



The Efficacy of Leviteracetam versus Carbamazepine for Epilepsy: A Meta-Analysis

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Abstract

Leviteracetam (LEV) is a novel antiepileptic drug with improved tolerance and safety, while carbamazepine (CBZ) represents classical antiepileptic drugs. So far, a systemic comparison of the efficacy and side effects of these two drugs is lacking. A literature review on the comparison of leviteracetam versus carbamazepine for patients with epilepsy was performed up to September 2013 using PubMed, EMBASE, the Cochrane Library and ISI web of science. Finally, 3 randomized controlled trials (RCT) studies met the criteria on comparing the efficacy of leviteracetam versus carbamazepine for patients with epilepsy were included for meta-analysis. Stata 11.0 was used to analyze and summarize the respective data. Three RCTs met the entry criteria. The relative risk (RR) and 95% and the confidence interval (CI) of leviteracetam versus carbamazepine for 6- and 12-month seizure free intervals were 1.0 (0.91-1.10) and 0.97 (0.84-1.13), respectively, for therapy discontinuation due to adverse events (AEs) were 0.62 (0.48-0.80) and 1.00 (0.94-2.05), respectively, and for withdrawal after 6- and 12-month treatment were 0.8 (0.64-0.99) and 0.87 (0.74-1.03), respectively. The RR and 95% CI for occurrence of headache, fatigue, diarrhea, vertigo, nasopharyngitis, depression, weight gain and rash were 0.88 (0.73-1.06), 1.08(0.63-1.83), 1.23 (0.66-2.28), 0.92 (0.49-1.71), 0.85 (0.59-1.22), 2.15 (1.26-3.68), 0.69 (0.45-1.04), 0.39 (0.23-0.68), respectively. The major outcomes such as rate of seizure freedom were similar between leviteracetam and carbamazepine. However, leviteracetam led to depression more frequently than carbamazepine, while carbamazepine caused rash more frequently. However, the limited numbers of available RCTs studies and included patients in this study made our results less convincing and accurate.

Keywords: Efficacy, Leviteracetam, Carbamazepine, Epilepsy, Meta-analysis

Introduction

Epilepsy is one of the most common neurological conditions in the world, with almost 70 million affected people worldwide (1). The median incidence of epilepsy was 50.4/100,000/year, while it was 45.0 for high-income countries and 81.7 for low- and middle-income countries (2, 3). Premature mortality in epilepsy was 8.8% yet it was 0.7% in normal population (4). Three fourths of the patients have treatable epilepsy and can lead near-

normal lives, yet 85% do not receive any treatment at all (2).

Leviteracetam (LEV) is one of the new antiepileptic drugs while carbamazepine (CBZ) is a classical antiepileptic drugs (AED). A meta-analysis comparing LEV with other second-generation antiepileptic drugs had been conducted; however, the comparison was indirect (5). LEV is a broad-spectrum anti-epileptic drug with a safe profile (6,

7). Among the side effects, tiredness (7.8%) and aggressiveness (5%) were the most common ones for of LEV. These were dose-related and the behavioral changes and even psychotic reactions were more commonly seen in younger patients (6, 7). CBZ remains one of the most commonly used AEDs worldwide especially in adults. However, in the elderly and in male patients it is a potent inducer of CYP450 system and is subject to auto induction with a considerably narrow therapeutic index (8-11).

Dieter Schmidt reported that the introduction of new AEDs have significant advantages compared to the old AEDs, particularly due to the absence of severe hypersensitivity reactions and detrimental drug interactions mediated by enzyme-induction in some new AEDs. However, well-controlled trials of recent-onset epilepsy did not find any evidence that the new AEDs were superior to the old AEDs in efficacy (12). French et al. pointed out that in spite of some desirable characteristics of new AEDs, they are much more expensive than standard drugs (13). Therefore, it is also important to determine whether the potential benefits are worth the additional cost.

There have been some debates of the two drugs, which are more suitable for epileptic patients. For this reason, we conducted a meta-analysis of published randomized controlled trials, comparing the efficacy represented by total withdrawal rate, the ADR-related withdrawal, the seizure-free rate, and different types of nervous system adverse events including headache, fatigue, diarrhea, vertigo, nasopharyngitis, depression, weight gain and rash after using two drugs of LEV and CBZ on patients with epilepsy.

