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Clinical efficacy and safety of the newer antiepileptic drugs as adjunctive treatment in adults with refractory partial-onset epilepsy: A meta-analysis of randomized placebo-controlled trials

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Metaanalysis;
RCTs

Summary
Objective: To evaluate the clinical efficacy and safety of the newer antiepileptic drugs (AEDs), namely, Eslicarbazepine (ESL), Retigabine/Ezogabine (RTG), Carisbamate (CAR), Lacosamide (LAC), Brivaracetam (BRI) or Perampanel (PER) as adjunctive therapy for adults with partial-onset seizures (POS).
Methods: A systematic review of Randomized placebo-controlled Trials (RCTs) of newer AEDs was conducted. Electronic databases and identified bibliographies were searched to retrieve RCTs. The primary outcomes were responder rates and withdrawal rates, adverse effects. Pooled effects of Odds Ratio (OR), Risk Ratio (RR) and Risk Differences (RD) were derived from meta-analysis implemented in Revmen 5.1.
Results: In total, 15 RCTs were included. All the studies contained a baseline and treatment phase. The pooled OR of all newer AEDs vs placebo was 2.16 (95%CI: 1.82, 2.57) for responder rates, 1.54 (1.12, 2.10) for withdrawal rates, 1.67 (1.34, 2.08) for adverse effects. The indirect comparisons between individual newer AED and all other newer AEDs suggested the similar results in responder rates (ORs, BRI 1.79 [—1.50, 5.08], RTG 1.41 [0.49, 2.33]).
Conclusions: The pooled ORs suggested newer AEDs might be more effective than placebo while with higher incidence of adverse effects. The indirect comparisons suggested BRI, followed by RTG, might be more effective than all other newer AEDs, which could be confirmed by future clinical studies.

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Introduction

Epilepsy is typically characterized by recurrent and unprovoked seizures (without any immediate identified causes) (Costa et al., 2011) caused by abnormal transmission of electrical signals and neuronal activity in the brain. Antiepileptic drugs (AEDs) can usually provide satisfactory control of symptoms for most of patients. Generally, about 50% of patients will achieve seizure remission on their initial monotherapy, seizure remission in another 15—25% of patients might be obtained after altering/adding one or more treatment modalities, and the remaining 20—30% patients would not achieve satisfactory seizure remission. Thus, patients without satisfactory seizure remission on two or more different AED therapies are usually defined as having refractory epilepsy (Begley et al., 1994; Preux and Druet-Cabanac, 2005). During the last decade, a number of newer AEDs with more desirable safety profile have been introduced into the market in order to offer better seizure control for patients with epilepsy, especially for those with refractory epilepsy. Consequently, add-on therapy with newer AEDs is now considered standard care for patients with refractory epilepsy (French et al., 2004).

In seeking market approval for these newer AEDs, pharmaceutical companies have provided the results of many randomized controlled trials (RCTs) as supporting evidence. Hence, there are quite a number of RCTs comparing the newer AEDs with placebo as adjunctive treatment for patients with partial-onset seizure. Not surprisingly, almost all the RCTs showed the newer AEDs offer better seizure control and demonstrate acceptable safety and tolerability in this population (Castillo et al., 2000; Chaisewikul et al., 2001; Costa et al., 2011; Jette et al., 2008; Lozsadi et al., 2008; Pereira et al., 2002; Ramaratnam et al., 2001; Saconato et al., 2009). However, due to relatively small number of enrolled participants in individual study and the lack of head-to-head comparisons between these newer drugs, uncertainties about the claimed efficacy or safety of the newer AEDs over traditional ones still exist. Furthermore, doctors would need strong evidence to justify the price of prescribing these newer interventions. It would be difficult for physicians to choose from many newer AEDs with all confirmed to be more effective than placebo.

To provide this information, we have conducted a systematic review and meta-analysis to synthesize the evidence regarding the magnitude of efficacy, safety, and tolerability of add-on newer AEDs in treating the refractory partial-onset seizure patients when compared to placebo, and to ascertain whether the newer AEDs are more effective than existing AEDs.

Methods

Data sources

An electronic literature search was performed using terms as followed: seizure(s), epilepsy, partial-onset epilepsy/seizures, refractory, adults, adjunctive/add-on therapy/treatment, double-blind, placebo-controlled, randomized trials, RCT (controlled) clinical trial, with one of following newer AEDs: Eslicarbazepine (ESL), Retigabine/Ezogabine (RTG), Carisbamate (CAR), Lacosamide (LAC), Brivaracetam (BRI) or Perampanel (PER) as an extension in Embase, Medline, Cochrane database from inception to the 30th January, 2012. These six AEDs were selected as they were introduced or invented within the last four years, and represent the newest generation of antiepileptic medication.

Additionally, a manual search was also conducted to retrieve additional literature from the bibliography of the identified articles from the electronic search.

Inclusion criteria

There were predefined criteria for the inclusion of relevant studies:

(1) Written in English and full text available.
(2) Adult participants who have failed at least one to two kinds of AEDs were explicitly diagnosed with partial-onset epilepsy according to the guideline of International League Against Epilepsy (ILAE).
(3) Double-blinded studies with a matched placebo or at least included a double-blinded, placebo-controlled arm.
(4) Reported the responder rate (50% reduction in seizure frequency comparing to baseline) and number of total patients in each group.
(5) The treatment duration was more than 4-weeks with at least 30 patients in each arm.

Data extraction

Information to be extracted included: the study design, drug dosage(s), patients' characteristics, diagnosis criteria, number of Intention to Treat (ITT) population and safety population. Primary outcomes information included: responder and seizure free rates (both comparing to baseline), withdrawal rates and withdrawal due to adverse effects, and adverse effects rates. Secondary outcomes information included: predefined adverse effect rate for dizziness, somnolence, fatigue, headache, nausea, and ataxia.

Two reviewers (LG and FLZ) independently performed the data extraction process while resolving any discrepancies via discussion. Only mutually agreed data were included in the analyses.

Definition

There is no unanimously accepted diagnosis guideline for refractory partial-onset epilepsy. Empirically, in our study, refractory partial-onset epilepsy was referred to patients who failed to respond to at least one or two kinds of AEDs before enrolled in the studies while still suffered more than 4 seizures per 28 days prior to the baseline of each research.

Data analysis

The Revman 5.1 software was utilized to perform the meta-analysis. In order to compare the newer AEDs with placebo, we used the random-effect of weighted Mantel-Haenszel