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Review

Efficacy and tolerability of brivaracetam compared to lacosamide, eslicarbazepine acetate, and perampanel as adjunctive treatments in uncontrolled focal epilepsy: Results of an indirect comparison meta-analysis of RCTs

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ABSTRACT

Background: Brivaracetam (BRV), eslicarbazepine acetate (ESL), lacosamide (LCM), and perampanel (PER) have been recently marketed as adjunctive treatments for focal onset seizures. To date, no randomized controlled trial (RCT) has directly compared BRV with ESL, LCM, or PER.
Purpose: To compare BRV with the other add-on AEDs in patients with uncontrolled focal epilepsy, estimating their efficacy and tolerability through an adjusted, common-reference based indirect comparison meta-analysis.
Methods: We systematically searched RCTs in which add-on treatment with ESL or LCM in patients with focal onset seizures have been compared with placebo. Efficacy and tolerability outcomes were considered. Random-effects Mantel–Haenszel meta-analyses were performed to obtain odds ratios (ORs) for the efficacy of BRV, LCM, ESL, or PER versus placebo. Adjusted indirect comparisons were then made between BRV and the other three AEDs using the obtained results, comparing the minimum and the highest effective recommended daily dose of each drug.
Results: Seventeen RCTs, with a total of 4971 patients were included. After adjusting for dose-effects, indirect comparisons showed no difference between BRV and LCM, ESL, or PER for responder rate and seizure freedom. Lower adverse events were observed with high dose BRV compared to high dose ESL or PER, but no difference was found in withdrawing because of adverse events.
Conclusions: Indirect comparisons do not demonstrate a significant difference in efficacy between add-on BRV and LCM, ESL, or PER in focal epilepsy, and might suggest a better tolerability of BRV than ESL, and possibly also PER, at the highest effective recommended dose.

1. Introduction

Epilepsy is one of the most common neurologic disorders, affecting almost 70 million people in the world [1]. Despite the introduction of third-generation antiepileptic drugs (AEDs), approximately 30% of patients with epilepsy continue having seizures [2,3]. In patients where monotherapy inadequately controls seizure, an adjunctive treatment may be necessary. However, intolerable adverse effects and pharmacological interaction may burden polytherapy. Hence, there is still an ongoing need for more novel AEDs with higher efficacy and better tolerability [4].

In last years, five AEDs have been approved as add-on treatments for patients with focal epilepsy: retigabine (ezogabine), eslicarbazepine acetate (ESL), lacosamide (LCM), perampanel (PER), and – more recently – brivaracetam (BRV). The use of retigabine has been nonetheless severely limited by the frequent

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occurrence of blue skin discoloration and eye abnormalities characterized by pigment changes in the retina following treatment with this AED [5].

Among the newest AEDs, BRV is thought to exert its antiepileptic effect by selectively binding to synaptic vesicle protein 2A (SV2A) – a mechanism of action shared by its precursor levetiracetam – with subsequent modulation of release of neurotransmitters into the synapse [6]. Brivaracetam has been shown to be more effective than levetiracetam in seizure control in animal models [6].

To date, no randomized controlled trial (RCT) has directly compared the efficacy of BRV with ESL, LCM or PER used as add-on treatments for focal epilepsy. To overcome this lack of information or insufficient evidence from direct head-to-head comparisons, sophisticated statistical methods have been developed to indirectly estimate the effect of two or more healthcare treatments or interventions. These methods are termed as indirect comparison, in that they exploit data from separate studies, differently from direct comparisons which use data from individual arms within the same head-to-head comparative RCTs. Basically, there are two kinds of indirect comparisons: namely, naive and adjusted indirect comparisons. While the former approach treats arms from different trials as if they were from the same trials and is therefore contraindicated for meta-analyzing data from RCTs, performing instead better for observational trials, the latter approach, using a comparator "in common", is more statistically rigorous and powerful.

However, the validity of these adjusted indirect comparisons depends on the methodological quality and similarity of the included trials [7]. On the other hand, they may provide useful information where data from direct comparisons do not exist. An indirect-comparison meta-analysis has previously assessed the efficacy and tolerability of LCM, PER, ESL, and retigabine [8], without including the BRV, whose use in humans has been approved only recently.

We, therefore, decided to compare BRV with LCM, ESL, or PER in patients with focal epilepsy uncontrolled by monotherapy, indirectly estimating their efficacy and tolerability through a common-reference based indirect comparison meta-analysis.

2. Methods

This review was guided by a written pre-specified protocol describing research questions, review methods, and a plan for data extraction and synthesis. The protocol is available online at: http://www.crd.york.ac.uk/PROSPERO/printPDF.php?RecordID=37279&UserID=1662.

2.1. Inclusion and exclusion criteria

Randomized controlled trials comparing add-on BRV (50 or 200 mg), LCM (200 or 400 mg), ESL (800 or 1200 mg) or PER (8 or 12 mg) versus placebo in the treatment of focal epilepsy (simple focal, complex focal or secondary generalized tonic–clonic seizures) in patients of any age were included.

Patients from any age group and diagnosed with focal epilepsy (simple focal, complex focal or secondary generalized tonic–clonic seizures) were included. Trials were not excluded on the basis of dose, duration of treatment, or length of follow-up.

Trials evaluating flexible-dose of AED were excluded.

2.2. Search methods

A comprehensive review of the literature was performed to minimize publication bias.

Electronic databases were searched using the following search strategy: "(brivaracetam OR lacosamide OR eslicarbazepine OR perampanel) AND epilepsy AND randomi*".

Following electronic databases and data sources were searched:

1. MEDLINE, accessed through PubMed;
2. Cochrane Central Register of Controlled Trials (CENTRAL);
3. EMBASE;
4. ClinicalTrials.gov (available at: https://clinicaltrials.gov/);
5. Handsearching of the references quoted in the identified trials;
6. Contact with authors and known experts to identify any additional data;
7. Most recent systematic reviews reporting data on BRV [9–11], ESL [8,12], LCM [8,13], and PER [8].

There were no language restrictions.

All searches were conducted on 13th March 2016.

2.3. Study selection and methodological quality assessment

Trials were scrutinized, and the methodological quality of all included studies evaluated. Study selection was done independently by two reviewers (FB and RN) and cross-checked for accuracy. Any disagreement was resolved through discussion.

Quality assessment included the following aspects of methodology: study design, definition and clinical relevance of outcomes, type of control, method of allocation concealment, total study duration, completeness of follow-up, intention-to-treat analysis, data concerning adverse effects, risk of bias, and conflict of interests. The randomized trials were judged on the reported method of allocation concealment and on the risk of bias as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] [14].

2.4. Type of outcomes

The following outcomes were chosen:

1. 50% responder rate, defined as the proportion of patients with 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomization baseline period ("responders");
2. Proportion of patients achieving seizure freedom during treatment period;
3. Proportion of patients experiencing any TEAE during treatment period;
4. Proportion of patients with TEAEs leading to study/treatment discontinuation.

For each outcome, an intention-to-treat primary analysis was made.

2.5. Data extraction

The following trial data were extracted: main study author and age of publication; country; type of participants (children and/or adults); total number, age, and sex of participants for each treatment group; seizure type; intervention details (dose, route of administration); proportion of patients with 50% or greater reduction in seizure frequency (responders) in each group; proportion of patients achieving seizure freedom in each group; proportion of patients with any treatment-emergent adverse event (TEAE), defined as an adverse events occurring after the first intake of study treatment in the double-blind phase, in each group; proportion of patients with TEAEs leading to discontinuation in each group.