Methods

Study characteristics

Participants: patients with epilepsy. Interventions: two anti-epileptic drugs. Comparisons: comparing the efficacy of the two drugs--leviteracetam versus carbamazepine. Outcomes: the outcomes including: total withdrawal rate, the ADR-related withdrawal, the seizure-free rate, and different types of nervous system adverse events, such as

headache, fatigue, diarrhea, vertigo, nasopharyngitis, depression, weight gain and rash; the follow-up duration was 12 months.

Search strategy

We searched all published articles included the two drugs in the databases MEDLINE, EMBASE, the COCHRANE library and ISI web of science (up to September 2013) by using the following keywords: (Epilepsy OR Seizure OR Epileptic Seizures) AND (LEV OR Leviteracetam) AND (Carbamazepine OR CBZ) AND (RCT OR Randomized Controlled Trials). We also scanned the reference lists of all included studies for additional references. We contacted the authors of included studies for additional eligible studies. There was no limitation regarding language and year. Two authors (Chengjuan J and Yayun W) reviewed the titles and abstracts of articles obtained from electronic databases respectively and decided which articles were eligible for full-text review.

Inclusion and exclusion criteria

We included RCTs that not only contained the therapy of LEV and CBZ, but also were double-blinded or open-label, had been performed in newly diagnosed epileptic patients or patients with partial or generalized epilepsy. We did not restrict the age of the patients.

We excluded studies if they explored only one of the two drugs, we also excluded repetitive articles, reviews, case-control studies and cohort studies and studies that were published as abstracts, letters, or commentaries.

Data extraction and quality assessment

To obtain the important information about the included articles for the Meta analysis, we designed a standard data abstraction form using excel 2003. Two authors, Chengjuan J and Yayun W (graduate students from Shandong University with a master degree), extracted data independently. When there was a controversy, they would discuss or resort to a librarian until consensus was reached. We extracted information on authors, journal, year of publication, country and region, study type, blinding, number of centers, sample size, age of patients, duration of follow-up, num-

ber of people with 6-month and 1-year seizure free intervals, number of patients discontinued therapy due to adverse reactions, and number of patients with different adverse reactions. We extracted data on ITT (intention to treat) population or PP (per protocol) population properly.

To assess the study quality, we used the five-point scale developed by Jadad et al. (14). They were assessed based on the following 3 aspects: randomization (0-2 points), double blinding (0-2 points) and withdrawals and dropouts (0-1 point). Scores ≤ 2 points indicated inferior quality of the study whereas scores ≥ 3 points supported the study with high quality.

The final summarized data was performed by using Stata 11.0.

Outcome measures

In this meta-analysis, we measured the total withdrawal rate, the ADR-related withdrawal, the seizure-free rate, and different types of nervous system adverse events. Zaccara reported that the classification of nervous system adverse events was divided into the following 5 broad classes: those affecting vigilance, those affecting the vestibule-cerebellar system, those affecting the motor system (including Chorea Parkinsonism, tremor), cognitive impairment, and psychiatric and psychological adverse effects (including anxiety, depression, dissociation, hallucination, cognitive impairment and behavioral disturbances) (15). There were still several uncertainties that needed clarification regarding psychological and psychiatric AEs. First, the subjective measures could not be quantified. Second, different patients had different thresholds for the adverse effects. Third, patients were susceptible to the covert influence from investigators. Therefore, the analytical results of the psychological and psychiatric AEs might deviate from the actual outcomes.

Analysis

We extracted the number of patients that had received LEV and CBZ therapies separately and the number of patients who had our desired observed measurements from each study.

We used Stata version 11.0 to perform the meta-analysis. The “metan” command in Stata was used to pool the OR across studies and generate a visual forest plot for inspection. We measured heterogeneity in results across studies using the Cochran Q (significance < 0.05) and I² statistic (16, 17). Our results indicated these studies were not homogeneous. When substantial heterogeneity was detected, the summary estimate was then calculated according to DerSimonian and Laird random-effects model (18). Otherwise, pooled estimates were based on the fixed effects model.

Sensitivity analysis was performed to assess the effects of selected study quality and clinical factors on the pooled outcome.

Egger’s test and Begg’s test were used to assess the possibility of publication bias, and a funnel plot was usually applied for visual inspection (19, 20). We considered the publication bias statistically significant when the $P < 0.05$ for Egger’s or Begg’s tests. When it contained no less than 10 included studies, publication bias could be evaluated through Egger’s test and Begg’s test.

