningful reduction of nonpsychotic behavioral side effects since the start of LEV? (p.166)”⁸ One of the secondary safety outcomes was a change in the maximum intensity of BAEs associated with LEV (investigator assessed). Intensity before and after BRV treatment was recorded as mild, moderate, severe or resolved. The criteria and definition of these intensity levels were unclear. Another secondary outcome was worsening or improvement of BAEs, as measured using Investigator Global Evaluation of Behavioral Side Effects (I-GEBSE). I-GEBSE is a seven-point scale measuring BAEs that ranged from “marked worsening” to

“marked improvement”. It was unclear whether this scale has been validated. Other outcomes of interest were freedom from BAE, TEAE and serious adverse events.

Eight of the included observational studies evaluated the overall psychiatric or behavioral adverse events.^{9,11-13,15-18} In addition, two of these studies compared the occurrences of specific AEs. Foo et al.¹² reported aggression and depressive symptoms. Zahnert and colleagues¹⁷ reported occurrence of several individual symptoms such as irritability, depression, aggression, agitation, psychosis, listlessness, anxiety, lability of affect and hysteria. Lastly, Hirsch et al.¹⁴ compared the occurrences of depression/mood lability/fear together as well as irritability/aggressiveness together.

The length of follow up in the included studies ranged from 12 weeks⁸ to 26 months.¹² Five studies had a 12 month follow up period with clinic visits at 3, 6 and 12 months,^{9,13,15,16,18} and three studies had a follow up duration of 6 months.^{11,14,17}

Summary of Critical Appraisal

In the single arm pre-post interventional trial by Yates et al.⁸ the study objectives were described clearly. Eligibility criteria for the patients, interventions and comparators and outcomes of interest were reported upfront and in detail. The details of BRV dosing, and the details of switching from LEV to BRV were clearly described. The study was conducted across several centers in the US, France, Germany and Spain. The facilities and treatment received by the patients were likely to be representative of the treatment majority of patient population would receive.

However, the study had several limitations.⁸ The study was conducted as an open label trial without blinding of patients or outcome assessors. It is possible that the self-reporting of behavioral adverse events was affected by subjective reporting by patients after switching to the new drug (BRV). The primary outcome of the study was assessed by the investigators as a “clinically meaningful reduction in BAE”. The definition of clinically meaningful reduction was unclear and the subjective assessment by investigators could introduce bias. The rationale regarding how these decisions were made was not reported. Similarly, for the other outcome “shift in maximum intensity” of BAE, the definition, criteria for each level of intensity and decision rationale were unclear. Among the patient population eligible, it was unclear how many patients were eligible and did not participate. It is possible that the patients who participated in the study were different from those who were eligible but did not participate. There was no random selection of participants. The study was exploratory in nature with only descriptive reporting of the outcomes before and after switch. No statistical analyses were conducted. Therefore, it is unclear whether the findings of the study were statistically significant. The participants were followed up for a relatively short time (12 weeks). When considering safety outcomes, it is possible that some adverse events could not occur within a short period of initiation of treatment. Lastly, the study was funded by pharmaceutical company that manufactured BRV, and most of the authors were employees of the company. This poses a potential conflict of interest and it was unclear from the publication what steps were taken to mitigate that risk.

The nine^{9,11-18} other included observational studies shared several strengths and limitations. All of them enrolled all eligible participants from the study centers (four single center,^{11,12,14,17} five multi center^{9,13,15,16,18}) providing ‘real world’ data from the participating clinics. The facilities and treatment received were representative of the treatment that the general patient population would receive. The studies did not have strict inclusion and exclusion criteria. Baseline characteristics of the participants were reported in adequate

details and included demographics, duration and type of epilepsy, and use of other concurrent medications. Eight studies^{9,11-13,15-18} described the objectives of the study clearly, and reported the outcomes of interest upfront. The details of BRV therapy (e.g., dose) and that of switching from LEV to BRV (e.g., titration, overnight versus gradual switch) were described in all nine studies.^{9,11-18}

The studies were not without limitations. All nine studies were observational in design with no random selection or blinding.^{9,11-18} All studies were of single arm, and patients were selected based on BRV treatment status. Adverse events during BRV treatment were then compared to those during LEV treatment prior to the study (at baseline before switch or during previous treatment with LEV). Safety outcomes of the study were self-reported either during interviews at clinic visits or extracted from previous medical records (about BAE with previous LEV use). This could increase the risk of recall bias and underreporting. All eight studies had a large proportion of patients, if not all, who were receiving concomitant treatment with other AEDs. It is possible that these concomitant medications could result in adverse events similar to those of interest and thus affect study findings. The results relevant to this report from all observational studies were obtained from subgroup analyses.^{9,11-18} Seven studies^{9,11-16} reported their findings in the form of numerical comparisons and descriptive analyses. No statistical tests were performed. This could lead to uncertainty of the true effect and significance of the results. In another two studies,^{17,18} as the results were from subgroup analyses, it is possible that there was a risk of type 1 error due to multiple testing. In one study, even though statistical significance and p values were reported, effect estimates, and confidence intervals were not reported along with simple outcome data.¹⁸ This made the interpretation of the results challenging and created uncertainty regarding their validity. The characteristics of patients who had previous exposure to LEV (switch or past treatment) were not compared to LEV naïve patients in any of the studies.^{9,11-18} It is possible that these patients were different from each other and thus affecting study outcomes. The number of patients lost to follow up were not reported in five studies.^{12,14,16-18} In two studies, more than a quarter of participants discontinued from the study.^{9,13} It was unclear whether the patients whose data was not available were different from this group as it was not reported. Lastly, authors of eight studies declared conflicts of interests related to pharmaceutical companies.^{9,11,13-18} It was unclear whether the findings of the study were affected by this or what steps were taken by the study authors to address this.

Overall, all included publications had limitations arising from non-randomized study design, subjective reporting of outcomes, limited clinical relevance of study findings due to the nature of descriptive analysis, reporting issues and potentially important conflicts of interest. None of the studies were conducted in Canada, making the generalizability to Canadian settings unclear.^{8,9,11-18}

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Appendix 4 presents the main study findings and authors' conclusions.

Clinical safety of brivaracetam versus levetiracetam in people with epilepsy with mental health conditions

Aggressive symptoms associated with LEV

One study reported that, among patients with pre-existing psychiatric or behavioral conditions (n = 73), more patients reported improvement of previous aggression with initiation of BRV (n = 13) than those who did not improve (n = 11).¹² Six patients reported new occurrence of aggression on BRV. Similarly, in patients with pre-existing intellectual disabilities, more patients reported improvement of previous aggression with BRV. However, no comparative statistical analyses were conducted.

Depressive symptoms associated with LEV

In one study, five patients (out of seven) who switched from LEV to BRV due to worsening of depressive symptoms had pre-existing depression.¹² Among them, three patients improved on BRV and two reported worsening of symptoms. However, the quality of evidence were low due to a small sample size (n = 7) and lack of statistical comparisons.

Clinical safety of brivaracetam in people with epilepsy with mental health symptoms related to levetiracetam treatment.

Overall psychiatric or behavioral AE associated with LEV:

Findings from nine included studies regarding overall psychiatric or behavioral AE on LEV suggested an improvement in BAE with BRV treatment.

Results from two studies^{17,18} showed that there was a statistically significant decrease in the occurrence of psychiatric or behavioral AE with BRV compared to prior LEV treatment. One study conducted among children and adolescents with epilepsy found that, out of 15 patients who experienced BAE while on LEV, only one patient continued to experience them after treatment with BRV (p < 0.001).¹⁸ The other study conducted in adults found that there were significantly fewer BAEs reported during treatment with BRV compared to during LEV treatment, either with previous LEV treatment (n = 15; p < 0.001, M₁ = 1.47, SD₁ = 0.74; M₂ = 0.2, SD₂ = 0.56; p < 0.001) or with direct switching from LEV to BRV (n = 31; M₁ = 1.26, SD₁ = 0.63; M₂ = 0.39, SD₂ = 0.67; p < 0.001).¹⁷

Results from one pre-post study⁸ showed that majority of patients who switched from LEV to BRV due to BAE had a “clinically meaningful reduction in BAE” and a reduction in the maximum intensity of BAE at the end of the treatment period. Out of 29 patients, 69% (n = 20) showed marked or moderate improvement in BAE (measured using I-GEBSE). Two patients had worsening of BAE on BRV. At the end of treatment period, 62.1% of patients reported complete freedom from BAE. However, the results were reported descriptively, and no statistical analyses were done.

Descriptive results from six studies also showed that majority of patients experiencing BAE on LEV reported improvement with BRV treatment.^{9,11-13,15,16} The proportion of patients reporting improvement in BAE after treatment with BRV ranged from 73%¹¹ to 83%.^{13,15}

Aggressive symptoms associated with LEV

Three studies reported descriptive results on the occurrence of aggressive symptoms with BRV treatment.^{12,14,17}

In one study, among 44 patients who experienced aggressive symptoms while on LEV, 27 patients (61%) reported no symptoms while on BRV, and 17 patients (39%) continued to

report similar symptoms.¹² Of note, among 90 patients who did not report aggressive symptoms while on LEV, 14 (16%) patients experienced them while on BRV.¹²

Hirsch et al.¹⁴ found that, with BRV treatment, occurrence of irritability and aggressive symptoms decreased in patients who switched from LEV to BRV as well as in those with previous exposure to LEV. Similarly, Zahnert et al.¹⁷ also found a decrease in aggressive symptoms after direct switch from LEV to BRV at baseline.

