Annals of Clinical and Medical Case Reports

Research Article **ISSN 2639-8109 | Volume 9**

Neuropsychiatric Profiles of Brivaracetam: A Literature Review

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Received: 04 May 2022
Accepted: 23 May 2022
Published: 27 May 2022
J Short Name: ACMCR

Citation:

Yuan-Han Yang, Neuropsychiatric Profiles of Brivaracetam: A Literature Review. Ann Clin Med Case Rep. 2022; V9(4): 1-8

Keywords:

Adverse effect; Behavior; Cognition; Brivaracetam; Levetiracetam

1. Abstract

Anti-seizure medications (ASMs) can cause cognitive or behavioral adverse drug reactions, which is a significant consideration when selecting an appropriate ASM. Brivaracetam (BRV) is a newer synaptic vesicle protein 2A ligand, which is expected to have less neuropsychiatric adverse effects due to its mechanism of action. To understand the impact of BRV on cognition and behavior compared with other ASMs, we conducted literatures searching from PubMed and MEDLINE databases. After the screening process, a total of two animal studies, one randomized controlled trial, one pooled-analysis of clinical trials, one controlled study and nine observational studies were included. Animal studies showed that BRV did not worsen cognition or behavior performance in rodents. Human studies showed that BRV had less cognitive adverse events compared with other second or third generation ASMs. In addition, currently available evidence suggests that behavioral disturbance is less common with BRV compared with levetiracetam. This review revealed that BRV has a limited impact on cognition and behavior. For patients who are intolerant to levetiracetam and have levetiracetam-related behavioral side effects, switching to BRV could be beneficial. However, the heterogeneity between studies makes the quality of the evidence weak and further trials are needed to confirm the findings.

2. Introduction

The primary goal of epilepsy treatment is to enable the patient to function normally and live their life, this can be achieved through the control of seizures, cognitive and psychiatric comorbidities and treatment adverse effects or social support [1,2,3]. Anti-seizure medication (ASM) might improve the patients' cognition and behavior by reducing seizures and interictal epileptic discharges, or by improving concomitant psychiatric manifestations [4,5]. However, the use of ASMs that alter ion channel and neurotransmitter functions can also be accompanied by cognitive or behavioral problems [5]. In the cognitive domain, attention and executive functions are most commonly affected by ASMs [6], while depression, irritability and aggressive behavior are frequently reported as ASM behavioral adverse effects [7]. These neuropsychological adverse effects can determine the drug retention rate and compromise overall patient wellbeing [8]. Therefore, a better understanding of the cognitive and behavioral profiles of ASMs is essential in epilepsy treatment. Although how ASMs affect cognition and behavior is not clear, several factors could influence the onset of cognitive or behavioral changes following ASM administration. ASM-related cognitive or behavioral impairment is related to higher doses, higher plasma levels, rapid upward titration and polytherapy [9]. Also, the drug's mechanism of action affects the cognitive and behavioral profiles of ASMs. It is known that ASMs modulating γ-aminobutyric acid neurotransmission, such as phenobarbital and topiramate, have a more detrimental effect on cognitive function and increased behavioral problems compared with those modulating voltage-gated channels [5, 10]. Brivaracetam (BRV) is a structurally similar analog of levetiracetam (LEV). Its primary antiepileptic mechanism of action relates to its selective, high-affinity binding with synaptic vesicle protein 2A (SV2A) ligand. Compared with LEV, BRV has a 15 to 30 fold higher affinity for SV2A [11]. Although the exact function of SV2A is still unclear, dysfunction of SV2A is thought to be involved in Alzheimer's disease and other types of cognitive impairment [12, 13]. LEV, one of the SV2A ligands, has been shown to cause cognitive improvements beyond its anti-seizure effects in both animal and human studies [14]. Since BRV is chemically closely related to LEV, it is expected to have favorable cognitive outcomes similar to LEV [15,16,17]. Reported changes in mood and behavior following BRV treatment raised concerns because LEV was also reported to be associated with high rates of behavioral problems [18, 19]. In a meta-analysis of randomized controlled trials (RCTs) which evaluated the adverse events of BRV, dizziness, fatigue and back pain were most commonly associated with BRV treatment, while psychiatric problems were not reported to be increased [20]. As for cognition, BRV was recognized as having a favorable cognitive profile in both animal and human studies [21,22]. However, there was insufficient data to accurately determine whether the cognitive or psychiatric profiles of BRV differed from other ASMs. The aim of this review was to assess the neuropsychological profiles of BRV compared with other ASMs.