Meta-regression is a method to assess the source of heterogeneity; however, it could not be evaluated with less than 10 included studies (21). In other words, as the number of included studies was small, it would produce bias when using meta-regression for analyzing the source of heterogeneity. Therefore, in this study we did not analyze the source of heterogeneity.

Results

Search results

The initial search identified 174 articles. After examining the titles and abstracts, only 35 articles were retained for full review. Thirty-five studies met our criteria for detailed analysis. Figure 1 shows the flow diagram for identifying the articles that were included in our final analysis. The 3 studies that met the inclusion criteria are summarized in Table 1. A total of 1696 epileptic patients were in the included studies.

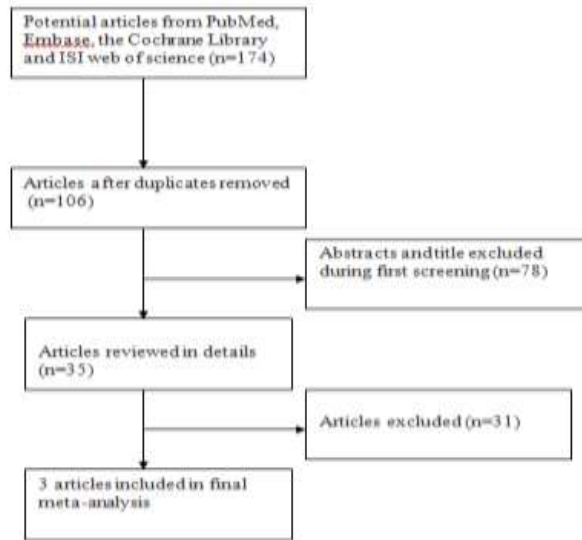


Fig. 1: Flow diagram of the literature search and trial selection process

Study characteristics and quality assessment

Four studies were potentially suitable for this analysis. Only 3 studies are finally included, as we were not able to obtain detailed information regarding the fourth study (22). Characteristics of the 3 selected studies are presented in Table 1. All 3 studies were published from 2007 to 2013 and they were all RCTs. One study was conducted in Italy (23), one in European countries and Australia (24), and one in European countries and South Africa (25). The follow-up duration was 12 months. All included patients were adults. The sample sizes of these studies ranged from 128 to 996. The eligible patients for two studies were patients with newly diagnosed epilepsy (23, 24), and one patient with late post-stroke seizures (23).

Table 1: Characteristics of the trials included in this meta-analysis

Reference	No. of sample size	Eligible patients	Daily dose	Maximum dose	Follow-up duration
25	576	patients with newly diagnosed epilepsy	LEV 1000 mg/day CBZ 400 mg /day	LEV 3000 mg/day, CBZ 1200 mg/day	12 months
23	128	Patients with Late Poststroke Seizures	LEV 1000 mg/day CBZ 600 mg /day	LEV 3000 mg/day, CBZ 1600 mg/day	12 months
24	992*	patients with newly diagnosed epilepsy	LEV 1000 mg/day CBZ 600 mg /day	LEV 3000 mg/day, CBZ 1600 mg/day	12 months

*only include CBZ stratum, VPA stratum not included

Brodie et al. proved that with increasing doses of LEV and CBZ, the rate of seizure freedom was higher. Consoli et al. summarized the number and percentage of abnormal EEGs, neuropsychological findings and number of patients with recurrence of seizures (23). Trinka et al. reported the quality of life, time to first seizure for focal seizures and generalized seizures, treatment withdrawal rate and seizure freedom rate of focal seizures and generalized seizures independently and separately recorded the number of patients with drug-related AEs, severe AEs, and serious AEs (24).

The quality of the RCTs was assessed according to the Jadad scale for quality. Outcome of quality assessment of RCTs are shown in Table 2. Only one study scored five points (25), the others scored 3 (23, 24). The scores implied that articles included in this meta-analysis were of high quality. As in the report, we included three eligible studies. The number of included studies was too small to perform analysis of bias of each study. If we analyze the risk of bias of each study, the results were unstable and believable.

Outcomes

1. Estimates of patients with seizure-freedom
(Fig. 2)

Information on seizure-free intervals for 6 months information was available for 1696 patients in all 3 trials. The common estimated risk ratio (RR) was 1.00 (95% CI: 0.91-1.10), favoring neither LEV nor CBZ, and was not statistically significant ($P=0.995$). Meanwhile there was evidence of

moderate heterogeneity between trials ($I^2=52.4\%$, $P=0.122$).