Depressive symptoms associated with LEV

Three studies reported descriptive results on the occurrence of depressive symptoms with BRV treatment.^{12,14,17}

Hirsch et al. found that, in patients who switched from LEV to BRV as well as in those with previous exposure to LEV, occurrence of depression, mood lability and fear decreased on BRV treatment.¹⁴ Among patients who directly switched from LEV to BRV at the study baseline, a decrease in depressive symptoms was observed in two studies.^{12,17}

Other behavioral AE associated with LEV

Zahnert et al.¹⁷ reported the number of patients reporting specific behavioral AE before and after switch from LEV to BRV. Compared to LEV treatment at baseline, informal numerical comparisons showed that fewer or no patients reported symptoms of irritability, agitation, psychosis, listlessness and anxiety while on BRV. There were no occurrences of lability of affect or hysteria while on LEV or BRV. No statistical analysis was performed.

Limitations

No relevant systematic reviews or head-to head randomized controlled trials were identified in the search. For the outcome overall psychiatric or behavioral AEs, all except two studies provided descriptive results only. Out of the two studies that statistically compared the groups regarding overall BAEs, reporting issues (no effect sizes or confidence intervals were reported) made the interpretation of results challenging. For all other outcomes, (e.g. aggressive symptoms, depressive symptoms) no statistical comparisons between BRV and LEV were conducted in the included studies. BAEs were self-reported by the patients, either during current BRV treatment or from history (for BAEs occurred during previous LEV treatments). This could lead to underreporting and affect the study results. Overall, due to the limited quality of included studies, such as observational study design, concomitant treatment with other AEDs, and potential conflicts of interests, the quality of evidence summarized in this report was low to moderate. At this time, BRV is approved for use in Canada in patients with partial onset seizures. As none of the included studies were conducted among patients only with partial onset seizures and none of the studies reported results grouped by the type of epilepsy, the implications of these results in a Canadian setting was unclear.

Conclusions and Implications for Decision or Policy Making

Ten single-arm nonrandomized studies were included in this research; one interventional study with a pre-post design⁸ and nine observational studies.^{9,11-18} No systematic reviews or head-to-head randomized controlled trials were identified.

The findings from one study indicated that, in patients with epilepsy with psychiatric comorbidities, BRV treatment could improve psychobehavioral adverse events such as

aggression and depressive symptoms associated with previous LEV treatment.¹² However, because of a small number of patients (n = 7) and descriptive nature of the results, the quality of evidence was low.

Among patients with epilepsy with mental health symptoms associated with previous LEV treatment, findings from the included studies suggested that switching to BRV could be beneficial in improving BAEs. One study conducted among pediatric and adolescent patients¹⁸ and another among adults¹⁷ found statistically significant decrease in the prevalence of overall BAE while on BRV treatment compared to that during LEV treatment. Descriptive results from seven other studies^{9,11-16} also indicated an improvement in BAE with BRV treatment. However, considering the limitations of the studies such as, non-randomized study design, concomitant treatment with other AEDs, subjective reporting of BAEs and potential conflicts of interests, the evidence was of low-to-moderate quality with low generalizability to other settings.

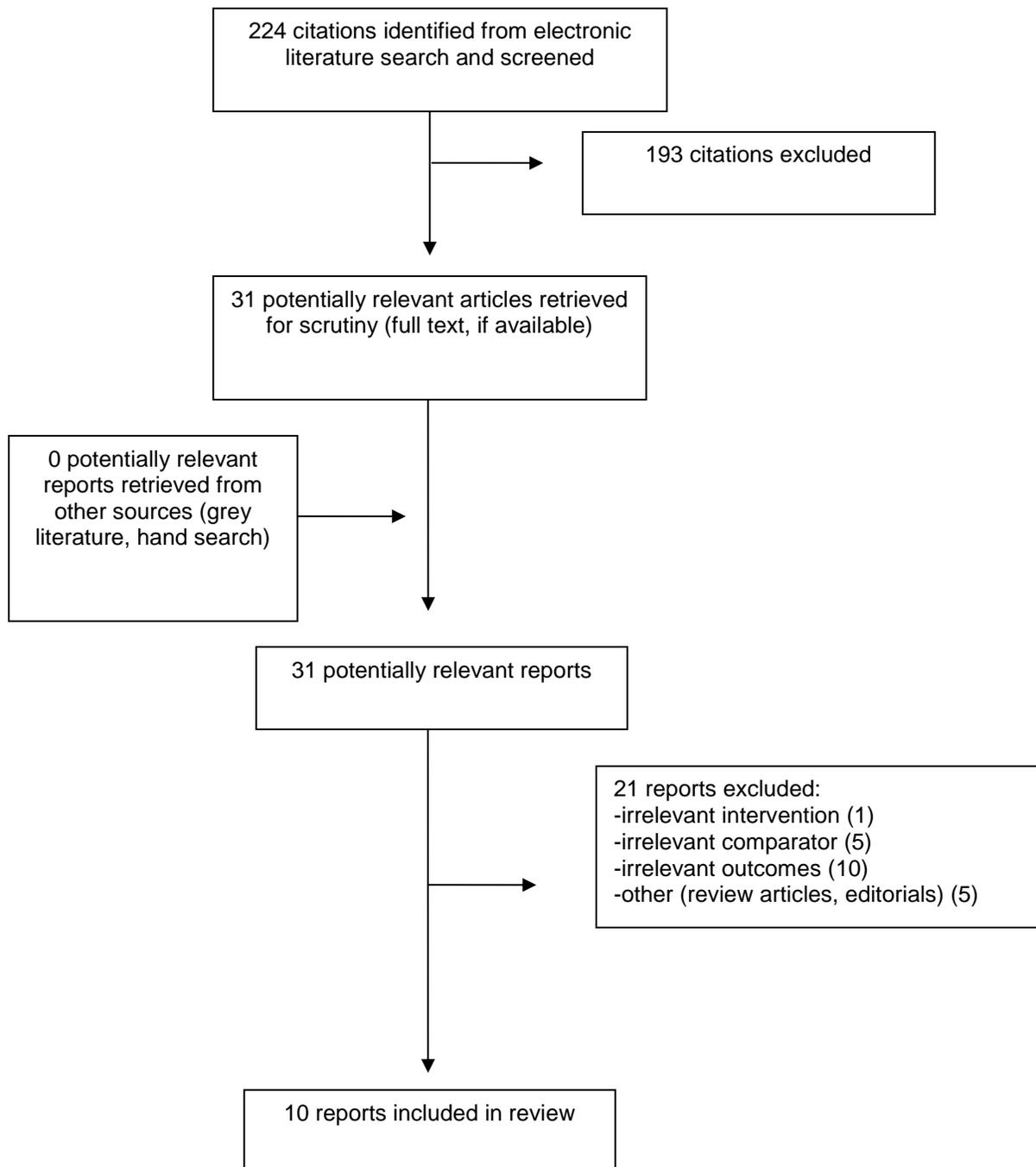
Descriptive results from three studies also showed improvement in specific BAEs associated with previous LEV treatment including aggression, depressive symptoms and irritability.

The main limitation of this report is the lack of comparative head to head trials between LEV and BRV, which has been pointed out by others in the literature.^{3,20} Most of the included studies provided only descriptive results, leading to uncertainty in interpreting true effect of the results. At this time, BRV is approved for use in Canada in patients with partial onset seizures.^{4,5} As none of the included studies were conducted among patients only with partial onset seizures and none of the studies reported results grouped by the type of epilepsy, the implications of these results in a Canadian setting was unclear. To conclude, limited quality descriptive evidence from the included studies suggest that psychiatric and behavioral adverse events associated with LEV treatment could be improved by switching to BRV. Well-designed randomized controlled with head to head comparisons, or well-designed pre-post studies with a large and adequate sample sizes are warranted to provide conclusive evidence on the comparative safety of BRV and LEV.