3. Materials and Methods

Search Strategy and Selection Criteria

We performed a literature search of the PubMed and MEDLINE databases for English articles containing "brivaracetam" in the title or abstract. The bibliographies from relevant publications were also reviewed for additional relevant studies. Studies were screened and then selected if they were original studies, including *in vitro* studies, animal studies, clinical trials or prospective and retrospective observational studies. Studies that did not compare BRV with other ASMs or did not evaluate "cognitive/behavioral/psychiatric" events were excluded. A total 297 articles were identified in the literature search. Of these, 37 underwent a full-text review and then 23 were excluded for not having cognitive/behavioral/psychiatric results or not comparing BRV with other ASMs (Figure 1). A total of 14 studies were included in the final review based on our search criteria; this included 2 animal studies and 12 human studies. The study design of the human studies were: one RCT, one pooled-analysis of clinical trials, one prospective controlled study, two prospective observational studies, six retrospective observational studies and one cross-sectional study. Information on the included studies is provided in Table 1.

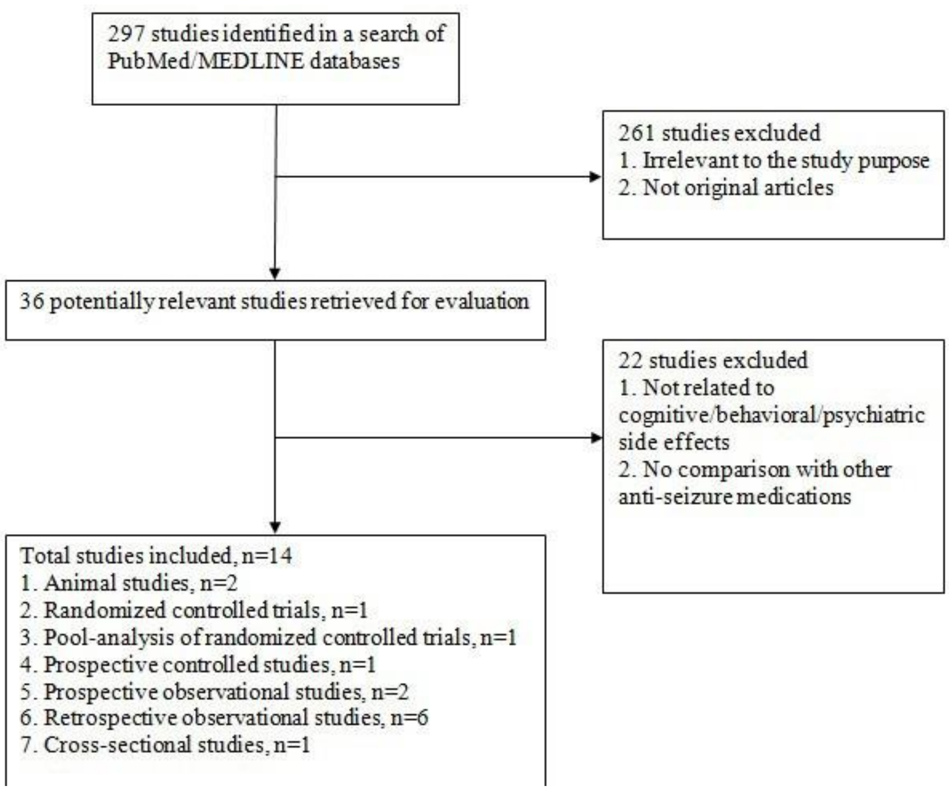

Figure 1. Flow chart of study inclusion.