Three studies including 1696 participants, reported seizure-freedom for 12 months. The pooled estimated risk ratio (RR) was 0.97 (95% CI: 0.84-1.13), also favoring LEV but without statistical significance ($P=0.725$). However quantitative heterogeneity was observed between trials ($I^2=73.8\%$, $P=0.022$).

Table 2: Outcome of quality assessment of RCTs by Jadad Scale

Reference	Randomization	Double Blinding	Withdrawals and Dropouts	Total Scores
25	2	2	1	5
23	2	0	1	3
24	2	0	1	3

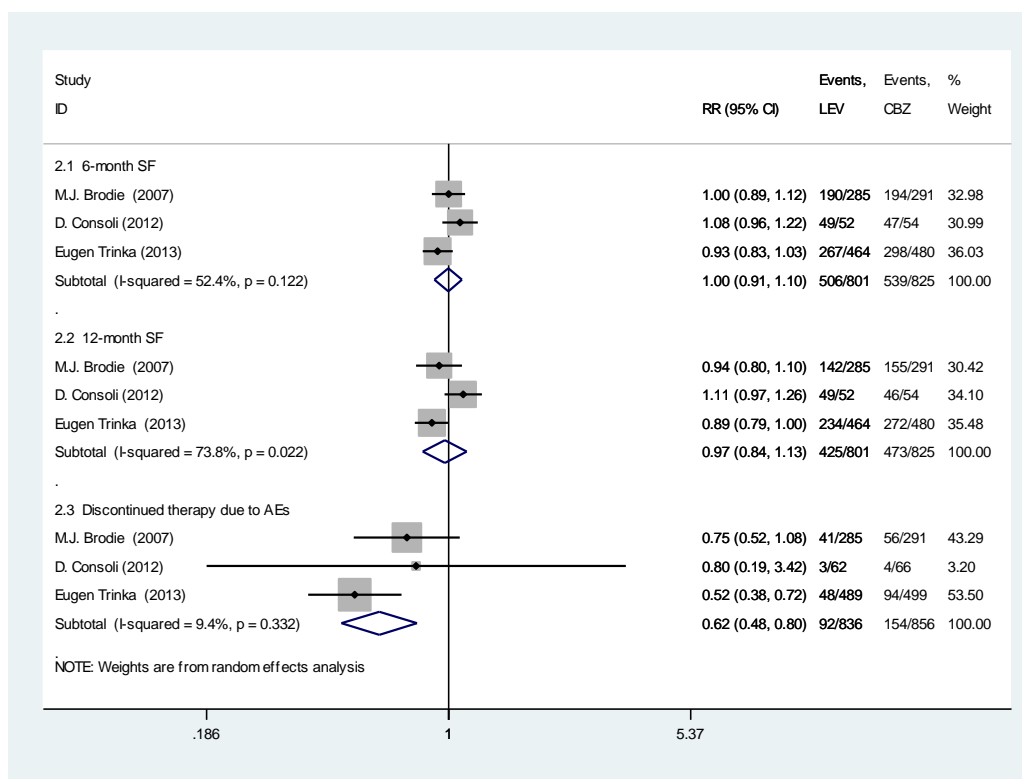


Fig. 2: Forrest plot for patients of seizure-freedom and those who had discontinued treatment due to AEs (SF is on behalf of seizure-freedom while AEs stands for adverse events)

2. Patients discontinued therapy due to AEs

Data comparing patients who had discontinued therapy due to AEs between LEV and CBZ was available in all included studies. The final pooled

estimated risk ratio (RR) was 0.62 (95% CI: 0.48-0.80), favoring LEV with statistical significance ($P\leq 0.001$).

No significant difference was shown between LEV and CBZ with respect to seizure freedom for 6 months or 12 months. Fewer LEV treated patients discontinued therapy due to AEs (RR: 0.62; 95% CI: 0.48-0.80).

3. Estimates of treatment withdrawal and patients with at least one AE (Fig. 3)

Data of two trials was available on treatment withdrawal for 6 months including 1568 patients. The pooled estimated risk ratio (RR) was 0.80 (95% CI: 0.64-0.99), favoring LEV. Moreover, there was no indication of heterogeneity between the included two trials ($I^2=0.0\%$, $P=0.624$).

As for treatment withdrawal for 12 months, all three trials were included. The estimates of pooled

RR was 0.87 (95% CI: 0.74-1.03), favoring LEV; however, without statistical significance ($P=0.110$). No sign of heterogeneity between studies was found ($I^2=0.0\%$, $P=0.992$).