References

1. Moshé SL, Perucca E, Ryvlin P, Tomson T. Epilepsy: new advances. *Lancet*. 2015;385(9971):884-898.
2. Public Health Agency of Canada. Epilepsy in Canada. 2018; <https://www.canada.ca/en/public-health/services/publications/diseases-conditions/epilepsy.html>. Accessed 2020 Nov 23.
3. Feyissa AM. Brivaracetam in the treatment of epilepsy: a review of clinical trial data. *Neuropsychiatr Dis Treat*. 2019;15:2587-2600.
4. Health Canada. Summary Basis of Decision (SBD) for Brivlera. 2016; <https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00284>. Accessed 2020 Nov 23.
5. Common Drug Review: Clinical review report. Brivaracetam (Brivlera). Ottawa (ON): CADTH; 2017: https://cadth.ca/sites/default/files/cdr/clinical/SR0484_Brivlera_CL_Report.pdf. Accessed 2020 Nov 23.
6. Zhang L, Li S, Li H, Zou X. Levetiracetam vs. brivaracetam for adults with refractory focal seizures: A meta-analysis and indirect comparison. *Seizure*. 2016;39:28-33.
7. Niespodziany I, Rigo J-M, Moonen G, Matagne A, Klitgaard H, Wolff C. Brivaracetam does not modulate ionotropic channels activated by glutamate, γ -aminobutyric acid, and glycine in hippocampal neurons. *Epilepsia*. 2017;58(11):e157-e161.
8. Yates SL, Fakhoury T, Liang W, Eckhardt K, Borghs S, D'Souza J. An open-label, prospective, exploratory study of patients with epilepsy switching from levetiracetam to brivaracetam. *Epilepsy Behav*. 2015;52(Pt A):165-168.
9. Steinig I, von Podewils F, Moddel G, et al. Postmarketing experience with brivaracetam in the treatment of epilepsies: A multicenter cohort study from Germany. *Epilepsia*. 2017;58(7):1208-1216.
10. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377-384.
11. Fonseca E, Guzman L, Quintana M, et al. Efficacy, retention, and safety of brivaracetam in adult patients with genetic generalized epilepsy. *Epilepsy Behav*. 2020;102:106657.
12. Foo EC, Geldard J, Peacey C, Wright E, Eltayeb K, Maguire M. Adjunctive brivaracetam in focal and generalized epilepsies: A single-center open-label prospective study in patients with psychiatric comorbidities and intellectual disability. *Epilepsy Behav*. 2019;99:106505.
13. Villanueva V, Lopez-Gonzalez FJ, Mauri JA, et al. BRIVA-LIFE-A multicenter retrospective study of the long-term use of brivaracetam in clinical practice. *Acta Neurol Scand*. 2019;139(4):360-368.
14. Hirsch M, Hintz M, Specht A, Schulze-Bonhage A. Tolerability, efficacy and retention rate of brivaracetam in patients previously treated with levetiracetam: A monocenter retrospective outcome analysis. *Seizure*. 2018;61:98-103.
15. Strzelczyk A, Kay L, Bauer S, et al. Use of brivaracetam in genetic generalized epilepsies and for acute, intravenous treatment of absence status epilepticus. *Epilepsia*. 2018;59(8):1549-1556.
16. Willems LM, Bertsche A, Bosebeck F, et al. Efficacy, retention, and tolerability of brivaracetam in patients with epileptic encephalopathies: A multicenter cohort study from Germany. *Front Neurol*. 2018;9:569.
17. Zahnert F, Krause K, Immisch I, et al. Brivaracetam in the treatment of patients with epilepsy-first clinical experiences. *Front Neurol*. 2018;9:38.
18. Schubert-Bast S, Willems LM, Kurlemann G, et al. Postmarketing experience with brivaracetam in the treatment of focal epilepsy in children and adolescents. *Epilepsy Behav*. 2018;89:89-93.
19. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-e34.
20. Steinhoff BJ, Staack AM. Levetiracetam and brivaracetam: a review of evidence from clinical trials and clinical experience. *Ther Adv Neurol Disord*. 2019;12:1756286419873518.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
<p>Fonseca et al., 2020¹¹</p> <p>Country: Spain</p> <p>Funding source: Non-funded</p>	<p>Study design: Retrospective observational study</p>	<p>Population: Patients with genetic generalized epilepsy</p> <p>Inclusion criteria: Minimum follow up of 6 months</p> <p>Exclusion criteria: patients without a definite diagnosis or those with other conditions that could have similar outcome.</p> <p>Number of participants: 37</p> <p>Relevant population: Patients with previous exposure to LEV</p> <p>Number of participants in the relevant analytical sample: Previous LEV exposure, n = 31 LEV naïve, n = 6</p> <p>Age of patients, mean (SD): 29.9 years (12.3)</p> <p>Sex of the patients: 27 % males</p> <p>Patients with psychiatric comorbidity, n (%): Not reported.</p>	<p>Intervention: Brivaracetam Daily dose, mean (135.1mg (79.2) Duration of treatment, mean (SD): 10.4 months (7.1)</p> <p>Comparator: Previous treatment with LEV</p> <p>25 patients (67.6%) received concomitant treatment with other AEDs (Lamotrigine, clobazam and valproate)</p>	<p>Study outcome: proportion of responders, seizure free rate, change in EEG, TEAE</p> <p>Relevant outcome: psychiatric/behavioral adverse events.</p> <p>Length of follow up: 6 months</p>
<p>Foo et al., 2019¹²</p> <p>Country: UK</p> <p>Funding source: Non-funded</p>	<p>Study design: Prospective observational study</p>	<p>Population: Patients ≥ 16 years of age with drug-resistant focal or generalized epilepsy.</p> <p>Exclusion criteria: not reported</p> <p>Number of participants, n =134</p> <p>Relevant population: Patients with previous exposure to LEV or those who switched from LEV therapy to BRV.</p> <p>Number of participants in the relevant analytical sample: Switch from LEV to BRV during study, n = 63 Previous LEV exposure, n = 71</p> <p>Age of the patients, mean (range):</p>	<p>Intervention: Brivaracetam Dose, median (range) = 200 mg (50 to 200 mg)</p> <p>Comparator: Levetiracetam (gradual switch)</p> <p>All patients received concomitant treatment with at least one other AEDs such as, Carbamazepine, valproate and Lamotrigine.</p>	<p>Study outcome: Proportion of responders, proportion of the seizure free, proportion of withdrawers, TEAE</p> <p>Relevant outcome: Behavioral adverse events such as aggression, depressive symptoms and sleep disruption.</p> <p>Length of follow up: 26 months</p>

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		<p>40 years (17 to 71 years)</p> <p>Sex of the patients, n (%) : 57 (42.5%) males</p> <p>Patients with psychiatric comorbidity: 54%</p>		
<p>Villanueva et al.,¹³ 2019 (BRIVA-LIFE)</p> <p>Country: Spain</p> <p>Funding source: University of Francisco de Vitoria (NIF-G-80480197) Madrid, Spain</p>	<p>Study design: Multicenter Retrospective observational study</p>	<p>Patients ≥ 16 years of age with focal epilepsy.</p> <p>Exclusion criteria: History of alcoholism or drug abuse in the year prior to the study, participation in other studies of antiepileptic drugs or medical devices.</p> <p>Total number of participants, N = 575</p> <p>Relevant population: Patients switching from LEV therapy to BRV during the study</p> <p>Number of participants in the relevant analytical sample: Switch from LEV to BRV during study, n = 223 Previous exposure to LEV, n = 419 LEV naïve, n = 106</p> <p>Age of patients, mean (range) = 41.9 years (16 to 88 years)</p> <p>Sex of the patients: 50.4% males</p> <p>Patients with psychiatric comorbidity: 244 (44.2%)</p>	<p>Intervention: Brivaracetam therapy Dose, mean (SD) = 66.9 (47) mg</p> <p>Comparator: Switch from LEV to BRV LEV dose at BRV initiation, mean (SD) = 1904.7 mg/day (823.6) Overnight switch in 81 patients, overlapping transition in 142 patients (over mean 21.5 days).</p> <p>All patients received concomitant treatment with other AEDs at baseline (median 3, IQR 2 to 3 such as LEV, Carbamazepine and Lamotrigine)</p>	<p>Study outcome: Seizure freedom, Proportion of responders, percentage seizure reduction and safety (Adverse events, discontinuations)</p> <p>Relevant outcome: Psychiatric adverse events</p> <p>Length of follow up: 12 months, with study visits at 3, 6 and 12 months.</p>
<p>Hirsch et al.,¹⁴ 2018</p> <p>Country: Germany</p> <p>Funding source: Not reported</p>	<p>Study design: Retrospective observational study</p>	<p>Patients between 11 and 70 years of age with epilepsy and was treated with BRV</p> <p>Inclusion criteria: availability of information 3 months prior to initiation of BRV and 6 months after initiation of BRV</p> <p>Exclusion criteria: None reported</p>	<p>Intervention: BRV Starting dose, mean (SD) = 116.4 mg (71) Final dose, mean (SD) = 153.2 mg (74.8)</p> <p>Comparator: 1)Switch from LEV to BRV 2) previous exposure to LEV</p>	<p>Study outcome: seizure frequency, responder rate, TEAE</p> <p>Relevant outcome: BAE</p> <p>Length of follow up: 6 months.</p>

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		<p>Number of participants : 102</p> <p>Relevant population: Patients with previous exposure to LEV or those who switched from LEV therapy to BRV.</p> <p>Number of participants in the relevant analytical sample: Switch from LEV to BRV, n = 62 Previous LEV exposure, n = 40</p> <p>Age of patients, mean(SD) = 42.5 years (15.8)</p> <p>Mean sex: 48 % males</p> <p>Patients with psychiatric comorbidity: 49 (48%)</p>	<p>Number of concomitant AED, mean = 1.6 (SD 1.9)</p>	
<p>Schubert-Bast et al., 2018¹⁸</p> <p>Country: Germany</p> <p>Funding source: Non-funded</p>	<p>Study design: Retrospective observational study (strobe)</p>	<p>Children and adolescents of age ≤ 17 years with focal epilepsy and was treated with BRV</p> <p>Inclusion criteria: Received at least one dose of BRV</p> <p>Exclusion criteria: None reported</p> <p>Number of participants : 34</p> <p>Relevant population: Patients with previous exposure to LEV or those who switched from LEV therapy to BRV.</p> <p>Number of participants in the relevant analytical sample: Switch from LEV to BRV, n = 20 Previous LEV exposure, n = 6 LEV naïve, n = 8</p> <p>Age of patients, mean(SD) = 12.2 years (4.2)</p> <p>Mean sex: 44.1 % males</p> <p>Patients with psychiatric comorbidity, n (%): Not reported</p>	<p>Intervention: BRV Starting dose, range = 10mg to 200 mg Target dose, range = 50 mg to 300 mg achieved in median 7 days time.</p> <p>Comparator: 1)Switch from LEV to BRV Median ratio of switch: 10:1 (range 5:1 to 25:1) 2) previous exposure to LEV</p> <p>Number of concomitant AED, median= 1 (range 1 to 3)</p>	<p>Study outcome: Retention, responder rate, seizure-free patients, TEAE</p> <p>Relevant outcome: psychobehavioral AE</p> <p>Length of follow up: 12 months, with study visits at 3, 6 and 12 months.</p>
<p>Strzelczyk et al., 2018¹⁵</p>	<p>Study design: Multicenter Retrospective</p>	<p>Patients with genetic generalized epilepsy</p>	<p>Intervention: BRV Starting dose, mean 65 mg (SD 29.8) Target</p>	<p>Study outcome: Drug retention, proportion of 50% responders,</p>