Table 1. Characteristics of the included studies.

Reference	Study subjects	Study design	BRV dose / duration	Comparison	Key findings
Animal studies					
Sanon et al. 2018. [23]	Kainic acid-induced epileptic rats	Experimental study with sham-operated controls	Single intraperitoneal injection BRV 30 mg/kg	Single intraperitoneal injection LEV 300 mg/kg	BRV-treated epileptic rats were significantly less aggressive and had more social behavior than LEV-treated epileptic rats
Nygaard et al. 2015. [24]	Transgenic Alzheimer disease mice (APP/PS1 and 3xTg-AD)	Experimental study with wild-type animals as controls	BRV continuous intraperitoneal infusion at rate of 8.5 mg/kg/day for 4 weeks	Oral ethosuximide in the drinking water at a concentration of 30 mg/ml	In APP/PS1 mice, only BRV reversed memory impairments, although both BRV and ethosuximide reduced abnormal spike-wave discharges
Human study					
Meador et al. 2011. [27]	16 healthy adult volunteers	Cross-over RCT	Two doses of BRV 10 mg	Two doses of LEV 500 mg, lorazepam 2 mg, and placebo	No cognitive performance difference between BRV, LEV and placebo. Lorazepam significantly worse cognitive performance.
Sarkis et al. 2018. [29]	Adults with focal epilepsy mostly, from add-on phase-III clinical trials	Pooled analysis of RCTs	BRV drug load was divided into low, average and high level. The drug load calculation was based on (prescribed daily dose/defined daily dose) per the World Health organization.	11 different ASMs including ESL, LCM, OXC, OXC XR, PER, PGB, TGB, TPM, TPM XR, VGB, ZNS. All ASMs divided into low, average and high drug load.	Less than 5% reported cognitive adverse events in BRV regardless of drug load. ASMs with the high cognitive side effects rates as compared to placebo were ESL, PER, PGB, TGB, TPM and VGB.
Yates et al. 2015. [31]	29 adults (age ≥ 16 years old) with focal epilepsy or primary generalized epilepsy, with LEV-induced behavioral adverse events	Prospective case-series	Target dose 50–200 mg/day, for 4 weeks	LEV 1000-3000mg/day at least for 4 weeks	93.1% of patients reported a clinically meaningful reduction in LEV-induced BAE after switching to BRV.
Hirsch et al. 2018. [32]	102 people with epilepsy irrespective of age (range 11-70 years) and seizure type	Retrospective case-series	Mean target dose 153.2mg (±74.8) / day, for a least 6 months follow-up	LEV, either just before starting treatment with BRV (i.e. direct switch from LEV to BRV in the study) or a previous treatment anytime in the past	In patients who switched to BRV due to LEV-related BAE, 57.1% reported improvement in behavioral side effects
Zahnert et al. 2018. [33]	93 people with epilepsy irrespective of age and seizure type	Retrospective case-series	Target dose 50-200mg/day, mean duration of follow-up 4.85 months	LEV, either just before starting treatment with BRV (i.e. direct switch from LEV to BRV in the study) or a previous treatment anytime in the past	Less LEV-related BAE by switching to BRV