The outcome with patients with at least one AEs, estimates of pooled RR was 1.00 (95%CI: 0.94-1.05), favoring neither LEV nor CBZ, and the results were not statistically significant ($P=0.889$). No evidence of heterogeneity between studies was observed ($I^2=0.0\%$, $P=0.992$).

LEV appeared to be associated with a lower rate of treatment withdrawal for 6 months compared to CBZ (RR: 0.80; 95% CI: 0.64-0.99). As for treatment withdrawal for 12 months and risk for patients with at least one AE, no significant difference was detected.

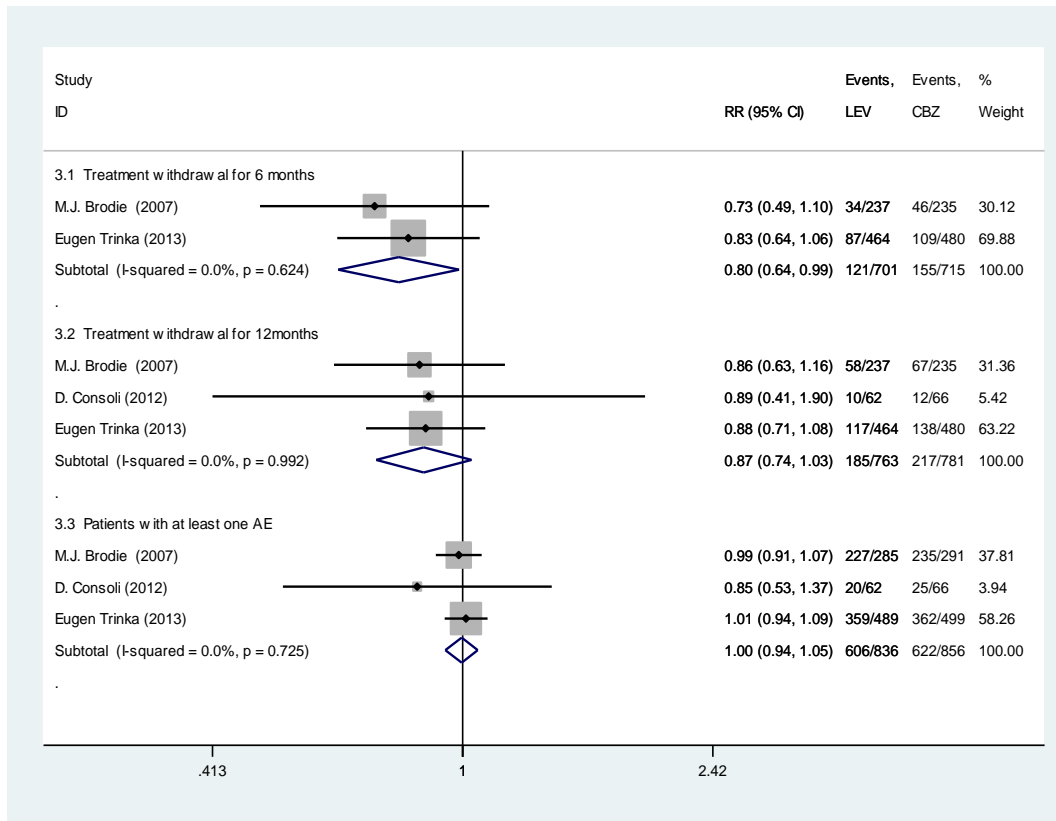


Fig. 3: Forrest plot for treatment withdrawal and patients with at least one AE

4. Estimates of several kinds of AEs (Fig. 4 & Fig.5)

Three studies reported the following four types of adverse events: headache, fatigue, diarrhea, and

vertigo. The pooled estimates indicated that there was no significant difference regarding the frequency of headaches, fatigue, diarrhea, and vertigo between patients treated with LEV and CBZ. The

pooled RR estimates for headache was 0.88 (95%CI: 0.73-1.06), for fatigue 1.08 (95% CI: 0.63-1.83), for diarrhea 1.23 (95%CI: 0.66-2.28), and for vertigo it was 0.92 (95% CI: 0.49-1.72). No quantitative heterogeneity was observed except for fatigue ($I^2=69.1\%$, $P=0.039$). Two studies involved the following additional adverse events: nasopharyngitis, depression, weight gain, and rash. No significant difference was detected on following two adverse events: nasopharyngitis ($P=0.380$) and weight gain ($P=0.078$).

