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Research Article

Brivaracetam Add-on Therapy for Epilepsy: Evidence Based Meta-analysis and Meta-regression of Randomized Controlled Trials

Anil DASARI, Dipika BANSAL, Kapil GUDALA

National Institute of Pharmaceutical Education and Research, Pharmacy Practice, Punjab, India

Summary

Objective: To evaluate the efficacy and safety of brivaracetam (BRV) as an add-on therapy for people with drug-resistant epilepsy.
Methods: Comprehensive literature search was done in PubMed, Cochrane Library and other databases for clinical trials (CTs) investigating the efficacy of BRV in the treatment of drug resistant epilepsy. 5 CTs having 12 dose groups including 2,187 patients comparing BRV (1212 patients) to placebo (975 patients) are pooled in the present analysis. Subgroup, sensitivity and meta-regression analysis are also performed.
Results: The pooled RD in favour of BRV over placebo for ≥50% seizure frequency reduction was 13% and 3% for complete seizure freedom. The pooled RD for the proportion of patients withdrawn, withdrawn due to adverse events (AEs) and experienced with AEs was in favour of placebo over BRV 3%, 1% and 5%, respectively. Meta-regression analysis was demonstrated no significant linear relationship to dose, but significant linear relationship to treatment duration.
Conclusion: Meta-analysis provides evidence supporting BRV effectiveness as an add-on treatment for drug-resistant epilepsy. However, results may not be generalizable due to the pooled trials were of relatively short duration, small sample size, heterogeneity and provide no evidence for the long-term efficacy of BRV.

Key words: Brivaracetam; Epilepsy; Meta-analysis; Meta-regression

Epilepside Brivaracetam Ek Tedavisi : Randomize Kontrollü Çalışmalarda Kanıta Dayalı Metaanaliz ve Metaregresyon

Özet

Amaç: İlaca dirençli epilepsi hastalarında brivaracetam'ın (BRV) ek tedavi olarak etkinliğini ve güvenilirliğini değerlendirmek.
Yöntem: BRV'nin ilaca dirençli epilepsi hastalarının tedavisinde etkinliğinin araştırılması için PubMed, Cochrane Kütüphanesi ve klinik çalışmalarla ilgili diğer bilgi bankalarından geniş kapsamlı literatür araştırılması yapıldı.
Bulgular: Plaseboyla kıyaslandığında havuzlanmış risk farkı BRV lehine olup nöbet sıklığında % 50'den fazla azalma için % 13, tam nöbetsizlik için ise % 3 idi. Çalışmadan yan etkilere bağlı çekilen ve yan etki deneyimleyen hastaların oranı BRV ile kıyaslandığında plasebo lehine olup havuzlanmış risk farkı çalışmadan çekilen hastalar için sırasıyla % 3, % 1 ve % 5 idi. Meta regresyon analizi dozla ilgili anlamlı lineer ilişki göstermezken, tedavi süresiyle ilgili anlamlı lineer ilişki göstermiştir.
Sonuç: Metaanaliz ilaca dirençli epilepsi hastalarında BRV'nin ek tedavide etkinliğini destekleyen kanıtlar sağlamaktadır. Ancak, sonuçlar çalışmaların kısa süreli olması , örneklem

büyüklüğünün küçük olması, heterojen olması ve BRV'nin uzun dönemli etkinliği ile ilgili hiçbir kanıt sağlamaması nedeniyle genellenemez.

Anahtar Kelimeler: Brivaracetam; Epilepsi; Metaanaliz; Metaregresyon

INTRODUCTION

Epilepsy affects more than 50 million adult people worldwide and approximately 2.4 million new cases are added each year with partial-onset seizures being the most common type (1). It accounts for 0.5% of the global disease burden (1). Monotherapy is the main stay of treatment although up to 30% of individuals fail to achieve complete seizure remission. Despite the availability of many new AEDs and optimized therapy, many patients remain inadequately controlled in past two decades, either due to adverse effects of AEDs or refractory seizures (2). Thus, there is definite need of newer AED which could control the refractory seizures not responding to conventional AEDs.

BRV is a novel AED that has been investigated as an add-on therapy for epilepsy. BRV is a high-affinity synaptic vesicle protein 2A (SV2A) ligand and has shown efficacy in wide range of animal models of partial-onset (focal) and generalized seizures (3-6). It also displays inhibitory activity at neuron-voltage dependent sodium channels and suppress generalized photoparoxysmal electroencephalographic responses in photosensitivity model of epilepsy (6-9). BRV was well tolerated as add-on therapy for refractory partial-onset seizures in adults but has shown consistent efficacy in early phase CTs (2,10-11). BRV exhibits linear pharmacokinetics over a wide dose range (10-600mg oral single dose) and is rapidly and completely absorbed after administration. It has elimination half-life of 7 to 8 hours and plasma protein binding of 20% (12-14). It is extensively eliminated as urinary metabolites within the 72 hours of ingestion (15).

Newer AEDs are generally taken as an "add-on" treatment with patient's existing medication. One-third of newly diagnosed patients continue as refractory seizures (16-17). It remains uncertain about the apparent contributory efficacy of AED treatment as well as a placebo effect remains an important issue. To assess these issues and to improve current strategies to develop new AEDs a clear understanding of the effectiveness of BRV for refractory epilepsy is required. This scenario prompted us to examine the evidence for placebo-corrected seizure freedom and seizure reduction following adjunctive treatment with BRV in refractory epilepsy. This report examines the efficacy and tolerability of BRV by evaluating data pooled from placebo controlled CTs.

