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Indirect comparison of third-generation antiepileptic drugs as adjunctive treatment for uncontrolled focal epilepsy

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ABSTRACT

Purpose: Eslicarbazepine (ESL), Lacosamide (LAC), Perampanel (PER) and Brivaracetam (BRV), have recently been marketed as third-generation antiepileptic drugs (AEDs). We conducted a meta-analysis to indirectly compare overall efficacy and tolerability between third-generation AEDs in uncontrolled focal epilepsy.

Methods: We performed an online database search using Pubmed, Embase, Cochrane Online Library, and Clinicaltrial.gov for all available randomized controlled trials (RCTs) that investigated the therapeutic effects over a range of AED doses versus placebo. We then compared clinical efficacy and tolerability between these newer AEDs using Indirect Treatment Comparison software.

Results: Nineteen RCTs with a total of 7245 patients were included in our study. There were no significant differences in the risk difference of 50% responder rates and seizure free rates between third generation AEDs, regardless of dose. The risk of treatment emergent adverse events was significantly higher with ESL and PER treatment compared to BRV at all doses combined. Withdrawal rates due to adverse events were also significantly higher in patients treated with the highest doses of LAC and PER versus BRV, while treatment with ESL or LAC was related to higher withdrawal rates versus BRV when all doses were combined.

Conclusions: Our analysis suggested there were no significant differences in efficacy between third generation AEDs in uncontrolled focal epilepsy. BRV may have the best tolerability profile. The other AEDs were associated with a higher risk for intolerable adverse, especially when taken at a high doses. The results from these indirect comparisons warrant further examination and verification through future well-designed trials.

1. Introduction

Treatment for epilepsy is highly dependent on antiepileptic drugs. However, despite appropriate medical therapy, epilepsy remains uncontrolled in one third of patients (Kwan and Brodie, 2000). The mechanism behind these treatment failures is far from clear, but the options for these patients were increasing since massive resources have been putting into the finding of newer antiepileptic drugs (AEDs) to solve this problem. In recent years, approximately 20 AEDs have been developed by pharmaceutical companies, which were classified to the third-generation AEDs (Luszczki, 2009). These newer AEDs, such as Eslicarbazepine (ESL), Lacosamide (LAC), Perampanel (PER) and Brivaracetam (BRV), have shown better seizure control and acceptable safety compared to placebo when used as add-on therapy for uncontrolled partial epilepsy in randomized controlled trials. These new drugs have been approved as adjunctive treatments for patients with focal epilepsy and have been marketed to offer better seizure control for such patients.

Even they were classified into one category, it is noticed that the mechanism of action of these drugs vary from each other. Some of these AEDs are improvements on old formulae such as ESL and BRV while others harness new mechanisms of actions and carry distinct pharmacological profiles as LAC and PER (Mula, 2016). Thus, in theory, they should have different efficacy and tolerability and it would be very important to make comparison between these new AEDs. However, since there was no direct comparison among these new drugs, it is still not clear if any of them could have a better efficacy over others as well as tolerability.

In order to provide some evidence for clinical decision, we combined the data from the pivotal clinical trials of ESL, LAC, PER and BRV compared with placebo, and then performed an indirect comparison meta-analysis to identify whether there are significant differences in efficacy and tolerability between these four newer AEDs.

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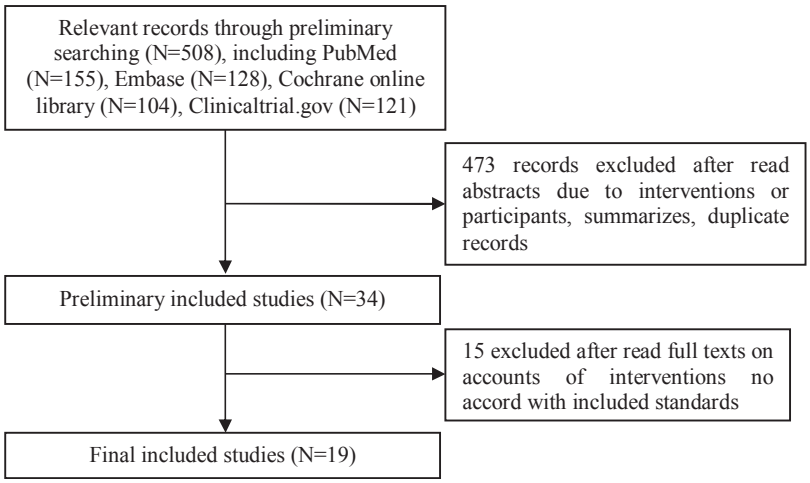

Fig 1. Selection of Stuides.