The RR estimates for nasopharyngitis was 0.85 (95% CI: 0.59-1.22) and for weight gain 0.69 (95% CI: 0.45-1.04). The pooled estimates showed that LEV caused depression more frequently than CBZ (RR: 2.15; 95% CI: 1.26-3.68), with no heterogeneity ($I^2=0.0\%$) and it was statistically significant ($P=0.005$). However, LEV led to a lower rate of rash than CBZ (RR: 0.39; 95% CI: 0.23-0.68), with no heterogeneity ($I^2=0.0\%$) and statistical significance ($P=0.001$).

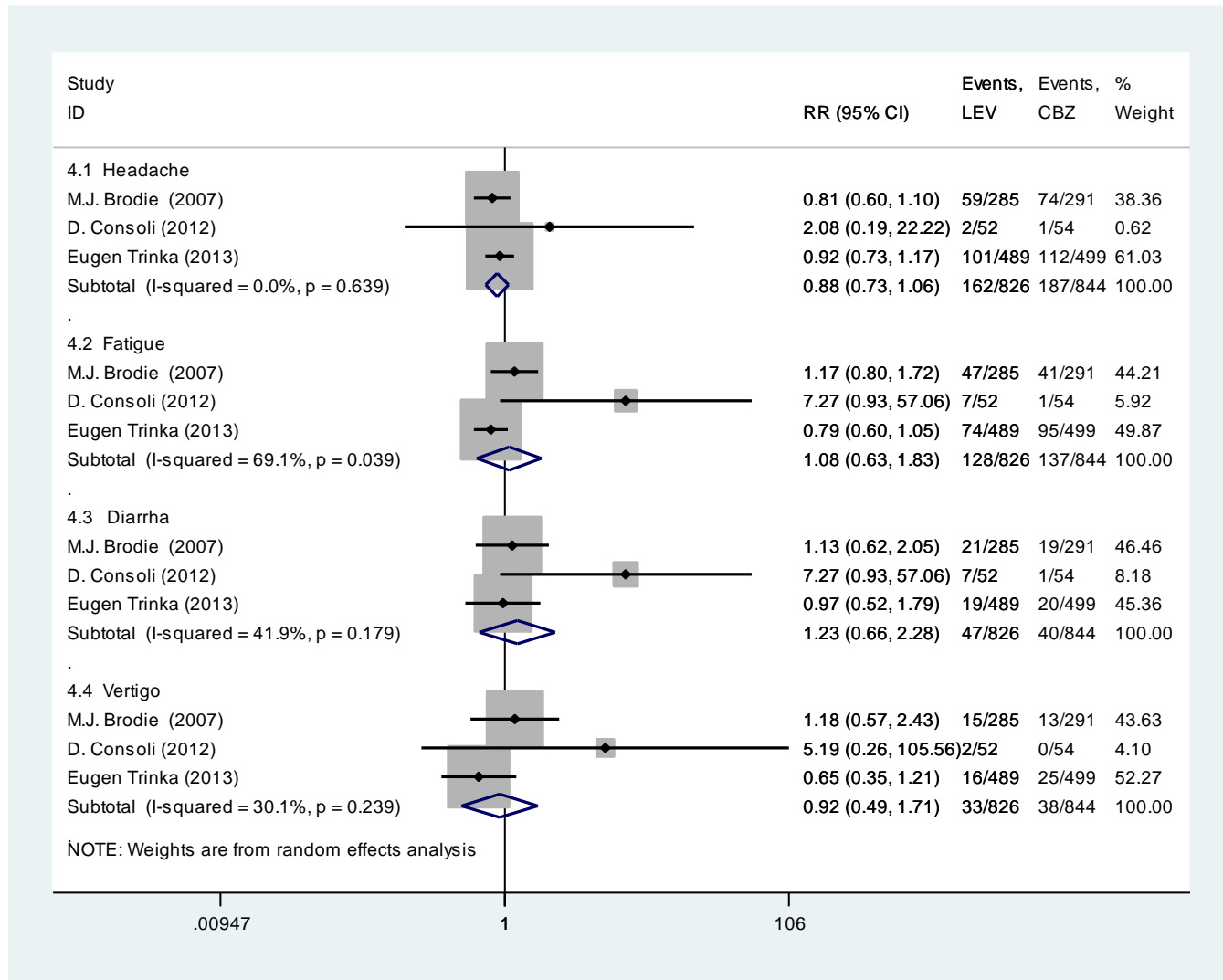


Fig. 4: Forrest plot for four adverse events: headache, fatigue, diarrhea, vertigo