MATERIAL AND METHODS

1 Literature Search

A comprehensive literature search carried out using PubMed, Cochrane Library, and other databases (up to January 2016) for CTs investigating the efficacy of BRV in the treatment of partial onset seizure (simple or complex partial) or secondary generalized seizures or generalized onset seizures using keywords epilepsy or seizure or convulsion and brivaracetam or UCB 34712 and randomized control trials or trials or placebo. Bibliographies and citation sections of retrieved articles had been reviewed for additional pertinent studies. Results of the study selection procedure were presented as per PRISMA guidelines.

2 Study selection

Order of study selection should be: Read title and abstract, check for relevance Filter relevant studies for reading complete full text will be read and included if (mention inclusion criteria) and excluded if (mention exclusion criteria).

Two members (AD and KG) of study group independently reviewed the titles and abstracts of all identified citations as per inclusion and exclusion criteria. An abstract was judged relevant if it reported original data, was published in English, reported results of RCTs of BRV. A study was included if it was randomized, placebo controlled, add-on trial of BRV, it recruited patients with drug resistant partial (simple partial or complex partial or secondary generalized) or generalized-onset epilepsy (1,2). Studies with pre-eclampsia, or eclampsia; if the study participants are having non-motor simple focal seizure as the only seizure type, seizures occurring only in cluster pattern, history or presence of status epilepticus during the 12 months prior to screening or during baseline, history or presence of pseudo seizures were excluded. Any discrepancies were resolved by consensus in meeting with third reviewer (DB).

3 Data extraction

The data was collected in four categories; method, outcome measure, interventions, and participants. In method section data of study design, study phase, method and type of randomization and study duration were collected. In outcome measure section data of primary, secondary efficacy outcomes (seizure remission rate, seizure free interval) and AEs were collected. In third category dose and dose escalation scheme, method of administration, treatment duration, and number of background drugs were collected. In the last category we have extracted data of age, type of seizure, seizure frequency, inclusion and exclusion criteria, total number of patients recruited, randomized, analyse and method of analysis. Additional information like author name and year of publication were also collected.

4 Outcome Measures

4.1 Primary Outcome

Primary outcome in this study is risk reduction which is calculated as risk difference (RD) in response rate between BRV and placebo. Where response rate is a measure of efficacy; it is defined as proportion of individuals who had a 50% or greater reduction in baseline adjusted seizure frequency.

4.2 Secondary outcome

Secondary outcome in this study is also risk reduction which is calculated as RD in response rate between BRV and placebo. The secondary outcomes were; seizure freedom which is defined as the proportion of individuals with successful seizure cessation at the end of the follow-up period, treatment withdrawal which is defined as the proportion of patients withdrawn from a study for any reason during the course of the treatment period. The treatment withdrawal rate is a global measure reflecting both efficacy and tolerability. Treatment withdrawal happens because of AEs, lack of efficacy or both. The withdrawal rate indicates discontinuation for AEs rather than lack of efficacy on seizure frequency in short duration trials (18). Another outcome measured is pooled AEs which is defined as the proportion of individuals withdrawn due to AEs and proportion of patients experienced AEs.

5 Risk of Bias Assessment in Included Studies

Two authors (AD, KG) independently made an assessment of the risk of bias for each trial using the Cochrane "Risk of bias" tool as described in the Cochrane Handbook for Systematic Reviews of Interventions (19). We discussed and resolved any discrepancies if arisen with third author (DB). We rated included studies as adequate, inadequate or unclear for five domains applicable to randomized controlled trials: randomization method, allocation concealment, blinding methods, incomplete outcome data and selective outcome reporting bias.

6 Data Synthesis

Primary outcome measure was to calculate the pooled RD of at least 50% seizure frequency reduction; secondary outcome measure was to calculate the pooled RD of seizure freedom, treatment withdrawal, treatment withdrawal due to AEs, and proportion of patients experienced any AE. To assess the significance of pooled effect estimate, we used Z-test; a P value <0.05 was considered to be statistically significant. To evaluate the heterogeneity among the studies, we used the I2 statistics; a value >50% indicates statistically significant for heterogeneity. If heterogeneity was observed, RD was pooled using random effects model otherwise fixed effect model was applied.

Subgroup analysis was done to estimate the source of heterogeneity, according to prescribed dose 5, 20, 50, 100, and 150mg per day and duration of treatment of each study 7, 10, 12 and 16 weeks. Sensitivity analysis was done to evaluate robustness of association by excluding the outliers. Furthermore, meta-regression was carried out for exploring relationship between dose and duration of treatment with efficacy.

An observed treatment effects may lead to differing conclusions stemming from varying inclusion criteria and study populations, variations in the study protocols (e.g. dose or length of follow-up) and random error. Differences in the observed treatment effects are often the result of between-study heterogeneity, or simply heterogeneity. While attempts to explore the impact of heterogeneity on a meta-analysis are important, a meta-analysis tacitly accepts heterogeneity by combining different studies in the search for a single underlying treatment effect (20).

As explained above, meta-regression analysis attempts to relate the effect size to study-level characteristics. This approach not only acknowledges between-study heterogeneity but also attempts to explain it at the study level. Similar to a classical meta-analysis, a meta-regression employs weights (typically random effects) to account for larger or more accurate studies. Because meta-regression analysis is observational in nature, rigorous causal associations cannot be directly ascertained. We fitted the following weighted linear regression.21 $RD = B0 + B1D/DTi + \in i$

Where D corresponds to dose of BRV among included study i and DT corresponds to duration of treatment among study i (i= 1, 2, 3, 4) and $\in$ i is an independently and identically distributed normal random variable with zero mean and fixed variance. Within the range of our explanatory variable, B1 represents the change in the RD for each increased dose of BRV and duration of treatment among included patients and B0 represents the intercept. Both funnel plot and Egger's test was used to assess the publication bias.