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
<p>Country: Germany</p> <p>Funding source: Non-funded</p>	observational study	<p>who received at least on dose of BRV</p> <p>Inclusion criteria: Received at least one dose of BRV Exclusion criteria: Not reported</p> <p>Number of participants : 61</p> <p>Relevant population: Patients with previous exposure to LEV or those who switched from LEV therapy to BRV during the study</p> <p>Number of participants in the relevant analytical sample: Switch from LEV to BRV during study, n = 31 LEV naïve, n = 30</p> <p>Age of patients, mean(SD) = 29.8 years (15.8) Twelve patients were < 18 years old.</p> <p>Mean sex: 32.7 % males</p> <p>Patients with psychiatric comorbidity, n (%): Not reported</p>	<p>dose, mean = 134.2 mg, SD = 54.3) achieved in median 7 days time.</p> <p>Comparator: Switch from LEV to BRV Median ratio of switch: 15:1 (range 7:1 to 40:1) Overnight switch in 26 patients, overlapping transition in 5 patients.</p> <p>Number of concomitant AEDs, median= 2 (range 1 to 4)</p>	<p>seizure frequency, TEAE</p> <p>Relevant outcome: psychobehavioral TEAE</p> <p>Length of follow up: 12 months, with study visits at 3, 6 and 12 months.</p>
<p>Willems et al.,2018¹⁶</p> <p>Country: Germany</p> <p>Funding source: Non-funded</p>	<p>Study design: Multicenter Retrospective observational study (STROBE)</p>	<p>Patients with epileptic encephalopathies who received at least on dose of BRV</p> <p>Number of participants: 44</p> <p>Relevant population: Patients with previous exposure to LEV or those who switched from LEV therapy to BRV during the study</p> <p>Number of participants in the relevant analytical sample: Switch from LEV to BRV during study, n = 24 Previous LEV exposure, n =13 LEV naïve, n = 7</p> <p>Age of patients, mean (SD) = 28.3 years (14.5) Nine patients were < 18 years old.</p>	<p>Intervention: BRV Starting dose, mean 66.3 mg (SD 26.0) Target dose, mean = 138.5 mg, SD = 50.6) achieved in median 6 days time.</p> <p>Comparator: 1)Switch from LEV to BRV Median ratio of switch: 15:1 (range 5:1 to 50:1) Mean dose 122.1mg (SD 72.1) Target dose, mean = 175.2 mg, SD = 70.1) Overnight switch in 21 patients, overlapping transition in 3 patients. 2) previous exposure to LEV</p>	<p>Study outcome: Retention, Responder rate, seizure free patients, TEAE</p> <p>Relevant outcome: psychobehavioral TEAE</p> <p>Length of follow up: 12 months, with study visits at 3, 6 and 12 months.</p>

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		<p>Mean sex: 61.4% males</p> <p>Patients with psychiatric comorbidity, n (%): Not reported</p>	<p>Number of concomitant AEDs, median= 2 (range 1 to 4)</p>	
<p>Zahnert et al., 2018¹⁷</p> <p>Country: Germany</p> <p>Funding source: Not reported</p>	<p>Study design: Retrospective observational study</p>	<p>Patients with epilepsy</p> <p>Inclusion criteria: at least one clinical follow-up data available</p> <p>Exclusion criteria: None reported</p> <p>Number of participants, N = 93</p> <p>Relevant population: Patients with previous exposure to LEV or those who switched from LEV therapy to BRV during the study</p> <p>Number of participants in the relevant analytical sample: Switch from LEV to BRV during study, n = 47 Previous LEV exposure, n = 87 LEV naïve, n = 6</p> <p>Age of patients, mean (SD) = 43.9 (17.3)</p> <p>Mean sex: 62.4% males</p> <p>Patients with psychiatric comorbidity, n (%): 42 (45.2%)</p>	<p>Intervention: BRV Daily dose, n: 50 mg, n = 26 100 mg, n = 55 150 mg, n = 4 200 mg, n = 8</p> <p>Comparator: 1) Switch from LEV to BRV Overnight switch in 43 patients, overlapping transition in 4 patients. 2) previous exposure to LEV</p> <p>81 patients (87%) received concomitant treatment with other AEDs including Lamotrigine, Lacosamide and valproate</p>	<p>Study outcome: Responder rates, seizure frequencies, adverse events</p> <p>Relevant outcome: Behavioral AE including psychiatric AE such as depression and anxiety.</p> <p>Length of follow up: 6 months, with study visits at 3 and 6 months.</p>
<p>Steinig et al., 2017⁹</p> <p>Country: Germany</p> <p>Funding source: Non-funded</p>	<p>Study design: Retrospective observational study</p>	<p>Patients with epilepsy (ILAE definition)</p> <p>Exclusion criteria: Lack of follow up data</p> <p>Number of participants, N = 262</p> <p>Relevant population: Patients with previous exposure to LEV or those who switched from LEV therapy to BRV during the study</p> <p>Number of participants in the relevant analytical sample: Switch from LEV to BRV during study, n = 133 Previous LEV exposure, n = 103</p>	<p>Intervention: BRV Starting dose, mean (SD) = 55.8 mg (27.7) Target dose, mean (SD) = 128.1 mg (49.2) achieved in median 7 days time.</p> <p>Comparator: Switch from LEV to BRV Median ratio of switch: 15:1 (range 2:1 to 40:1) Mean starting dose 125.5 mg (SD 77.9) Target dose, mean = 175.7 mg, (SD 60.0)</p>	<p>Study outcome: Retention rates, seizure freedom, responder rates, TEAE</p> <p>Relevant outcome: psychobehavioral TEAE</p> <p>Length of follow up: 12 months, with study visits at 3, 6 and 12 months.</p>

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		<p>LEV naïve, n = 26</p> <p>Age of patients, mean (SD) = 40.0 years (16) Nine patients were < 18 years old.</p> <p>Mean sex: 49.2% males</p> <p>Patients with psychiatric comorbidity, n (%): Not reported</p>	<p>Overnight switch in 105 patients, overlapping transition in 28 patients. 2) previous exposure to LEV</p> <p>All patients received concomitant treatment with other AEDs (median two at baseline) such as LEV, lamotrigine, lacosamide and valproate</p>	
<p>Yates et al., 2015⁸</p> <p>Country: USA and Europe (France, Germany and Spain)</p> <p>Funding source: UCB Pharma</p>	<p>Study design: Phase 3b, open label, single arm prospective multicenter study (pre-post measurements)</p>	<p>Patients ≥ 16 years of age with partial onset seizure or primary generalized epilepsy.</p> <p>Inclusion criteria: patients receiving LEV (1-3 g/day) in whom discontinuation of LEV was warranted within 16 weeks of initiation because of BAEs. Patients should also have been receiving 2-3 AEDs including LEV in doses which were stable for ≥ 4 weeks.</p> <p>Exclusion criteria: Cluster or flurry seizures, history of psychogenic nonepileptic seizures, status epilepticus during the year prior; patients receiving LEV for > 16 weeks; rapidly progressing brain disorder, brain tumor, or other serious uncontrolled disease.</p> <p>Number of participants, n = 29</p> <p>Number of participants in the relevant analytical sample, n = 29</p> <p>Age of patients, mean (SD) = 35.8 (11.8)</p> <p>Mean sex: 51.7% males</p> <p>Patients with psychiatric comorbidity, n (%): Not reported</p>	<p>Intervention: BRV Initial dose 100 mg (twice daily) in the evening following last dose of LEV in the morning. No titration.</p> <p>Comparator: Switch from LEV to BRV LEV: (1-3 g/day) for up to 16 weeks.</p> <p>Study process: Screening period of ≤ 1 week, followed by a retrospective baseline period (4 weeks to record Seizure frequency on LEV, 16 weeks to record BAEs on LEV)</p>	<p>Relevant study outcomes: clinically meaningful reduction in BAE (physician assessed); change in intensity of BAE (investigator assessed); Investigator Global Evaluation of Behavioral Side Effects (I-GEBSE); freedom from BAE, TEAE, withdrawal due to BAE, and serious adverse events.</p> <p>Other secondary outcomes: seizure frequency, seizure days, seizure freedom, health related quality of life (patient and investigator assessed)</p> <p>Length of follow up: 12 weeks</p>

AE = adverse events; AED = antiepileptic drug; BAE = behavioral adverse events; BRV = brivaracetam; EEG = electroencephalogram; LEV = levetiracetam; SD = standard deviation; TEAE = treatment emergent adverse events

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist¹⁰

Strengths	Limitations
Fonseca et al., 2020¹¹	
<ul style="list-style-type: none"> • The objectives of the study were clearly described. • The main outcomes to be measured were reported upfront and defined clearly. • Baseline characteristics of the participants were reported in detail. • One patient (2.6%) dropped out of the study. The study analysis was conducted after excluding data from this participant. • Study participants were recruited from one center over the same period. The facilities and treatment received were representative of the treatment majority of patients might receive. 	<ul style="list-style-type: none"> • The study was retrospective observational in design without random selection or concealment of allocation. • All patients in the study were given other antiepileptic medications throughout the study. It is possible that these concomitant medications could lead to confounding bias by affecting the study outcomes and adverse events. • The authors reported only numerical values of patients who had the outcome relevant to the current report. These results were exploratory in nature and had low clinical relevance. • It is unclear whether the authors performed sample size calculations to ensure adequate power. • The study had a relatively short follow time of 6 months. The TEAE that occurred after that period would not be captured in the study.
Foo et al., 2019¹²	
<ul style="list-style-type: none"> • The objectives of the study were clearly described. • The main outcomes to be measured were reported upfront and defined clearly. • Baseline characteristics of the participants were reported in detail. The selection criteria was kept broadly increasing the generalizability of the results. • When probability values were reported, actual p values were used rather than just indicating statistical significance. • All patients who were eligible were enrolled in the study (no random selection). The facilities and treatment received were representative of the treatment majority of patients might receive. • The authors had no conflict of interests to declare. 	<ul style="list-style-type: none"> • The study was prospective observational in design without random selection or concealment of allocation. • All patients in the study were given other antiepileptic medications throughout the study. It is possible that these concomitant medications could lead to confounding bias by affecting the study outcomes and adverse events. • It was unclear whether the baseline characteristics and use of concomitant antiepileptic drugs were different in patients with pre-existing psychiatric or behavioral disorder compared to those without. It is possible that the groups were different from each other. • Similarly, baseline characteristics of patients with and without intellectual disabilities were not compared and reported. • It was unclear whether the patients who switched from LEV to BRV during the study were different from those who did not. • For the results relevant to this report (psychiatric adverse events), only numerical comparison of the outcomes between the groups were reported. No statistical tests were done. • Simple outcome data of the outcomes that were comparatively analyzed were not reported. For the results of chi square tests, the test statistic or degrees of freedom were not reported. • It is unclear if and how many patients were lost to follow up during the study period.