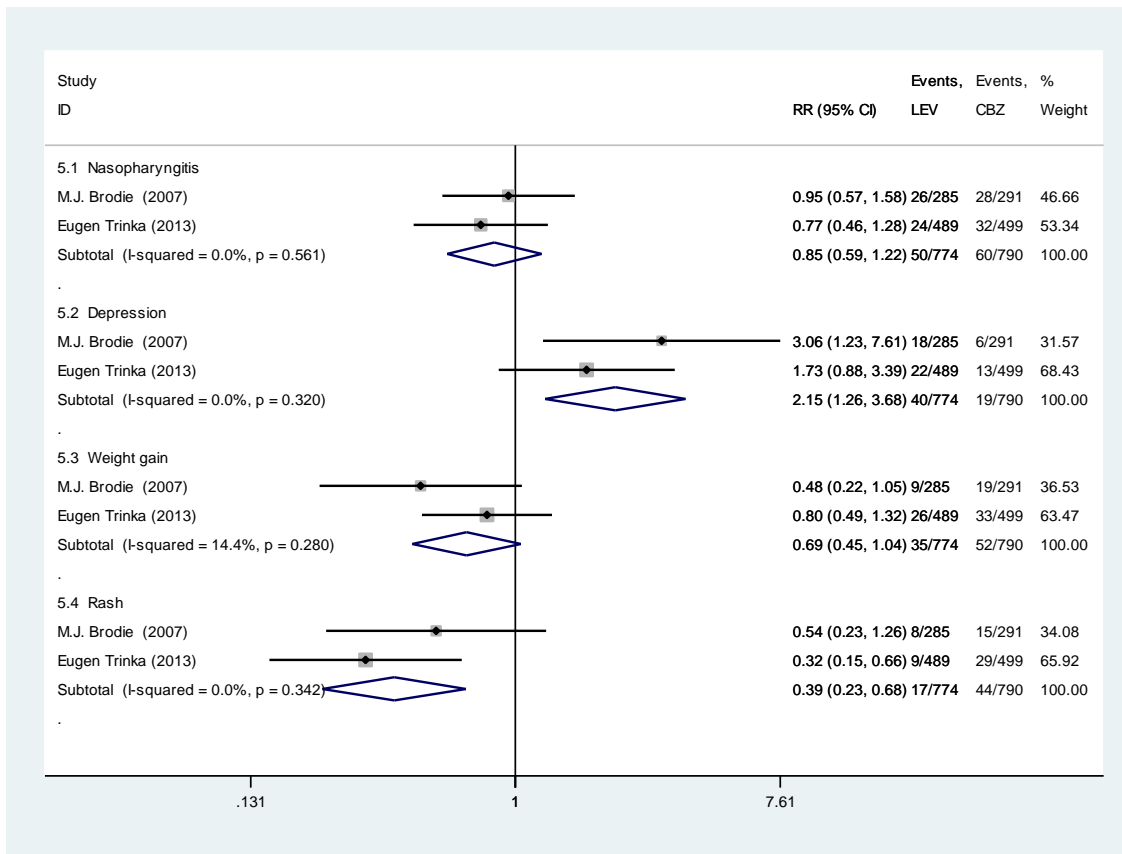


Fig. 5: Forrest plot for another four adverse events: nasopharyngitis, depression, weight gain, rash

Discussion

The number of included studies is small. The possible reasons are as follows: Firstly, we had strict inclusion and exclusion criteria to guarantee the quality of this report. Secondly, LEV is a novel anti-epileptic drug, and there are few studies comparing LEV and CBZ. Thirdly, the number of RCT is small; the number of included RCT is smaller. We have searched all possible studies to find only 3 eligible RCT for our report.

Based on pooled estimates from this meta-analysis, we concluded that LEV had significant advantages in patients who had discontinued therapy due to AEs and treatment withdrawal for 6-month compared to CBZ. LEV appeared to be more effective for 12-month seizure freedom and lead to lower treatment withdrawal for 12-month compared to CBZ. However, no statistically significant difference was found. Regarding seizure freedom for 6-

month and the number and rate of patients with at least one AE, there was no difference observed between LEV and CBZ. LEV and CBZ brought about almost similar rates of seizure freedom for 6-month or 12-month, i.e., there was no major difference between the 2 drugs regarding the main outcomes. This was consistent with several studies (22, 24-26). Moreover, when the participants were adults with post-stroke partial and generalized tonic-clonic seizures, LEV and CBZ were still equally efficacious (23). When it comes to treatment withdrawal for 6-month, LEV is slightly superior to CBZ. The pooled estimates of this analysis favored LEV as it could decrease the number of participants who discontinued therapy due to AEs and treatment withdrawal.