Steinig et al. 2017 [34]	262 people with epilepsy irrespective of age (range 5-81 years) and seizure type	Retrospective cohort study	Target dose 50-200mg/day (mean 128.1 ± 49.2 mg /day), duration of treatment 1 day to 12 months	LEV, either just before starting treatment with BRV (i.e. direct switch from LEV to BRV in the study) or a previous treatment anytime in the past	Patients with BAE on LEV were more likely to develop BAE on BRV (odds ratio 3.48, 95% confidence interval 1.53–7.95).
Toledo et al. 2019. [35]	37 adults (age ≥ 17 years old) with epilepsy, and 1:1 control group	Prospective case-control study	Target dose 50-300mg/day, fol- low-up for 6 months	Control group with any other ASM except LEV, including LCM, ESL, LTG, ZNS, PER, OXC, CBZ, VPA, CLB	BRV improved anger, depression and anxiety mood scores significantly, but related to good seizure control
Ortega et al. 2018 [36]	39 adults with focal epilepsy	Cross-sectional study	100-200mg/day	Other ASMs including LEV, ESL, OXC, LCM, VPA, CLB, LTG, CZP	No differences in anger, depression and anxiety scores between the two groups
Foo et al. 2019 [39]	134 adults (≥ 16 years old) with drug resistant epilepsy, all had previous exposure to LEV	Prospective case-series	50-200mg/day, mean duration of treatment 11 months	LEV, either just before starting treatment with BRV (i.e. direct switch from LEV to BRV in the study) or a previous treatment anytime in the past	Improvement in aggression and depression in patients switching from LEV to BRV due to LEV-related behavioral symptoms.
Theochari et al. 2019. [40]	25 adults with drug resistant epilepsy and psychiatric comorbidities	Retrospective case-series	50-200 mg/day, median duration of treatment 8.5 months	LEV, either just before starting treatment with BRV (i.e. direct switch from LEV to BRV in the study) or a previous treatment anytime in the past	Improvement in BAE in patients switching from LEV to BRV due to LEV-related behavioral symptoms.
Villanueva et al. 2019. [42]	575 adults with (≥16 years old) with focal epilepsy	Retrospective case-series	25-350 mg/day, 12 months follow-up	LEV, either just before starting treatment with BRV (i.e. direct switch from LEV to BRV in the study) or a previous treatment anytime in the past	Improvement in BAE in patients switching from LEV to BRV due to LEV-related behavioral symptoms. Psychiatric comorbidities not related to BRV-associated BAE.
Schubert-Bast et al. 2018. [45]	34 children and adolescents (≤17 years old) with focal epilepsy	Retrospective case-series	Target dose 50-300 mg/day, Duration of treatment 25 days to 24 months	LEV, either just before starting treatment with BRV (i.e. direct switch from LEV to BRV in the study) or a previous treatment anytime in the past	Significantly lower prevalence of BAE in BRV.

ASM= Anti-seizure medication, BAE = behavioral adverse event, BRV = Brivaracetam, CBZ = Carbamazepine, CLB = Clobazam, CZP = Clonazepam, ESL = Eslicarbazepine acetate, LCM= Lacosamide, LEV = Levetiracetam, LTG = Lamotrigine, OXC = Oxcarbazepine, PBG = Pregabalin, PER= Perampanel , RCT = Randomized controlled trial, , TPM = Topiramate, VGB = Vigabatrin, VPA = Valproic acid, XR = Extended-release, ZNS = Zonisamide.

4. Results

Data from Animal Studies

Two animal studies investigated the cognition and behavioral profiles of BRV, one compared BRV with LEV [23], while the other compared BRV with ethosuximide, which is another ASM [24]. BRV did not worsen the cognitive or behavioral performance in either study. Furthermore, BRV even improved spatial memory in a mouse model of Alzheimer's disease [24]. The first animal study used kainic acid-treated rats, which mimic temporal lobe epilepsy, to test the behavioral effects of BRV and LEV [23]. The BRV-injected rats showed significantly less aggressive behavior compared with the LEV-injected rats, and the learning ability of the two groups was similar. In the other study, which used an APP/PS1 mouse model of Alzheimer's disease, chronic treatment with BRV reduced epileptiform activities and reversed spatial memory impairment, although it did not affect markers of hyperexcitability or brain amyloid-beta concentration [24]. Ethosuximide has also been previously shown to significantly reduce epileptiform activity, but it has not demonstrated the ability to reserve memory deterioration. Combined with previous studies on LEV [25, 26], this study highlighted the unique role of SV2A in cognition improvement, beyond the elimination of seizures.