Strengths	Limitations
Villanueva et al., 2019¹³	
<ul style="list-style-type: none"> • The objectives of the study were clearly described. • The main outcomes to be measured were reported upfront and defined clearly. • Baseline characteristics of the participants were reported in detail. • The reason for switching from LEV to BRV (low efficacy, AE or both) as well as the details of switching (dose and transition) were reported. • Simple numerical data for the outcomes relevant to this report were described. • All patients who met the inclusion criteria were enrolled in this retrospective study. Study participants were recruited from 18 centers over the same period. The facilities and treatment received were representative of the treatment majority of patients might receive. These increased the generalizability of the results. • 	<ul style="list-style-type: none"> • The study was retrospective observational in design without random selection or concealment of allocation. • All patients in the study were given other antiepileptic medications throughout the study. It is possible that these concomitant medications could affect the study outcomes and adverse events. • For the results relevant to this report (psychiatric adverse events), only numerical comparison of the outcomes between the groups were reported. No statistical tests were done. • The types of psychiatric adverse events (e.g., aggression, depression) and their frequencies were not reported separately. • 170 (29.5%) of the study participants were discontinued from the study due to lack of efficacy, AE or both. Though these patients were included in the safety analyses, their characteristics were not reported. Thus, it was unclear whether the patients who discontinued BRV were different from those who did not. • Some subgroup analyses (age, stroke status etc.) were not described upfront, making it unclear whether they were planned a priori. • It was unclear whether a sample size calculation was done a priori to ensure adequate power. • Several coauthors declared conflicts of interest related to pharmaceutical companies. It was unclear whether these affected the results of this study.
Hirsch et al., 2018¹⁴	
<ul style="list-style-type: none"> • Baseline characteristics of the participants were reported in detail. • The details of intervention such as starting dose and final doses of BRV were reported. • All patients who met the inclusion criteria were enrolled in this retrospective study. Study participants were recruited from a center in Germany over the same period. The facilities and treatment received were representative of the treatment majority of patients might receive. These increased the generalizability of the results • Simple outcome data of psychiatric AE in patients who switched from LEV to BRV and with previous LEV exposure were reported. 	<ul style="list-style-type: none"> • The objectives of the study were not clearly described. • The study was retrospective observational in design without random selection or concealment of allocation. • The main outcomes to be measured were reported upfront and defined clearly. • It was unclear how many patients in the study were receiving concomitant AEDs (mean number was 1.6) It is possible that these concomitant medications could affect the study outcomes and adverse events. • For the results relevant to this report (psychiatric adverse events), only descriptive results of the outcomes between the groups were reported. No statistical tests were done. • It was unclear how many patients were lost to follow up. • It was unclear whether a sample size calculation was done a priori to ensure adequate power. • Several coauthors declared conflicts of interest related to pharmaceutical companies. It was unclear whether these affected the results of this study.
Schubert-Bast et al., 2018¹⁸	
<ul style="list-style-type: none"> • The objectives of the study were clearly described. • The main outcomes to be measured were reported upfront and defined clearly. 	<ul style="list-style-type: none"> • The study was retrospective observational in design without random selection or concealment of allocation.

Strengths	Limitations
<ul style="list-style-type: none"> Baseline characteristics of the participants were reported in detail. The details of intervention such as titration ratio, starting doses and final doses of BRV were reported. All patients who met the inclusion criteria were enrolled in this retrospective study. Study participants were recruited from four centers in Germany over the same period. The facilities and treatment received were representative of the treatment majority of patients might receive. These increased the generalizability of the results. Simple outcome data of psychiatric AE in patients who switched from LEV to BRV and with previous LEV exposure were reported. 	<ul style="list-style-type: none"> All patients in the study were given other antiepileptic medications throughout the study (median 1). It is possible that these concomitant medications could affect the study outcomes and adverse events. For the outcome relevant to this report (psychobehavioral AE) the results were reported only on its statistical significance. Results of comparative analysis including effect sizes and confidence intervals were not reported. It was unclear which statistical methods were used to compare the groups. The authors reported that different types of TEAE (e.g., agitation, depression, anxiety) were collected and recorded in detail during the study. However, the occurrences of each of these events within the switch group and LEV naïve groups were not reported separately, but rather under an umbrella of 'psychobehavioral TEAE'. AE outcomes on LEV were obtained from history while taking LEV in the past self-reported by patients during interview during clinical follow up as recorded by the physician. This could increase the risk of recall bias and underreporting. Several coauthors declared conflicts of interest related to pharmaceutical companies. It was unclear whether these affected the results of this study.
Strzelczyk et al., 2018¹⁵	
<ul style="list-style-type: none"> The objectives of the study were clearly described. The main outcomes to be measured were reported upfront and defined clearly. Baseline characteristics of the participants were reported in detail. The details for switching from LEV to BRV (dose and transition) were reported along with the dose and target levels of BRV in LEV naïve patients. Simple outcome data of TEAE in patients who switched from LEV to BRV and LEV naïve patients were reported. All patients who met the inclusion criteria were enrolled in this retrospective study. Study participants were recruited from several centers in Germany over the same period. The facilities and treatment received were representative of the treatment majority of patients might receive. These increased the generalizability of the results. 	<ul style="list-style-type: none"> The study was retrospective observational in design without random selection or concealment of allocation. It was unclear whether any concomitant AEDS were used during the study period. It was unclear whether the baseline characteristics and use of other antiepileptic drugs were different in patients who switched from LEV to BRV or and those who were naïve to LEV. It is possible that these groups of patients were different from each other. For the outcome relevant to this report (psychobehavioral TEAE) the results were reported only on its statistical significance. Results of comparative analysis including effect sizes, confidence intervals and actual probability values were not reported. It was unclear which statistical methods were used to compare the groups. The authors reported that different types of TEAE (e.g., agitation, depression, anxiety) were collected and recorded in detail during the study. However, the occurrences of each of these events within the switch group and LEV naïve groups were not reported separately, but rather under an umbrella of 'psychobehavioral TEAE'. It was unclear whether any patients were lost to follow up or discontinued BRV. These details were not reported. It was unclear whether a sample size calculation was done a priori to ensure adequate power. Several coauthors declared conflicts of interest related to pharmaceutical companies. It was unclear whether these affected the results of this study.

Strengths	Limitations
Willems et al., 2018¹⁶	
<ul style="list-style-type: none"> • The objectives of the study were clearly described. • The main outcomes to be measured were reported upfront and defined clearly. • Baseline characteristics of the participants were reported in detail. • The details for switching from LEV to BRV (dose and transition) were reported along with the dose and target levels of BRV in LEV naïve patients. • Simple outcome data of TEAE in patients who switched from LEV to BRV and LEV naïve patients were reported. • All patients who met the inclusion criteria were enrolled in this retrospective study. Study participants were recruited from several centers in Germany over the same period. The facilities and treatment received were representative of the treatment majority of patients might receive. These increased the generalizability of the results. 	<ul style="list-style-type: none"> • The study was retrospective observational in design without random selection or concealment of allocation. • It was unclear whether the baseline characteristics and use of other antiepileptic drugs were different in patients who switched from LEV to BRV or and those who were naïve to LEV. It is possible that these groups of patients were different from each other. • TEAE outcomes were self-reported by patients during interviews increasing the risk of recall bias and underreporting. • For the outcome relevant to this report (psychobehavioral TEAE) the results were reported only on its statistical significance. Results of comparative analysis including effect sizes and confidence intervals were not reported. • It was unclear whether any patients were lost to follow up or discontinued BRV. These details were not reported. • It was unclear whether a sample size calculation was done a priori to ensure adequate power. • Several coauthors declared conflicts of interest related to pharmaceutical companies. It was unclear whether these affected the results of this study.
Zahnert et al., 2018¹⁷	
<ul style="list-style-type: none"> • The objectives of the study were clearly described. • The main outcomes to be measured were reported upfront and defined clearly. • Baseline characteristics of the participants were reported in detail. • Adverse events related to the intervention were reported in details. • All patients who met the inclusion criteria were enrolled in this retrospective study. Study participants were recruited from the study center in Germany over the same period. The facilities and treatment received were representative of the treatment majority of patients might receive. These increased the generalizability of the results. 	<ul style="list-style-type: none"> • The study was retrospective observational in design without random selection or concealment of allocation. • It was unclear whether the baseline characteristics and use of other antiepileptic drugs were different in patients who switched from LEV to BRV, with previous LEV exposure and those who were naïve to LEV. It is possible that these groups of patients were different from each other. • AE outcomes were self-reported by patients during clinical follow up as recorded by the physician. This could increase the risk of recall bias and underreporting. • The details for switching from LEV to BRV (dose and transition) were reported along with the dose and target levels of BRV in LEV naïve patients. • Simple outcome data for the main findings were not reported. For the outcomes relevant to this report, (behavioral AE), the comparative analyses were not reported clearly. • It was unclear whether any patients were lost to follow up or discontinued BRV. These details were not reported. • It was unclear whether a sample size calculation was done a priori to ensure adequate power. • Several coauthors declared conflicts of interest related to pharmaceutical companies. It was unclear whether these affected the results of this study.