The adverse events were difficult to compare between studies because of several factors such as lack of standardized descriptions of adverse events, objective quantifiable measures and sever-

ity of most complaints not considered in reports, and the variation in methods for data collecting consisted of the difficulties (27). In this meta-analysis, we selected 8 kinds of AEs to compare the differences between LEV and CBZ.

Wieshmann thought that LEV had a different side effect profile than older AEDs. In the study, the AEs were reported by patients themselves. Moreover, the observation should be further tested by randomized studies (28). ADs of antiepileptic drugs involved changes in hematology and chemistry, hypersensitivity, infection, behavioral symptoms, changes in cognition, accidents and deaths, changes in sleep patterns, weight change, and so on. LEV was considered to have significant advantages over CBZ regarding cognitive functions (23,26,29). One study researched current antiepileptic drugs on quality of life (QOL) of epileptic patients to conclude that patients treated with LEV obtained higher QOL scores than patients treated with CBZ (30). Another study conducted in Korea showed that patients with drug-refractory epilepsy demonstrated that LEV intake resulted in significant improvement in QOL(31). Bachmann et al. discovered that patients treated with LEV monotherapy had lower platelet counts than patients on CBZ monotherapy, with no difference in Hb or WBC (32). Further studies should focus on the mechanism by which LEV might affect thrombocyte count or function. In 2003, a review analyzing randomized, controlled clinical trials showed that LEV appeared to be a weight neutral AED (33). Recently, through a retrospective observational study, Pickrell et al. pointed out that LEV was associated with significant weight gain, and CBZ was not associated with significant weight changes (34). There is great debate on weight change.

We did not find strong evidence that CBZ was more likely to induce AEs such as headaches, fatigue, diarrhea, vertigo, nasopharyngitis and weight gain than LEV. However, LEV was associated with a higher rate of depression, while CBZ appeared to cause a higher rate of rash.

In this meta-analysis, we included as many different AEs as possible to obtain as much detail on adverse effects of antiepileptic drugs as possible.

In fact, different studies contained varied AEs making it difficult to collect the data we needed. We finally selected 8 types of ADs to be included in this meta-analysis. The pooled estimates indicated that LEV was more inclined to result in depression while CBZ could cause rash more frequently. Currently, a lot of controversy exists on the relationship between depression and antiepileptic drugs. On the one hand, depression is one of the considerable reasons that require withdrawal of LEV (28, 35, 36). On the other hand, LEV intake has been shown to improve depression (31). CBZ was always considered effective in depression, with great improvements in major depressive disorders (37-39). Analysis of the included three RCTs demonstrated that the effect of CBZ on depression was more satisfying than that of LEV, which corresponded to the studies above. To clarify the existing controversy regarding depression due to LEV, a large RCT is still needed. The results of this study on rash were in agreement with the study by H. Arif that showed that rash rates were higher with CBZ than LEV (40). This could be explained by the theory that LEV can decrease the incidence of hypersensitivity. In addition, LEV seemed to be the better choice when patients were anxious regarding headache, vertigo, nasopharyngitis, and weight gain. However, no evidence with statistical significance was found. CBZ could probably be recommended when patients worry about fatigue and diarrhea, even though there is no data with to support this.

Conclusion

The major outcomes such as rate of seizure freedom were similar between LEV and CBZ. However, LEV led to depression more frequently than CBZ, while CBZ caused rash more frequently. LEV seemed to be the better choice when patients were anxious regarding headache, vertigo, nasopharyngitis, and weight gain. CBZ could probably be recommended when patients worry about fatigue and diarrhea.

The deficiencies of this analysis are as follows:

1. The number of included RCTs studies and patients are inadequate, which makes the results less convincing and accurate.

2. Lack of uniform criteria and quantitative evaluation for adverse events of antiepileptic drugs makes it difficult to collect data on ADs and to conclude accurate results.

Therefore, a quantitative criterion for the selection of ADs in epileptic patients is needed.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

Acknowledgement

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