Data from Human Studies

Comparison of Cognitive Profiles between BRV and other ASMs: Only two studies reported on the cognitive effectof BRV compared with other ASMs, including one RCT and a pooled-analysis of clinical trials. The RCT included 16 healthy participants and compared their neuropsychological outcomes after acute dosing with BRV (10mg x 2 dose), LEV (500mg x2 dose), lorazepam (2mg x 2 dose) and a placebo [27]. There were no significant differences in the neuropsychological outcomes be-tween BRV, LEV, and the placebo, and all were superior to lora- zepam on the cognitive neurophysiological test. However, these results may not reflect the chronic or dose-dependent cognitive profiles of the drugs. The BRV dose administered in this study was much lower than the therapeutic dose of 50-200mg/day [28]. The pooled data-analysis of phase III trials investigated treatment-re- lated cognitive and fatigue side effects from second and third gen-eration ASMs [29]. Only data on adult patients with focal epilepsy and an add-on study design were included. Reported cognitive side effects were compared among 12 different ASMs. The results in- dicated that the rate of cognitive adverse events in BRV was as low as the placebo regardless of the drug load. Drugs which had more frequent cognitive side effects compared with the placebo included, eslicarbazepine, perampanel, pregabalin, tiagabine, topiramate and vigabatrin, indicating a clear dose response effect. In summary, BRV has favorable cognitive outcomes compared withother second and third generation ASMs.

Comparison of psychiatric and behavioral profiles be- tween BRV and other ASMs: The majority of studies included in this review were a comparison of the psychiatric and behavioral properties of BRV and LEV. Psychiatric and behavioral adverse events have been reported as one of the drawbacks of using LEV [30]. As the mechanism of action for BRV is similar to LEV, a comparison of these two medications has received a lot of attention. Several studies have shown a reduction in behavioral adverse events in patients who switched from LEV to BRV [31,32,33,34]. The first study was a prospective care series which evaluated the behavioral adverse events of BRV in 29 epilepsy patients who switched from LEV to BRV due to LEV–related behavioral changes [31]. In this study, the BRV initial dose was 200mg/day and the treatment duration was 12 weeks. The effects of the drugs were examined by patient self-reporting. Clinical meaningful improvement in behavioral adverse events was found in 27/29 (93.1%) patients who switched from LEV to BRV. A limitation of this study was the small sample size, the use of descriptive statistics only and the open-label design. The second study, a retrospective single-center, case-series study in clinical practice, showed improved behavioral side effects (mostly depression, irritability and aggressiveness) in 28/49 patients (57.1%) who were directly switched from LEV to BRV due to intolerable LEV-induced behavioral side effects [32]. The duration of BRV therapy was a minimum of 6 months and the mean target dose was 153.2mg/day. The main limitation of this study was the small sample size, a lack of standardized assessment of the adverse effects and the use of descriptive statistics only. In another retrospective care series of 93 epilepsy patients, BRV was compared with LEV [33]. 47 patients were switched from LEV to BRV directly within the study, but 87 patients had prior use of LEV in their medical history; the remaining 6 participants had never used LEV before. The BRV target dose ranged from 50 to 200mg/day. Behavioral adverse events occurred in 22.6% of patients and cognitive impairment occurred in 5.4% of patients during their BRV treatment (mean follow follow-up time 4.85 months). A significant reduction in LEV-related behavioral adverse events (either current or in the past) was achieved by switching to BRV therapy. Finally, a multicenter retrospective cohort study examined the tolerability of BRV (target dose ranged from 50 to 200 mg/day) compared with that of LEV (direct switch to BRV and past treatment) in epilepsy patients [34]. A total of 262 patients with epilepsy were included. The treatment duration was one day to 12 months. Among the patients who switched from LEV to BRV due to LEV-induced behavioral adverse events, 57.1% (20/35) reported improved side effects. A history of behavioral adverse events during their previous LEV treatment was associated with a higher likelihood of developing behavioral adverse events with BRV. Two similar studies compared BRV with ASMs other than LEV [35, 36]. A small prospective study of 37 patients assessed anger, depression and anxiety levels prior to and after 3-6 months of BRV (the maintenance dose ranged from 50 to 300mg/