Strengths	Limitations
Steinig et al., 2017⁹	
<ul style="list-style-type: none"> • The objectives of the study were clearly described. • The main outcomes to be measured were reported upfront and defined clearly. • Baseline characteristics of the participants were reported in detail. • The details for switching from LEV to BRV (dose and transition) were reported along with the dose and target levels of BRV in LEV naïve patients. • Simple outcome data of BAE in patients who switched from LEV to BRV and LEV naïve patients were reported. Authors also reported effect sizes, estimates of random variability (confidence intervals and standard deviations), actual probability values were reported when they were >0.001. Appropriate statistical tests were used in comparative analyses. • All patients who met the study criteria were enrolled in this retrospective study. Study participants were recruited from multiple centers in Germany over the same period. The facilities and treatment received were representative of the treatment majority of patients might receive. These increased the generalizability of the results. 	<ul style="list-style-type: none"> • The study was retrospective observational in design without random selection or concealment of allocation • It was unclear whether the baseline characteristics and use of other antiepileptic drugs were different in patients who switched from LEV to BRV, with previous LEV exposure and those who were naïve to LEV. It is possible that these groups of patients were different from each other. • AE outcomes were self-reported by patients during clinical follow up as recorded by the physician. This could increase the risk of recall bias and underreporting. • The authors reported that different types of nonpsychotic BAE (e.g., agitation, depression, anxiety) were collected and recorded in detail during the study. However, the occurrences of each of these events within the switch group and LEV naïve groups were not reported separately, but rather under an umbrella of BAE. • Among all participants, 6-month follow up was available for 192 patients (73.2%). It was unclear whether the patients whose data was not available were different from this group. • The timing of measurement of BAE was unclear. • Several coauthors declared conflicts of interest related to pharmaceutical companies. It was unclear whether these affected the results of this study.
Yates et al., 2015⁸	
<ul style="list-style-type: none"> • The objectives of the study were clearly described. • The main outcomes to be measured were reported upfront. • The patient inclusion exclusion criteria and the baseline characteristics of the participants were clearly described. • The intervention and comparators of the study were clear. The details of BRV dosing, and the details of switching from LEV to BRV were clearly described. • Three (10.3%) patients did not complete the study. The reason for discontinuation was reported. • The study was conducted in several centers in the US and Europe. The facilities and treatment received were representative of the treatment majority of patients might receive. • 	<ul style="list-style-type: none"> • The study was an open labels single arm prospective study without randomization or blinding. • All patients in the study received other concomitant antiepileptic medications. It is possible that these concomitant medications could affect the study outcomes and adverse events. • The study was exploratory in nature. The study outcomes were presented as numerical comparisons. No statistical analysis was performed. • Among the source population, it was unclear how many patients were eligible for the study and did not participate. There was an increased risk of selection bias because of this. It is possible that the patients who participated in the study were different from those who were eligible but did not participate. • The participants were followed up for a relatively short time (12 weeks). When considering safety outcomes, it is possible that some adverse events could not occur within a short period of initiation of treatment. • The outcome 'shift in maximum intensity of the BAE' was assessed by the investigator. The mode of assessment and the definitions of intensity (mild, moderate or severe' were unclear. • The primary outcome of the study was investigators assessment in clinically meaningful reduction in BAE. The subjective assessment of outcome using a yes or no

Strengths	Limitations
	<p>question could introduce bias. The rationale regarding how these decisions were made was not reported.</p> <ul style="list-style-type: none"> • The study was funded by UCB pharma, which manufactures BRV. Most of the study authors including the primary author were employees of UCB pharma.

AE = adverse events; BAE = behavioral adverse events; BRV = brivaracetam; LEV = levetiracetam; TEAE = treatment emergent adverse events

Appendix 4: Main Study Findings and Authors' Conclusions

Table 5: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Fonseca et al., 2020¹¹	
<p>Relevant study findings:</p> <p>Psychiatric AE <i>Among patients with previous exposure to LEV, n = 31</i> "In total, 83.8% of subjects had previously used LEV. These patients started BRV because of lack of efficacy (51.6%), drug intolerance (29%) or both (12.9%), and because of other situations (6.5%). (p. 4)"</p> <ul style="list-style-type: none"> ○ Patients with Psychiatric AE on LEV, n = 19 ○ Among them, patients with TEAE on BRV, n/N (%) = 5/19 (26.3%) <p>"...in 19 patients with a history of LEV-related psychiatric AEs, these events were resolved with BRV in 73.7% of cases. (p. 4)"¹¹</p>	<p>"Seizure control in GGE can be achieved under BRV treatment. It has significant responder and retention rates at 6 months of follow-up, and nearly two-thirds of patients remain seizure-free. It also offers a good safety profile, particularly in patients with previous intolerance to LEV. Brivaracetam can, therefore, be considered a suitable option for GGE treatment, especially when other AEDs are not well tolerated. (p. 6)"¹¹</p>
Foo et al., 2019¹²	
<p>Relevant study findings:</p> <p>Psychiatric or behavioral AE: "The majority of patients switching from LEV to BRV because of psychiatric or behavioral AE reported an improvement to their symptoms. (p. 4)"¹² (Data not reported)</p> <p>Aggression: <i>Overall:</i> "In the 44 patients who previously reported aggression on LEV, we observed 17 (39%) patients experiencing the same when taking BRV and 27 (61%) patients reported no aggression. In the remaining 90 patients who reported no history of aggression with LEV, 14 (16%) patients experienced aggression on BRV. (p. 3)"¹²</p> <p><i>Patients with pre-existing psychiatric/ behavioral conditions (n = 73)</i></p> <ul style="list-style-type: none"> ○ Previous aggression improved with BRV, n (%) = 13 (18) ○ Previous aggression not improved with BRV, n (%) = 11 (15) ○ New aggression on BRV, n (%) = 6 (8) ○ No aggression on LEV or BRV, n (%) = 43 (59) <p><i>Patients with no history of pre-existing psychiatric/ behavioral conditions (n = 61)</i></p> <ul style="list-style-type: none"> ○ Previous aggression Improved with BRV, n (%) = 14 (23) ○ Previous aggression not improved with BRV, n (%) = 6 (10) ○ New aggression on BRV, n (%) = 8 (13) ○ No aggression on LEV or BRV, n (%) = 33 (54) <p><i>Patients with diagnosed intellectual disability (n = 41)</i></p> <ul style="list-style-type: none"> ○ Previous aggression Improved with BRV, n (%) = 8 (20) ○ Previous aggression not improved with BRV, n (%) = 7 (17) ○ New aggression on BRV, n (%) = 3(7) ○ No aggression on LEV or BRV, n (%) = 23 (56) <p><i>Patients with no intellectual disability (n = 93)</i></p> <ul style="list-style-type: none"> ○ Previous aggression Improved with BRV, n (%) = 19 (20) 	<p>"Given the fewer AED options available to patients with generalized epilepsies, our results would support further efficacy studies in this patient population. There is, however, a higher incidence of sedation, somnolence, and aggression across all patient groups, hence, patient education and caution need to be exercised when considering BRV particularly in patients with preexisting depression and behavioral disorders. Patients who have discontinued LEV may still benefit from BRV despite the lower than expected improvement to seizure control given the potential benefits from an AE perspective. (p.4)"¹²</p>

Main study findings	Authors' conclusion
<ul style="list-style-type: none"> ○ Previous aggression not improved with BRV, n (%) = 10 (11) ○ New aggression on BRV, n (%) = 11 (12) ○ No aggression on LEV or BRV, n (%) = 53 (57) <p>“Treatment-related aggression due to LEV may not predict the likelihood of aggression with BRV irrespective of whether the patient has associated psychiatric/behavioral issues or intellectual disability. (p. 4)”¹²</p> <p>Depressive symptoms:</p> <p><i>Overall:</i></p> <p>“Seven patients reported symptoms of depression on LEV. Six patients had pre-existing diagnosis of depression and complained of worsened symptoms on LEV. In these 10 patients, six (60%) reported improvement to their mood symptoms, three (30%) stopped BRV because of worsened mood symptoms, and one (10%) stopped because of excessive sedation. In the remaining 5 patients reporting new symptoms of depression without previous psychiatric comorbidity, all 5 improved following a switch from LEV to BRV. (p. 4)”¹²</p> <p><i>Among patients who switched from LEV to BRV during the study:</i></p> <ul style="list-style-type: none"> ○ Patients switched from LEV to BRV because of worsening depressive symptoms, n (%) = 7/63 (11%) ○ Among them, five had previously diagnosed with depression. ○ “Of these 5 patients, 3 (60%) improved on stopping BRV and the remaining 2 (40%) reported further worsened depressive symptoms. (p. 4)”¹² ○ “In the 2 patients with no previous history of depression, both reported resolution of depressive symptoms on switching to BRV. (p. 4)”¹² 	
Villanueva et al., 2019¹³	
<p>Relevant study findings:</p> <ul style="list-style-type: none"> ○ Patients switched from LEV to BRV, n = 223 ○ Reason for switching, n (%) ○ Poor efficacy: 145 (65) ○ Adverse events: 33 (14.58) ○ Combination of poor efficacy and adverse events: 41 (18.4) <p>Safety outcomes, n (%)</p> <p><i>Among patients who switched due to any reason, N = 223</i></p> <ul style="list-style-type: none"> ○ Psychiatric AE : not reported <p><i>Among patients who switched due to adverse events, N = 74</i></p> <ul style="list-style-type: none"> ○ Psychiatric AE : not reported <p><i>Among patients who switched due to psychiatric adverse events, N = 53</i></p> <ul style="list-style-type: none"> ○ Any psychiatric AE: <ul style="list-style-type: none"> ➤ At 3 months = 7 (13.3) ➤ At 6 months = 8 (15.1) ➤ At 12 months = 9 (17) ○ Mild psychiatric AE <ul style="list-style-type: none"> ➤ At 3 months = 3 (5.7) ➤ At 6 months = 3 (5.7) ➤ At 12 months = 4 (7.5) ○ Moderate psychiatric AE <ul style="list-style-type: none"> ➤ At 3 months = 3 (5.7) ➤ At 6 months = 4 (7.5) 	<p>“ 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. (p. 367)”¹³</p>