RESULTS

A total of 391 citations were identified initially, from Pub-Med, Cochrane Library, and other databases. After reviewing identified citations, we included 391citations after removing duplicate records and screened 391citations. From 391 records, 347 records were excluded after screening the titles. 21 studies were excluded from remaining 44 records due to not relevant. On further review 15 and 3 studies were excluded from remaining 23 studies as they were not met inclusion and exclusion criteria and case reports respectively. Finally, five full text articles were included in the final analysis (Figure 1).

1 Study Characteristics

Included five RCTs contained a total of 2,187 patients comparing BRV (1212 patients) to placebo (975 patients) in adults aged between 16-70 years (Table 1). All included studies were randomized, double blinded. Three studies used central permuted block randomization while two used interactive voice response system for randomization (2,10,22-24). Two studies

were phase IIb trials while the other three were phase III trials (2,10,22-24). In all included studies, the recruited participants were eligible to be enrolled in the double blind trial if they were found to partial (simple or complex partial or secondary generalized) or generalized on-set seizures and were currently taking 1 to 2 or 1 to ≥3 AEDs during baseline period evaluation. Baseline period was minimum of 4 week (three) and maximum of 8 week (two studies) followed by minimum of 710, 10 2, 1223-24 and 1622 weeks treatment period(2,10,22,23,24). Study medication were administered twice daily orally in each study. French et al and Biton et al have compared placebo with 5, 20, and 50 mg of BRV, Paesschen et al compared placebo with 50 and 150mg of BRV and Ryvlin et al compared placebo with 20, 50 and 150 mg of BRV. All four of these were fixed dose ranging studies where the patients were randomized in 1:1:1:1 manner. Kwan et al conducted flexible dose escalation study where they compared placebo with 20-150 mg BRV and the patients were randomized in 3:1 manner. BRV was initiated at 20 mg/day and up-titration was done 2-weeklyed in a stepwise manner to 50, 100, or 150 mg/day based on the investigator's assessment of efficacy and tolerability during dose finding period (8 weeks). Patients received the dose which they received at the end of the dose-finding period during the maintenance period of 8 weeks.

2 Risk of Bias of Included Studies

Quality assessment based on Cochrane handbook revealed that the studies had largely low or unclear risk of bias. The risk of bias graph of included studies is given in Figure 2.

3 Publication Bias

The examination of a funnel plot for primary and secondary outcomes suggest evidence of no publication bias which was further conformed by Egger's test.

4 Primary Outcome

4.1 50% or Greater Seizure Frequency Reduction

Random effect model was used for pooled analysis due to significant heterogeneity between studies were observed (I2= 40.1%) (Table 2). Pooled analysis of 5 studies having 12 dose groups demonstrated that weighted pooled RD of 13% (95% CI 10-17, p<0.001) for 50% or greater seizure frequency reduction of adjunctive AED therapy versus placebo. The multivariable-adjusted RD of ≥50% seizure reduction for each study and all studies combined are shown in Figure 3. We also performed subgroup analysis according to dose received (5, 20, 50, 100, and 150 mg/day) and duration of treatment (7, 10, 12 and 16 weeks) results were found to be significant different except for 5mg dose (p = 0.062) (Table 2). Our results were robust as shown by sensitivity analysis, where analysis performed by removing one study at a time showed similar effect estimate (9-16) as that of pooled effect estimate. Funnel plot demonstrated that there was no publication bias which was even observed in Egger's test (p = 0.082) (Table 2).

5 Secondary Outcome

5.1 Seizure Freedom

Fixed effect model was used for pooled analysis as no significant heterogeneity was observed (I2= 59.1%) (Table 2). Pooled weighted analysis showed that RD of 3% (95% CI 2-5, p = 0.006) for seizure freedom of adjunctive AED therapy versus placebo. The multivariable-adjusted RD of seizure freedom for each study and all studies combined are shown in Figure 3. We performed subgroup analysis according to prescribed dose (5, 20, 50, 100, and 150 mg) and treatment period of each study (7, 10, 12 and 16 weeks) results were found to be significant different for 20mg (p = 0.05) and 50mg (p = 0.001) and no significant difference for 16 week

treatment duration (p = 0.111) (Table 2). We also performed sensitivity analysis for checking robustness of results; as RD values lay within the range of 1-3, thus clearly showing that no impact of any single study on pooled RD. Funnel plot demonstrated that there was no publication bias which was even observed in Egger"s test (p = 0.609) (Table 2).

5.2 Proportion of Patients Withdrawn from Trial due to Any Reason

No significant heterogeneity was found (I2= 71.2%) (Table 2), fixed effect model was used to compute pooled effect of estimate. Pooled analysis of RD of 3% (95% CI 1-6) for proportion of patients withdrawn due to any reason of adjunctive AED therapy versus placebo. However the results were not found to be statistically significant (p = 0.222). The multivariable-adjusted RD of proportion of patients withdrawn for each study and all studies combined are shown in Figure 4. Further, we found no statistically significant difference in this outcome among the studies sub-grouped on the basis of prescribed dose except 50mg (p = 0.019) and 150mg (p = 0.021) as well as we also found no statistical significance difference in this outcome among the studies sub-grouped according to the duration of treatment except 10 weeks (p = 0.000) (Table 2). Sensitivity analysis showed that RD values lie between the range (2-7) and this clearly indicating that any single study had no major effect on pooled RD. Visual examination of funnel plot indicates minimal asymmetry, again conformed by Egger's test (p = 0.281) (Table 2), demonstrating that little or no publication bias.