day) add-on treatment [35]. Mood status was assessed using objective and standardized tools (State Trait Anger Expression Inventory 2 and Hospital Anxiety and Depression Scale) [37, 38]. Compared with the control group who were taking any other ASM except for LEV, the BRV group had a significant improvement in all mood scores. The improvements in the control group were not significant. However, the beneficial effects on mood were possibly influenced by the good seizure response to BRV.

Another small cross-sectional study, which analyzed 39 focal epilepsy adults, also compared levels of anger, anxiety and depression between BRV (dose ranged from 100 to 200mg/day) and a control group [36]. Patients with active psychiatric disease or cognitive impairment were excluded. In the control group, 22 patients received other ASMs including LEV. Their mood status was assessed using the State Trait Anger Expression Inventory 2 and Hospital Anxiety and Depression Scale. No statistical differences were found between the 2 groups. However, it was difficult to draw strong conclusions from this study because of its study design, the small sample size and the highly selected participants. Previous studies have shown that patients with epilepsy were at a higher risk of psychiatric and behavioral disturbances following ASM treatment if they had a history of psychiatric disorders [18]. One prospective observational study included patients with drug resistant focal or generalized epilepsy (n=134); all of them were treated with LEV in the past or at the start of the study [39]. More than half of the patients had a psychiatric or behavioral disorder (54%) and one third of the subjects had intellectual disabilities (31%). The study compared psychobehavioral adverse effects between BRV (dose range 50 to 200mg) and LEV treatment. A higher incidence of depression and aggression following BRV treatment was found compared with all previous patient group studies. Although the study reported that BRV treatment could decrease aggressive and depressive symptoms associated with previous LEV treatment in epileptic patients with psychiatric comorbidities, the quality of evidence was low because of a lack of statistical comparisons. It is unclear whether the high number of patients with psychiatric comorbidities or intellectual disabilities affected the occurrence of BRV behavioral adverse events. Twenty-five patients with drug-resistant epilepsy and co-existing psychiatric disorders were enrolled in another small, retrospective, observational study, to investigate the occurrence of behavioral adverse events following BRV treatment [40]. The majority of patients had a history of treatment with LEV (91.6%). The study reported that the existence of psychiatric comorbidities did not influence the development of behavioral adverse events following BRV treatment. The rates of depression and aggression following adjunctive BRV treatment, were similar to those reported by a previous study [41]. Furthermore, more than two third of patients who had a history of LEV-related adverse events did not develop behavioral adverse events following BRV treatment, showing that BRV may be better tolerated than LEV in patients with psychiatric comorbidities. In real word practice, BRV seems to be a safe ASM alternative, even in the presence of psychiatric disorders. A retrospective post-marketing study in clinical practice, which involved 575 patients with focal epilepsy, compared tolerability between BRV (target dose ranged from 25 to 350mg/day) and LEV (direct switch to BRV and previous LEV) over 12 months [42]. 14.3% of patients reported BRV-related behavioral adverse events. The patients who switched to BRV because of LEV-related behavioral adverse events, had less frequent adverse events than with their LEV treatment. A history of psychiatric conditions did not influence BRV tolerability. As in adults, cognitive and behavioral impairments are more often found among epileptic children than those without epilepsy [43, 44]. There was one retrospective, multicenter case series reporting efficacy and safety profiles in children. [45] Thirty-four children and adolescents (≤17 years) with focal epilepsy, were treated with BRV (target dose range between 50 and 300mg/day) for between 3 weeks and 2 years, and most of them were currently or previously being treated with LEV. Compared with LEV, BRV had a significantly lower rate of behavioral adverse effects (e.g. depression, aggression or irritability) while the impact on memory or cognition was not mentioned. In summary, current available evidence suggests that behavioral disturbance is less common following BRV treatment compared with LEV, regardless of whether the patient is an adult or a child or has psychiatric comorbidities. Switching to BRV may be beneficial for patients who have intolerable LEV-related behavioral side effects, even though one study indicated that a history of LEV-related behavioral adverse effects was a predictor of behavioral adverse effects with BRV treatment.