Main study findings	Authors' conclusion
<ul style="list-style-type: none"> ➤ At 12 months = 4 (7.5) ○ Severe psychiatric AE <ul style="list-style-type: none"> ➤ At 3 months = 1 (1.9) ➤ At 6 months = 1 (1.9) ➤ At 12 months = 1 (1.9) ○ Discontinuation due to Psychiatric AE <ul style="list-style-type: none"> ➤ At 3 months = 2 (3.8) ➤ At 6 months = 2 (3.8) ➤ At 12 months = 3 (5.7) <p>“... 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%). (p. 363)”¹³</p>	
Hirsch et al., 2018¹⁴	
<p>Relevant study findings:</p> <p>Behavioral adverse events: <i>Among patients who switched from LEV to BRV at baseline, n = 60</i></p> <ul style="list-style-type: none"> ○ Depression/mood lability/ fear, n (%) <ul style="list-style-type: none"> ➤ Before switch = 33 (55%) ➤ After switch = 14 (23%) ○ Irritability/aggressiveness, n (%) <ul style="list-style-type: none"> ➤ Before switch = 16 (27%) ➤ After switch = 5 (8%) ○ Other side effects (non-BAE), n (%) <ul style="list-style-type: none"> ➤ Before switch = 6 (10%) ➤ After switch = 1 (1.7%) ○ Unclear/no side effects, n (%) <ul style="list-style-type: none"> ➤ Before switch = 5 (8%) ➤ After switch: no side effects= 34 (64%); unclear = 2 (3.3%) <p>“Overall, in 28 out of 49 patients (57.1%) with affective side effects a better tolerability after switch from LEV to BRV was documented. (p. 100)”¹⁴</p> <p><i>Among patients with previous treatment with LEV, n = 42</i></p> <ul style="list-style-type: none"> ○ Depression/mood lability/ fear, n (%) <ul style="list-style-type: none"> ➤ Before switch = 6 (14%) ➤ After switch = 5 (12%) ○ Irritability/aggressiveness, n (%) <ul style="list-style-type: none"> ➤ Before switch = 8 (19%) ➤ After switch = 3 (7%) ○ Other side effects (non-BAE), n (%) <ul style="list-style-type: none"> ➤ Before switch = 10 (24%) ➤ After switch = 2 (5%) ○ Unclear/no side effects, n (%) <ul style="list-style-type: none"> ➤ Before switch = 18 (43%) ➤ After switch = 32 (76%) <p><i>In a subgroup of patients with genetic epilepsy who switched from LEV to BRV (n = 7):</i> BRV treatment was discontinued “in 2 patients as psychiatric symptoms present under LEV treatment did not improve after switch to BRV. (p. 100)”¹⁴</p>	<p>“Our results suggest that for patients experiencing tolerability problems or an insufficient treatment response with LEV, substitution of LEV treatment by BRV appears to be an interesting option. In a majority of patients who suffered from substantial psychiatric adverse effects from LEV a relevant improvement was achieved by switching to BRV, however, there remains a relevant percentage of patients who complain the same spectrum of psychiatric adverse effects from BRV. We conclude that especially in patients with problematic psychiatric comorbidity and/or a history of severe psychiatric adverse events under antiepileptic medication a high vigilance concerning these symptoms remains necessary when BRV is introduced. (p. 102)”¹⁴</p>

Main study findings	Authors' conclusion
Schubert-Bast et al., 2018¹⁸	
<p>Relevant study findings:</p> <p>Behavioral adverse events, n (e.g., aggression, depression, irritability) <i>Among patients with previous exposure to LEV, n = 26 (switched from LEV to BRV at baseline or with prior exposure to LEV):</i></p> <ul style="list-style-type: none"> ○ BAE reported under LEV = 15 (57.7) (reported at switch or in the past while exposed to LEV) ○ BAE reported under LEV and BRV = 1 (3.8) ○ BAE reported in overall study participants (N = 34), n = 2 (5.9%) <p>"Notably, the prevalence of psychobehavioral TEAEs was significantly lower in patients undergoing BRV treatment versus in patients during LEV intake (p <0.001). (p. 91)"¹⁸ (Data not reported)</p>	<p>"A relevant reduction in seizure frequency and seizure-free rates can potentially be achieved using BRV in children and adolescents with focal epilepsy in clinical practice. The adverse events seem comparable with that of other frequently used AEDs, with mostly psychobehavioral and unspecific TEAEs occurring. A direct switch from LEV to BRV seems also feasible at a ratio of 10:1 in the pediatric population. Patients who experience psychobehavioral TEAEs associated with LEV should be offered an option to switch to BRV. (p. 93)"¹⁸</p>
Strzelczyk et al., 2018¹⁵	
<p>Relevant study findings:</p> <p>Psychobehavioral TEAE: "Psychobehavioral TEAEs occurred in five of 30 (17%) patients who had previously reported psychobehavioral TEAEs on LEV and in four of 31 (13%) patients who did not experience psychobehavioral TEAEs on LEV or were not exposed to LEV (not significant). (p. 1553)"¹⁵(Data not reported)</p>	<p>"We conclude that high seizure-free rates can be achieved using BRV for GGE in clinical practice, even in a cohort wherein 84% of patients had been previously exposed to LEV. Furthermore, BRV appears to be a useful option for patients experiencing psychobehavioral TEAEs associated with LEV, and immediate switching appears feasible. (p. 1554)"¹⁵</p>
Willems et al., 2018¹⁶	
<p>Relevant study findings:</p> <p><i>Among all study participants, N = 44</i></p> <p>Psychiatric TEAE, n (%)</p> <ul style="list-style-type: none"> ○ TEAE reported under BRV = 6 (13.6) ○ TEAE under BRV leading to withdrawal = 4 (9.1) ○ TEAE reported only under LEV = 14 (31.8) (reported at switch or in the past while exposed to LEV) ○ TEAE reported under LEV and BRV = 2 (4.5) <p>"BAE were observed in four patients that had had BAE while exposed to LEV (n=4/18), while two patients had BAE on BRV who had had no BAE on LEV or were not exposed to LEV in the past (n = 2/26, p = 0.35). (p. 3)"¹⁶</p>	<p>" BRV is effective and well-tolerated in patients with EE and the pattern of TEAEs compares with other AEDs in frequent use. Efficacy of BRV does not seem to depend on whether patients have previously been exposed to LEV or not. A direct switch from LEV to BRV is feasible for patients with EE. Taken in conjunction with other post-marketing studies on focal or idiopathic generalized epilepsies, it seems that BRV is a reasonable treatment option for patients with epileptic encephalopathies. (p. 6)"¹⁶</p>
Zahnert et al., 2018¹⁷	
<p>Relevant study findings:</p> <p>Behavioral adverse events related to LEV treatment, n (%) <i>Among patients receiving LEV treatment at baseline (N = 36)</i></p>	<p>"In summary, we demonstrated that BRV might be a promising option for the treatment of epilepsies, especially for those patients who suffer from side effects of LEV therapy. BRV seems to offer the</p>