5.3 Proportion of Patients Withdrawn Due to AEs

Significant heterogeneity was found (I2= 0%) (Table 2). So, analysis was done using random effect model. Pooled weighted RD was about 1% (95% CI 1-3) for proportion of patients withdrawn due to AEs of adjunctive AED therapy versus placebo, but the results were not statistically significant (p = 0.164). The multivariable-adjusted RD of each study and all studies combined are shown in Figure 4. On subgroup analysis according to prescribed dose (5, 20, 50, 100, and 150 mg) and duration of treatment (7, 10, 12 and 16 weeks), we did not find any significant difference (Table 2). Sensitivity analysis demonstrated the robustness of pooled RD and that RD values lied within the range as that of main pooled analysis (1-3). This clearly showed that no single study had a major impact on pooled RD. Visual examination of funnel plot showed asymmetry, even though Egger"s test (p = 0.554) conformed that little or no publication bias (Table 2).

5.4 Proportion of Patients Experienced with AEs

As we found heterogeneity (I2= 0%), a random effect model was chosen instead of fixed effect model. The pooled weighted results showed that RD of 5% (95% CI 1-9, p = 0.024) for proportion of patients experienced AEs of adjunctive AED therapy versus placebo. The multivariable-adjusted RD of each study and all studies combined are shown in Figure 4. We did not find any significant difference in pooled estimate of RD, as the studies were sub-grouped according to prescribed dose (5, 20, 50, 100, and 150 mg/day) and treatment period except 12 weeks (p = 0.002) (Table 2). Sensitivity analysis also revealed the robustness of results as the pooled estimate RD by excluding single study lied between the same range (1-9) as pooled effect estimate, clearly demonstrating that no single study had major effect on pooled RD. Visual examination of funnel plot revealed that little or no publication bias, further conformed by Egger's test (p = 0.398) (Table 2).

6 Co-relation of BRV Dose and 50% or Greater seizure Frequency Reduction

The results of the meta-regression analysis were presented graphically in Figure 5 , as

well as the fitted meta-regression line and expected 95% confidence bands. Specifically, the intercept (β0) is estimated as 0.122 (95 % CI: 0.066-0.177) and β1 is estimated as 0.0001 (95% CI: -0.0005 to 0.0007). These findings suggest no statistical significant linear relationship between dose of BRV in study population and the observed effectiveness of 50% or greater seizure frequency reduction in a given study.

• The total Q of each effect size about the grand mean can be partitioned into its component parts - the Q due to the variation in effect size that can be explained by subgroup membership, and the part that can"t. The Q-between (in the traditional model) and the Q-model (in the regression) are both 0.115 with df = 1 and p = 0.73. Each tells us that effect size was not differs between subgroups.

• The Q-within (in the traditional model) and the Q-residual (in the regression) are both 18.18 with df = 10 and p = 0.052. Each tells us that the assumptions of the fixed-effect model have not been violated.

• The Q-total in each case is 18.3 with df = 11 and p = 0.074. Each tells us that effect sizes were not varying when we ignore subgroups and do not work with deviations of all studies from the grand mean.

• The Q-values are additive. Q-between plus Q-within equals Q-total.

7 Co-relation of Duration of Treatment of BRV and 50% or Greater Seizure Frequency Reduction

The results of the meta-regression analysis were presented graphically in Figure 6 , as well as the fitted meta-regression line and expected 95% confidence bands. Specifically, the intercept (B0) is estimated as 0.323 (95 % CI: 0.159-0.487) and B1 is estimated as -0.016 (95% CI: -0.029 to -0.002). These findings suggest a statistically significant linear relationship between duration of treatment of BRV in study population and observed effectiveness of 50% or greater seizure frequency reduction in a given study.

• The total Q of each effect size about the grand mean can be partitioned into its component parts - the Q due to the variation in effect size that can be explained by subgroup membership, and the part that cannot.

• The Q-between (in the traditional model) and the Q-model (in the regression) are both 5.62 with df = 1 and p = 0.01. Each tells us that effect size was differs between subgroups.

• The Q-within (in the traditional model) and the Q-residual (in the regression) are both 12.68 with df = 10 and p = 0.241. Each tells us that the assumptions of the fixed-effect model have not been violated.

• The Q-total in each case is 18.3 with df = 11 and p = 0.074. Each tells us that effect sizes were not varying when we ignore subgroups and do not work with deviations of all studies from the grand mean.

• The Q-values are additive. Q-between plus Q-within equals Q-total.