5. Discussion

In this literature review, the available data suggests that BRV has low neuropsychological side effects compared with other ASMs, especially LEV. Tolerability is a major concern in clinical practice and the choice of ASM is often based on a comparison of tolerability profiles for the drugs, as well as their efficacy. Adverse cognitive and behavioral effects have been reported to be one of the most important tolerability problems in ASM treatment [46]. Cognitive and behavior complications of ASMs are caused by multiple factors, and the drug's mechanism of action is an important contributor [9,10]. BRV acts as a high-affinity ligand of SV2A. However, BRV differs from LEV because it does not inhibit high voltage calcium channels and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [11]. A previous study has shown that AMPA receptors might be involved in the aggressive behavior and irritability side effects often caused by topiramate, perampanel, and LEV [47]. Therefore, paucity of AMPA receptor blocking may provide a plausible explanation for why BRV has fewer behavioral symptoms than LEV. No relevant head-to head RCTs comparing the cognitive or behavioral adverse effects of BRV and other ASMs in patients with epilepsy, were identified in our literature search. Only one small sample RCT reported that the cognitive profile of BRV, including patient-reported adverse effects, neuropsychological measures and neurophysiologic tests, was similar to LEV and the placebo in healthy volunteers. However, data from healthy volunteers needs to be interpreted carefully because it lacks clinical conditions which are important contributors to the development of cognitive and behavioral adverse effects in ASM treatment, such as pre-existing brain function or comorbidities [18, 48]. Moreover, the short treatment period in healthy volunteer studies may be inadequate to determine the neuropsychological consequences of long-term ASM treatment. The published studies were heterogeneous in study population, study design and the measurement of cognition and behavior changes. For study population, the seizure types looked at in the different studies varied. For outcomes, cognitive or behavioral effects were self-reported by patients in the majority of the included studies, while three studies used objective measures [27, 35, 36]. Among the studies which compared BRV and LEV, three studies only provided descriptive results [31, 32, 40]. A lack of statistical comparisons between the groups makes interpretation of the results challenging. Therefore, it was difficult to draw strong conclusions based on the currently available evidence, in terms of the absence of direct head-to-head comparative ASM studies and standardized approaches to ASM-induced cognitive and behavior changes. Additional studies with larger sample sizes and appropriate experimental designs may help further determine the cognitive and behavior effects of BRV compared with other ASMs.

6. Conclusion

In the present review, BRV was reported to have favorable cognitive effects compared with other second and third generation ASMs and less behavioral adverse events than its structural analog LEV. For patients who are intolerant to LEV and have LEV-related behavioral side effects, switching to BRV could be beneficial. We hope that further research will be conducted in this area to provide a more thorough understanding of the cognitive and behavioral profiles of ASMs.

7. Funding

This study is supported partially by Kaohsiung Medical University Research Center Grant (KMU-TC109B03) and Department of Neurology, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan, grant No. KMTTH-DK109009.

8. Acknowledgement

This study was supported by National Health Research Institutes (NHRI-11A1-CG-CO-06-2225-1) and Kaohsiung Medical University Research Center (KMU-TC110B03).

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