2. Methods

2.1. Data sources and search

We searched online databases including Pubmed, Embase, Cochrane Online Library and Clinicaltrial.gov (https://www.clinicaltrial.gov/) with no limits on language. The search yielded from the establishment of each database to July 30th, 2017. The words used in this search included: epilepsy, placebo, randomi*, with one or more of the following AEDs: eslicarbazepine(ESL), lacosamide(LAC), perampanel (PER), brivaracetam (BRV). Two reviewers independently reviewed the titles and abstracts from the search results for any article or trial that was potentially relevant.

2.2. Selection of studies

Inclusion criteria:

1. Study design: randomized, double-blind, placebo-controlled trials evaluating ESL, LAC, PER, BRV vs. placebo as an add-on treatment for uncontrolled focal epilepsy.
2. Population: Adult participants diagnosed with partial-onset epilepsy according to the guideline of International League Against Epilepsy (ILAE,1981) (ILAE, 1981) and failed at least one to two kinds of AEDs.
3. Outcomes: all data had to come from full journal publications or summaries of clinical trial reports; at least one of the following measures must be have been included in the studies: 50% responder rate, seizure-free rate, treatment-emergent adverse events (TEAEs), withdrawal rates due to adverse events(AEs), and serious adverse events (SAEs).

Exclusion criteria: design of trial is not double-blind, placebo-controlled or non-RCTs; trials use newer AEDs as monotherapy.

2.3. Data extraction and evaluation of evidence

The following trial data were extracted by two reviewers independently: number of patients (intent-to-treat[ITT]), sex of participants for each treatment group, age, duration of epilepsy, intervention details (dose, route of administration), percentage of concomitant AEDs at baseline, the kind of concomitant AEDs, study duration, proportion of patients with 50% or greater reduction in seizure frequency in each group; proportion of patients achieving seizure freedom in each group; proportion of patients with any treatment emergent adverse event (TEAE); proportion of patients with AEs leading to discontinuation in each group; proportion of patients with SAEs. Two reviewers independently extracted relevant information from each eligible study. The bias of included studies was assessed using the guideline for assessing risk of bias in the Cochrane handbook 5.1.0 (The Cochrane Collaboration, 2011). Any disagreement was resolved through discussion.

2.4. Outcome measures

To measure the efficacy and tolerability of the included AEDs, we chose the following outcomes: 1. 50% responder rate, defined as the proportion of patients with 50% or greater reduction in seizure frequency during the treatment period compared to the pre-randomization baseline period; 2. Seizure free rate, defined as the proportion of patients achieving seizure freedom during treatment period;

3. The proportion of patients with any treatment-emergent adverse events (TEAEs). TEAEs were defined as adverse events that considered to be related to study medication by investigator.
4. Withdrawal rates due to adverse events(AEs);
5. The proportion of patients with serious adverse events (SAEs). SAEs were defined as AEs that were life-threatening, which can result in death, a persistent or significant disability, a congenital birth defector hospitalization.

2.5. Data analyses

2.5.1. Conventional meta-analyses

We compared the efficacy and tolerability of add-on ESL, LAC, PER or BRV versus placebousing Review Manager 5.3 (Cochrane Collaboration, http://tech.cochrane.org/revman/download). The Mantel–Haenszel model, RD, and 95% confidence interval (CI) were used to compare dichotomous variables. Statistical heterogeneity was assessed using the I^2 test. We used the fixed-effect model for comparisons with $I^2 < 50\%$, and the randomized effect model for comparisons with$I^2 \geq 50\%$.

2.5.2. Common reference-based indirect comparisons

We performed indirect comparisons using the RDs obtained in the conventional meta-analyses. To perform indirect comparison, we used the framework proposed by ICWG (Indirect Comparisons Working Group) (ICWG, 2009) to assess whether the overall characteristics of the trials included in the meta-analyses differed systematically. We assessed clinical heterogeneity by comparing the distribution of important patient factors between studies (age, epilepsy type, duration of epilepsy) and trial factors (study design, type of control group and measurements of outcomes). The RD (with 95% CI) for each indirect comparison was estimated according to the ITC software (Canadian Agency for Drugs and Technologies in Health, Indirect Treatment Comparison software, Ottawa, Ontario, Canada) (Bucher et al., 1997). The Bucher approach was applied for indirect comparisons (Higgins