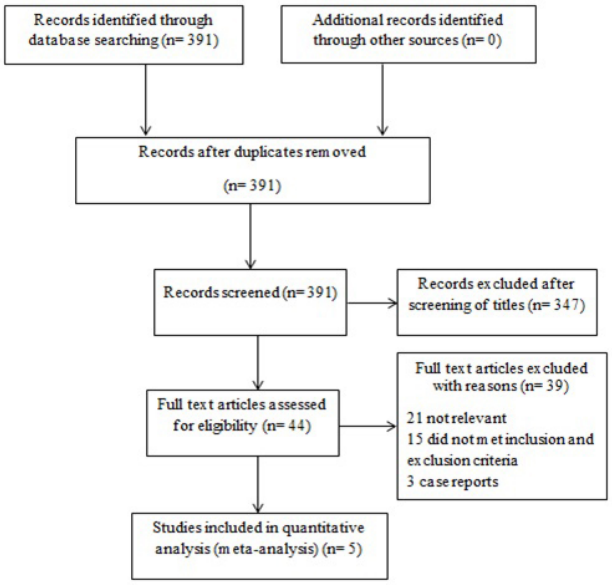

Figure 1: *Flowchart representing the selection process*

Table 1. Study Characteristics

Study characteristics	French et al, 2010	Paesschen et al, 2012	Kwan et al, 2013	Ryvlin et al, 2014	Biton et al, 2014
Study design	R, DB, PG	R, DB, PG	R, DB, PG	R, DB, PG	R, DB, PG
Method of randomization	Central, PB	Central, PB	Central, PB	C, IVRS	C, IVRS
Randomization Ratio	1:1:1:1	1:1:1:1	3:1	1:1:1:1	1:1:1:1
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo
Study Phase	IIb	IIb	III	III	III
Dosing type	DR	DR	DE	DR	DR
Baseline Period (weeks)	4	4	4	8	8
Treatment duration (Week)	7	10	16 (8-dose finding, 8-maintenance)	12	12
Dose, mg/day	5, 20, 50	50, 150	20-150	20, 50, 100	5, 20, 50
Method of administration	Oral	Oral	Oral	Oral	Oral
Treatment Duration, Week	7	10	16	12	12
Background AEDs	1-3	1-3	1-3	1-3	1-3
Primary outcome = % reduction in baseline adjusted focal seizure frequency/week	Yes	Yes	Yes	Yes	Yes
Baseline Seizure frequency/week#	2.18 (NR)	2.32 (1.45-4.5)	2.25 (1.24-4.37)	1.95 (1.28-3.78)	2.52 (1.5-6.05)
Age, year	16-65	16-65	16-70	16-70	16-70
Age, year*	33.12 (12.2)	37.5 (11.3)	35.6 (11.5)	37.2 (13.1)	38.15 (12.45)
Gender, Male n (%)	110 (53)	70 (44)	NR	227 (57)	195 (49)
Epilepsy Duration, year*	19.9 (12.2)	21.9 (13.1)	NR	21.8 (12.9)	23.9 (12.5)
Seizure Type	Simple, complex partial, secondary generalization, generalized unclassified	Simple and complex partial, secondary gen, generalized and cluster type	Partial and generalized seizures	Partial seizure	Partial seizure
Patients Randomized	210	157	480	399	400
Efficacy Analysis, ITT	316	209	480	598	584

R, Randomized; DB, Double Blind; PG, Parallel-group; PB, Permuted Block, IVRS, Interactive Voice Response System; DR, Dose range; DE, Dose escalation; *Mean (SD); # Median (Q1-Q3); AEDs, Anti-epileptic drugs; SD, Standard deviation; NR, Not reported; ITT, Intention-to-treat