Main study findings	Authors' conclusion
<p>“The mean number of LEV-AE was reduced significantly in patients who were immediately switched from BL on LEV to BRV ($n = 32$) ($p < 0.001$, $M_1 = 1.56$, $SD_1 = 0.95$; $M_2 = 0.5$, $SD_2 = 0.84$). (p. 4)”¹⁷</p> <p>“Significant reductions in LEV-BAE were observed between BL on LEV and the most recent follow-up on BRV ($n = 31$; $p < 0.001$, $M_1 = 1.26$, $SD_1 = 0.63$; $M_2 = 0.39$, $SD_2 = 0.67$)... (p. 4)”¹⁷</p> <ul style="list-style-type: none"> ○ Overall behavioral AE: <ul style="list-style-type: none"> ➤ Reported under LEV at baseline = 31 (86.6) ➤ Reported under BRV during study = 10 (27.8) ○ Irritability <ul style="list-style-type: none"> ➤ Reported under LEV at baseline = 9 (25) ➤ Reported under BRV during study = 3 (8.3) ○ Depression <ul style="list-style-type: none"> ➤ Reported under LEV at baseline = 10 (27.8) ➤ Reported under BRV during study = 3 (8.3) ○ Aggression <ul style="list-style-type: none"> ➤ Reported under LEV at baseline = 9 (25) ➤ Reported under BRV during study = 3 (8.3) ○ Agitation <ul style="list-style-type: none"> ➤ Reported under LEV at baseline = 5 (13.9) ➤ Reported under BRV during study = 2 (5.6) ○ Psychosis <ul style="list-style-type: none"> ➤ Reported under LEV at baseline = 3 (8.3) ➤ Reported under BRV during study = 1 (2.8) ○ Listlessness <ul style="list-style-type: none"> ➤ Reported under LEV at baseline = 2 (5.6) ➤ Reported under BRV during study = 0 (0) ○ Anxiety <ul style="list-style-type: none"> ➤ Reported under LEV at baseline = 2 (2.8) ➤ Reported under BRV during study = 0 (0) ○ Lability of affect <ul style="list-style-type: none"> ➤ Reported under LEV at baseline = 0 (0) ➤ Reported under BRV during study = 0 (0) ○ Hysteria <ul style="list-style-type: none"> ➤ Reported under LEV at baseline = 0 (0) ➤ Reported under BRV during study = 0 (0) <p><i>Among patients with previous treatment with LEV (not at baseline) (N = 21)</i></p> <p>“Patients who were not currently on LEV treatment, but who had discontinued LEV in the past due to AE ($n = 21$), reported a significantly smaller amount of those LEV-associated AEs after being treated with BRV ($n = 21$; $p < 0.001$, $M_1 = 1.4$, $SD_1 = 0.75$; $M_2 = 0.19$, $SD_2 = 0.51$). (...) similar results emerged regarding BAE ($n = 15$; $p < 0.001$, $M_1 = 1.47$, $SD_1 = 0.74$; $M_2 = 0.2$, $SD_2 = 0.56$) ... (p. 4)”¹⁷</p> <p>Discontinuation of BRV</p> <p>Number of patients who discontinued BRV treatment, n/N (%) = 26/93 (28%)</p> <p>Patients who discontinued due to Behavioral AE, n/N (%) = 12/93 (12.9%)</p> <p>Most frequent AE leading to discontinuation was anxiety, $n = 4$ (4.3%)</p> <p>“An immediate switchback to LEV was performed in 10/26 patients who discontinued BRV. Of these patients, eight were followed up: seven (87.5%) of those showed clinical improvement. (p. 3)”¹⁷</p>	<p>chance to improve therapeutic effectiveness and broadens the therapeutic spectrum to facilitate personalized treatment. (p. 6)”¹⁷</p>

Main study findings	Authors' conclusion
Steinig et al., 2017⁹	
<p>Relevant study findings:</p> <p>Behavioral adverse events, n:</p> <p><i>Among patients with previous exposure to LEV, n = 236 (switched from LEV to BRV at baseline or with prior exposure to LEV):</i></p> <ul style="list-style-type: none"> ○ BAE while on LEV, n = 57 <ul style="list-style-type: none"> ➤ BAE while on BRV, n/N (%) = 13/57 (22.8%) ➤ No BAE while on BRV, n/N (%) = 44/57 (77.2%) ○ No BAE while on LEV, n = 179 <ul style="list-style-type: none"> ➤ BAE while on BRV, n/N (%) = 14/179 (7.8%) ➤ No BAE while on BRV, n/N (%) = 165/179 (92.2%) <p><i>Among patients who switched from LEV to BRV at baseline, n = 133</i></p> <ul style="list-style-type: none"> ○ BAE while on LEV, n = 35 <ul style="list-style-type: none"> ➤ BAE while on BRV, n/N = 8/35 ➤ No BAE while on BRV, n/N = 27/35 ○ No BAE while on LEV, n = 98 <ul style="list-style-type: none"> ➤ BAE while on BRV, n/N = 5/98 ➤ No BAE while on BRV, n/N = 93/98 ○ Among patients who switched from LEV to BRV due to adverse events (n = 51): "Nonpsychotic BAE improved in 20 cases (57.1%), whereas an aggravation was seen in 2 cases (5.7%). (p. 1213)"⁹ <p><i>Among patients or with prior exposure to LEV, n = 106</i></p> <ul style="list-style-type: none"> ○ BAE while on LEV, n = 22 <ul style="list-style-type: none"> ➤ BAE while on BRV, n/N = 5/22 ➤ No BAE while on BRV, n/N = 17/22 ○ No BAE while on LEV, n = 81 <ul style="list-style-type: none"> ➤ BAE while on BRV, n/N = 9/81 ➤ No BAE while on BRV, n/N = 17/22 <p><i>Among patients with no prior exposure to LEV, n = 26</i></p> <ul style="list-style-type: none"> ○ BAE while on BRV, n/N (%) = 4/ 26 (15.4%) 	<p>"The occurrence of BAE during previous LEV exposure was a significant predictor of a higher likelihood for psychobehavioral side effects with BRV treatment. However, BRV appears to be a useful option for patients experiencing BAE associated with LEV, and immediate switching appears feasible. (p.1215)"⁹</p>
Yates et al., 2015⁸	
<p>Relevant study findings:</p> <p>Clinically meaningful reduction in BAE: "The majority of patients (n=27 [93.1%]) who switched from LEV to BRV had a clinically meaningful reduction in BAEs, as determined by the investigator, at the end of the treatment period. (p. 166)"⁸</p> <p>Shift in maximum intensity of nonpsychotic BAE at the end if treatment period (12 weeks): "A reduction in the maximum intensity of primary BAEs associated with discontinuation of LEV was seen in 27/29 (93.1%) patients, and no patients reported a worsened intensity from baseline to the end of the treatment period. (p. 166)"⁸</p> <ul style="list-style-type: none"> ○ <i>Mild BAE at baseline:</i> 	<p>"Overall, results from this small study suggest that patients who experience BAEs warranting the discontinuation of LEV treatment might benefit from a switch to BRV without titration. However, results should be interpreted with caution owing to the small sample size, lack of prospective baseline seizure data, short treatment period, and open-label design. Therefore, further confirmation of these results in future randomized, blinded studies would be of interest. (p. 168)"⁸</p>

Main study findings	Authors' conclusion
<ul style="list-style-type: none"> ➤ Resolved, n (%) = 1 (3.4) ➤ Mild, n (%) = 1 (3.4) ➤ Moderate, n (%) = 0 ➤ Severe, n (%) = 0 ○ <i>Moderate BAE at baseline:</i> <ul style="list-style-type: none"> ➤ Resolved, n (%) = 10 (34.5) ➤ Mild, n (%) = 3 (10.3) ➤ Moderate, n (%) = 1 (3.4) ➤ Severe, n (%) = 0 ○ <i>Severe BAE at baseline:</i> <ul style="list-style-type: none"> ➤ Resolved, n (%) = 8 (27.6) ➤ Mild, n (%) = 2 (6.9) ➤ Moderate, n (%) = 3 (10.3) ➤ Severe, n (%) = 0 ○ <i>Total BAE at baseline:</i> <ul style="list-style-type: none"> ➤ Resolved, n (%) = 19 (65.5) ➤ Mild, n (%) = 6 (20.7) ➤ Moderate, n (%) = 4 (13.8) ➤ Severe, n (%) = 0 <p>Improvement in BAE, measured using I-GEBSE: “A total of 20/29 (69.0%) patients showed a marked or moderate improvement in BAEs, measured by the I-GEBSE. There was a slight improvement of BAEs in 4/29 patients. One patient (3.4%) had slight worsening, and one patient (3.4%) had marked worsening of BAEs. I-GEBSE data were missing for one patient (3.4%).(p. 166)”⁸</p> <p>Freedom from BAE: “At the end of the treatment period, complete abatement (events which ended during the treatment period) from primary BAEs was reported for 18 (62.1%) patients. Of these, three (10.3%) had freedom from BAEs throughout the treatment period. (p. 166)”⁸</p> <p>Median time to primary BAE resolution: 15 days</p>	

AE = adverse events; BAE = behavioral adverse events; BRV = brivaracetam; I-GEBSE = Global Evaluation of Nonpsychotic Behavioral Side Effects; LEV = levetiracetam; SD = standard deviation; TEAE = treatment emergent adverse events

Appendix 5: Further Information

Previous CADTH Reports

CADTH. Brivaracetam. Reimbursement review. 2017; <https://cadth.ca/brivaracetam>. Accessed 2020 Nov 23.

Additional References

Publications with an alternative outcome

Asadi-Pooya AA, Sperling MR, Chung S, et al. Efficacy and tolerability of adjunctive Brivaracetam in patients with prior antiepileptic drug exposure: A post-hoc study. *Epilepsy Res.* 2017 Mar;131:70-75.

[PubMed: PM28279891](#)

Lattanzi S, Cagnetti C, Foschi N, Provinciali L, Silvestrini M. Brivaracetam add-on for refractory focal epilepsy: A systematic review and meta-analysis. *Neurology.* 2016 Apr 05;86(14):1344-1352.

[PubMed: PM26944275](#)

Zhu LN, Chen D, Xu D, Tan G, Wang HJ, Liu L. Newer antiepileptic drugs compared to levetiracetam as adjunctive treatments for uncontrolled focal epilepsy: An indirect comparison. *Seizure.* 2017 Oct;51:121-132.

[PubMed: PM28854405](#)

Zhang L, Li S, Li H, Zou X. Levetiracetam vs. brivaracetam for adults with refractory focal seizures: A meta-analysis and indirect comparison. *Seizure.* 2016 Jul;39:28-33.

[PubMed: PM27236448](#)

Publications with an alternative comparator

Gillis RME, Wammes-van der Heijden EA, Schelhaas HJ, Tan IY, Festen DAM, Majoie M. Efficacy and tolerability of brivaracetam in patients with intellectual disability and epilepsy. *Acta Neurol Belg.* 2020 Mar 10. Online ahead of print.

[PubMed: PM32157673](#)