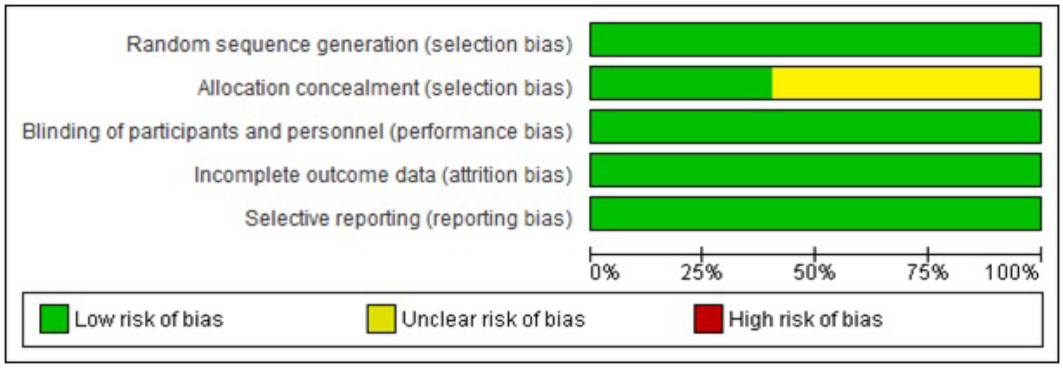

Figure 2: *Risk of bias graph*

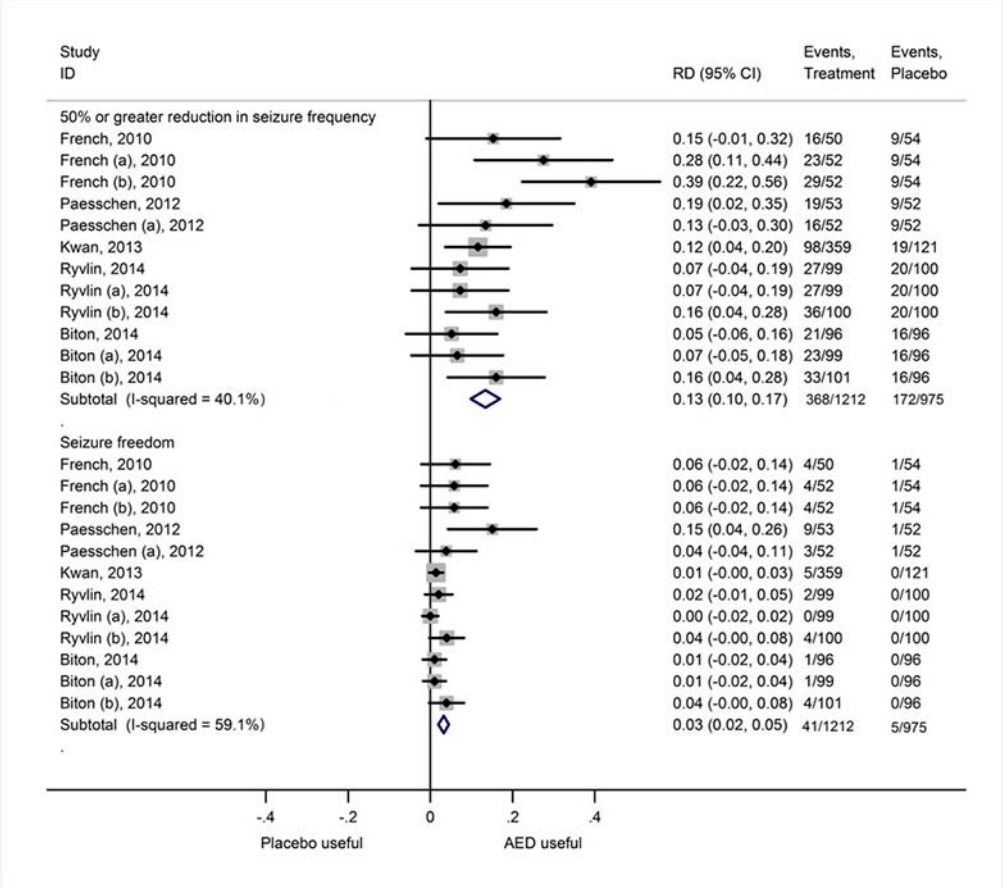

Figure 3: *50% or greater seizure reduction and seizure freedom: Pooled estimate of risk difference (RD) and 95% confidence intervals (CIs) of 50% or greater seizure frequency reduction and seizure freedom associated with BRV use based on 5 studies (randomized control trials) having 12 dose groups involving 2,187 epileptic participants. Squares indicate RD in each study. The square size is proportional to the weight of the corresponding study in the meta-analysis; the length of horizontal lines represents the 95% CI. The blue colour outlined diamond indicates the pooled RD and 95% CI (random model and fixed-effects).*

Table 2. Overall effect estimates of Brivaracetam and according to study characteristics

Study	Studies N	Patients N	RD (95% CI)	P value	Test of heterogeneity		Test of publication bias
					Q value (d.f)	I2 (%)	Egger's P
≥50% Seizure Frequency Reduction							
All studies	12	2,187	0.13 (0.10-0.17)*	<0.001	11	40.1	0.082
Sensitivity analysis	12	2,187	0.13 (0.09-0.16)	<0.001			
Brivaracetam Dose Subgroup							
5 mg/day	2	296	0.09 (-0.00-0.18)	0.062			
20 mg/day	3	500	0.11 (0.04-0.19)	0.002			
50 mg/day	4	607	0.18 (0.11-0.24)	<0.001			
100 mg/day	1	200	0.16 (0.04-0.28)	0.01			
150 mg/day	2	584	0.12 (0.05-0.19)	<0.001			
Brivaracetam Duration of Treatment (Week) Subgroup							
7	3	316	0.27 (0.18-0.37)	<0.001			
10	2	209	0.16 (0.04-0.28)	0.007			
12	1	1182	0.10 (0.05-0.15)	<0.001			
16	6	480	0.12 (0.04-0.20)	<0.001			
Seizure freedom							
All studies	12	2,187	0.03 (0.02-0.05)¤	0.006	11	59.1	0.609
Sensitivity analysis	12	2,187	0.02 (0.01-0.03)	0.002			
Brivaracetam Dose Subgroup							
5 mg/day	2	296	0.03 (-0.01-0.06)	0.109			
20 mg/day	3	500	0.02 (-0.00-0.05)	0.05			
50 mg/day	4	607	0.05 (0.02-0.08)	0.001			
100 mg/day	1	200	0.04 (-0.00-0.08)	0.068			
150 mg/day	2	584	0.02 (-0.00-0.04)	0.072			
Brivaracetam Duration of Treatment (Week) Subgroup							
7	3	316	0.06 (0.01-0.11)	0.014			
10	2	209	0.09 (0.03-0.16)	0.004			
12	1	1182	0.02 (0.01-0.03)	0.004			
16	6	480	0.01 (-0.00-0.03)	0.111			
Proportion of patients Withdrawn due to any reason							
All studies	12	2,187	0.03 (0.01-0.06)¤	0.222	11	71.2	0.281
Sensitivity analysis	12	2,187	0.03 (-0.02-0.07)	0.22			
Brivaracetam Dose Subgroup							
5 mg/day	2	296	0.06 (-0.00-0.013)	0.065			
20 mg/day	3	500	-0.02 (-0.06-0.03)	0.462			
50 mg/day	4	607	0.05(0.01-0.10)	0.019			
100 mg/day	1	200	-0.02 (-0.09-0.05)	0.579			
150 mg/day	2	584	0.07 (0.01-0.12)	0.021			
Brivaracetam Duration of Treatment (Week) Subgroup							
7	3	316	-0.05 (-0.11-0.00)	0.053			
10	2	209	0.26 (0.15-0.36)	0.000			
12	1	1182	0.02 (-0.01-0.05)	0.136			
16	6	480	0.02 (-0.04-0.08)	0.552			
Proportion of patients withdrawn due to AEs							
All studies	12	2,187	0.01 (-0.01-0.03)*	0.164	11	0	0.554
Sensitivity analysis	12	2,187	0.01 (-0.01-0.03)	0.186			
Brivaracetam Dose Subgroup							
5 mg/day	2	296	0.04 (-0.01-0.08)	0.165			
20 mg/day	3	500	0.00 (-0.03-0.04)	0.812			
50 mg/day	4	607	0.01 (-0.02-0.04)	0.433			
100 mg/day	1	200	0.01 (-0.05-0.07)	0.733			
150 mg/day	2	584	0.01 (-0.03-0.05)	0.671			
Brivaracetam Duration of Treatment (Week) Subgroup							
7	3	316	-0.03 (-0.07-0.01)	0.182			
10	2	209	0.01 (-0.05-0.06)	0.743			
12	1	1182	0.03 (0.00-0.05)	0.024			
16	6	480	0.01 (-0.04-0.05)	0.802			
Proportion of patients experienced AEs							
All studies	12	2,189	0.05 (0.01-0.09)*	0.024	11	0	0.398
Sensitivity analysis	12	2,189	0.05 (0.01-0.09)	0.02			
Brivaracetam Dose Subgroup							
5 mg/day	2	297	0.03 (-0.08-0.14)	0.59			
20 mg/day	3	501	0.07 (-0.01-0.15)	0.096			
50 mg/day	4	607	0.06 (-0.02-0.13)	0.137			
100 mg/day	1	200	0.10 (-0.04-0.24)	0.15			
150 mg/day	2	584	-0.00 (-0.09-0.08)	0.947			
Brivaracetam Duration of Treatment (Week) Subgroup							
7	3	316	0.00 (-0.11-0.11)	0.974			
10	2	209	-0.04 (-0.16-0.09)	0.579			
12	1	1184	0.09 (0.03-0.14)	0.002			
16	6	480	0.01 (-0.09-0.11)	0.884			

CI, Confidence interval; d.f, Degrees of freedom; RD, Risk difference; ¤, Fixed effect model; *, Random effect model

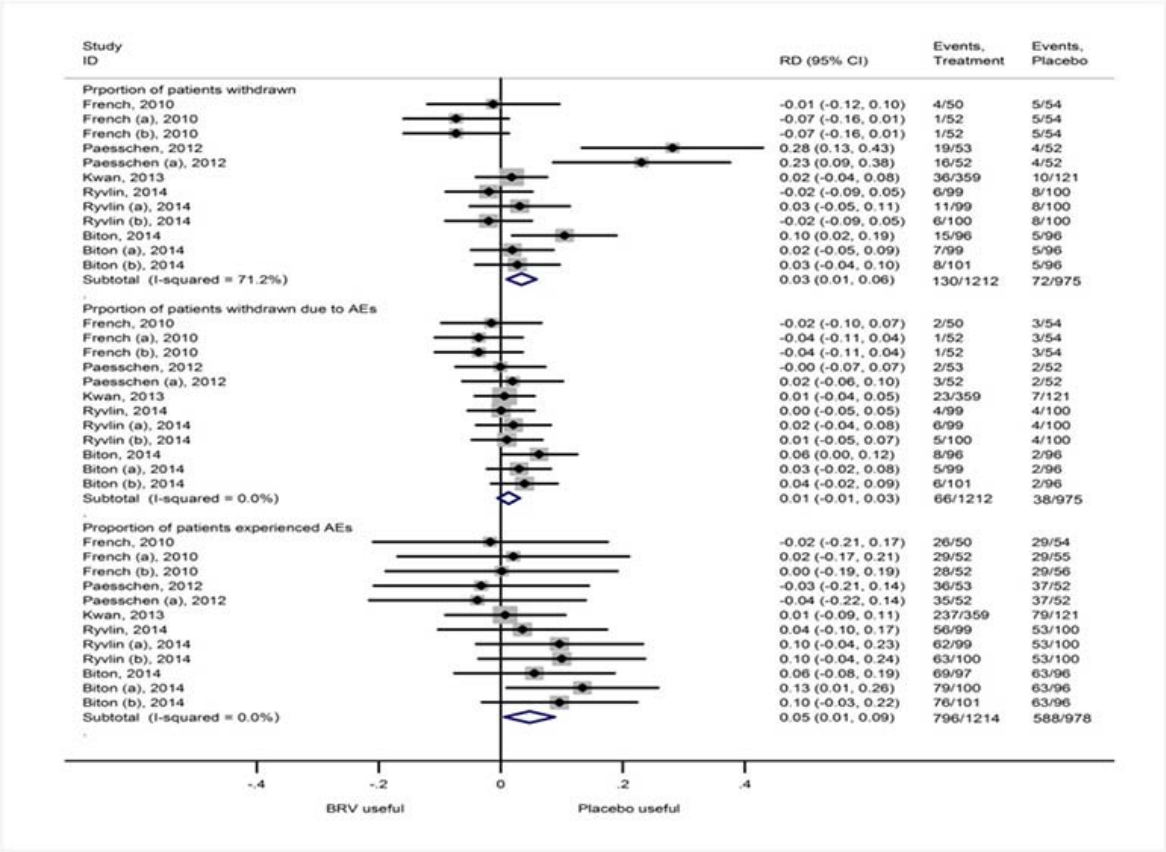

Figure 4: *Safety outcomes: Pooled estimate of risk difference (RD) and 95% confidence intervals (CIs) of safety outcomes associated with BRV use based on 5 studies (randomized control trials) having 12 dose groups involving 2,187 epileptic participants. Squares indicate RD in each study. The square size is proportional to the weight of the corresponding study in the meta-analysis; the length of horizontal lines represents the 95% CI. The blue colour outlined diamond indicates the pooled RD and 95% CI (fixed-effects and random model).*

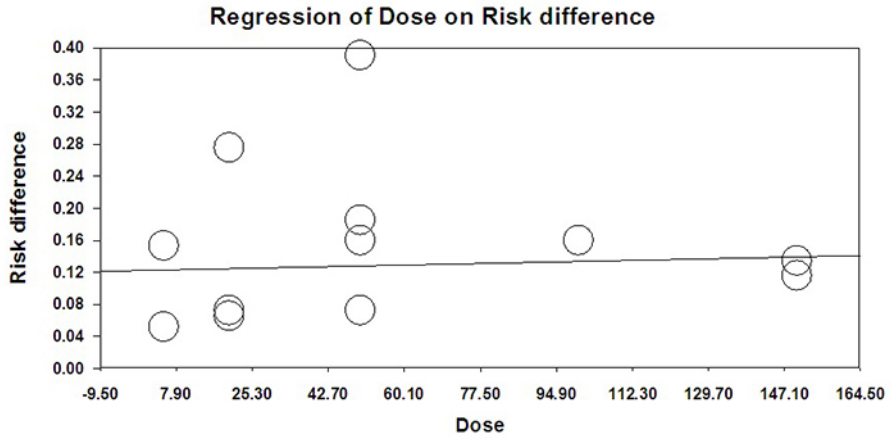

Figure 5: *Fixed effect model-regression of risk difference on dose: In the graph, each study is represented by a circle that shows the actual co-ordinates (observed effect size by dose) for that study. The size (specifically, the area) of each circles is proportional to that study's weight in analysis. Since this analysis is based on the fixed effect model, the weight is simply the inverse of the within-study variance for each study. The centre line shows the predicted values. A study performed relatively close.*

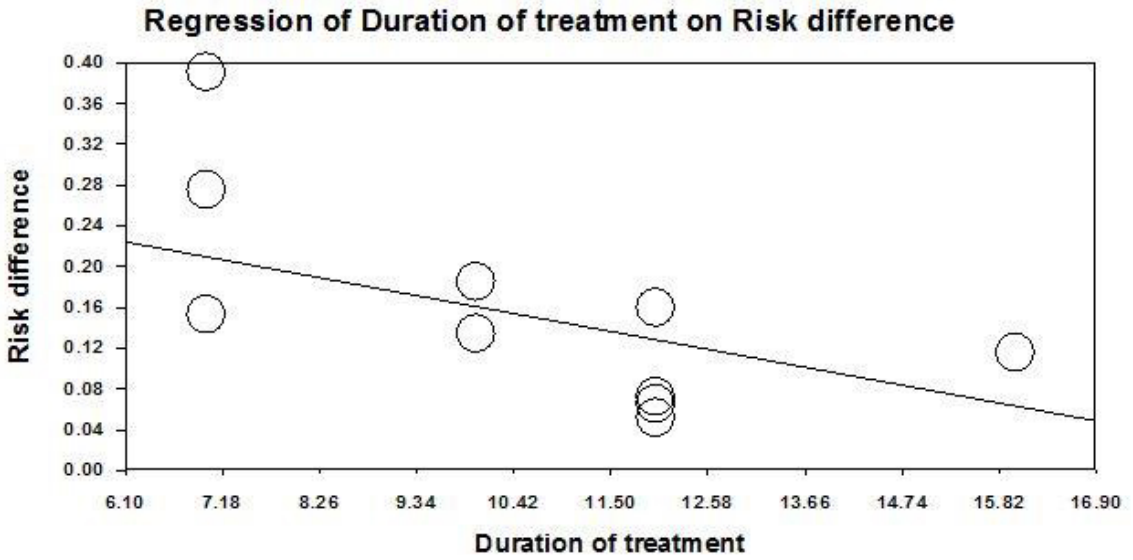

Figure 6: *Fixed effect model-regression of risk difference on dose: In the graph, each study is represented by a circle that shows the actual co-ordinates (observed effect size by dose) for that study. The size (specifically, the area) of each circles is proportional to that study's weight in analysis. Since this analysis is based on the fixed effect model, the weight is simply the inverse of the within-study variance for each study. The centre line shows the predicted values. A study performed relatively close.*

DISCUSSION

The present meta-analysis included 5 studies and all were double blinded placebo controlled trials. All included trials reported response rate as intention to treat analysis. The overall effect estimate of efficacy showed BRV is effective in reducing the minimum 50% seizure frequency reduction when used as add-on therapy for epilepsy. Treatment is increasing 13% to develop minimum 50% seizure frequency reduction as compared to placebo. Pooled effect estimate RD revealed that BRV increasing the 3% to develop seizure free as compared to placebo. We were done sub-group analysis according to the dose received by patients (5, 20, 50, 100, and 150 mg) and duration of treatment of each study 7, 10, 12 and 16 weeks, results were found to be coherent with that of pooled main analysis. We also estimated the relationship of dose and duration of treatment to efficacy through meta-regression model, found that there was no significant linear relationship in efficacy according to dose, but significant linear relationship was observed between duration of treatment and efficacy. No publication bias and sensitivity analysis was also showed that results were consistent as that of polled estimate RD. So, estimated results might be reliable.

Pooled effect estimate RD of all studies showed that proportion of patients withdrawal due to any reason and due to AEs from BRV is more likely to be withdrawn as compared to placebo, although it found to be no statistical significant ($p = 0.222$ and $p = 0.164$, respectively). This is likely to represent the problem with tolerability rather than poor seizure control due to short duration of trials, such as those reviewed here.18 Coming to the proportion of patients experienced with AEs, overall effect estimate RD demonstrated that BRV group have significantly more likely to occur AEs than placebo. Commonly reported AEs are headache, somnolence, dizziness, fatigue, nausea, and nasopharyngitis.

Commonly produced severe AEs are convulsion, status epilepticus, and humerus fracture. The majorly reported AEs were belonged to mild to moderate in both group"s placebo and BRV.

Although, the results of this meta-analysis provides a proof of efficacy of BRV as add-on for epilepsy with regard to seizure reduction, it does not tell us comparison with other AEDs because there is no randomized control trial that allow comparison of each other for add-on treatment. This is very important issue for clinicians who are faced with an ever-increasing number of antiepileptic drugs to choose from. To address this question, active controlled studies will required prospectively to provide the evidence. This is needed to enable clinicians to make an evidence-based choice between antiepileptic drugs. The main important limitations of the present study include small sample size, shorter duration of treatment and heterogeneity.

CONCLUSION

Meta-analysis provides evidence supporting BRV effectiveness as an add-on treatment for drug-resistant epilepsy. However, the pooled trials were of relatively short duration and provide no evidence for the long-term efficacy of BRV. In the short term use BRV as an add-on has been shown to be associated with several AEs. Apparently, further investigation on the efficacy and safety of BRV as add-on treatment for drug-resistant epilepsy is needed.

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Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

Ethical Publication Statement

I confirm that I have read the Journal"s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. I do not have any conflict of interest to disclose.

Correspondence to:
Dipika Bansal
E-mail: dipikabansal079@gmail.com

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