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Efficacy of antiepileptic drugs in the adjunctive treatment of refractory partial-onset seizures: Meta-analysis of pivotal trials

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ABSTRACT

Objective: In the absence of randomized clinical trials (RCTs) assessing the relative efficacy of antiepileptic drugs (AEDs), meta-analyses are useful resources for informing treatment choices. This meta-analysis assesses the relative efficacy and tolerability of AEDs for adjunctive treatment of refractory partial onset seizures (POS).

Methods: A systematic literature review was conducted to identify pivotal AED trials serving as the basis for US Food and Drug Administration (FDA) approval. Inclusion criteria: 1) double-blind, placebo-controlled, parallel-group design, with 8- to 14-week maintenance period; 2) enrolled patients ≥16 years with refractory POS, including complex partial seizures; 3) study was conducted between 1993 and 2013; and; 4) patients received FDA-approved dosage. Outcomes analyzed: 1) 50% responder rate (≥50% reduction from baseline in seizure frequency); 2) seizure freedom (proportion of seizure-free patients); and 3) discontinuation due to adverse events (AEs). DerSimonian and Laird random-effects model was used to derive odds ratios (OR) and 95% confidence intervals (CI).

Results: A total of 29 publications for 11 AEDs (eslicarbazepine, ezogabine, gabapentin, lacosamide, levetiracetam, perampanel, pregabalin, tiagabine, topiramate, vigabatrin, and zonisamide) were included in the meta-analysis. Tiagabine 56 mg/day (OR 8.82, 95% CI: 2.77–28.11), pregabalin 600 mg/day (OR 8.08, 95% CI: 5.45–11.98), and vigabatrin 3000 mg/day (OR 6.23, 95% CI: 1.46–26.20) had the highest OR versus placebo of 50% response. The odds of seizure freedom were ≥7 times greater than placebo for levetiracetam 3000 mg/day (OR 11.00, 95% CI: 2.08–58.06), vigabatrin 3000 mg/day (OR 7.41, 95% CI: 1.31–41.84), and ezogabine 1200 mg/day (OR 7.09, 95% CI: 0.36–58.06). Patients were more likely to discontinue any AED (except low-dose pregabalin) than placebo.

Conclusion: In this meta-analysis of > 9000 patients, those treated with AEDs were more likely than placebo to achieve seizure response or freedom. Patients receiving pregabalin, tiagabine, and vigabatrin had the highest odds of ≥50% reduction in seizures, and patients receiving ezogabine, levetiracetam, and vigabatrin had the highest odds of seizure freedom.

1. Introduction

The number of antiepileptic drugs (AEDs) approved for the adjunctive treatment of refractory partial-onset seizures (POS) has increased dramatically in the past 2 decades, with the aim of providing better seizure control and improved safety and tolerability profile relative to older AEDs. However, this influx of available AEDs can make drug selection difficult, especially given the lack of head-to-head comparisons of AEDs. Randomized clinical trials (RCTs) of AEDs are generally designed to assess their efficacy, tolerability, and safety compared with placebo; therefore, the results from these trials fail to address the relative efficacy of AEDs, leaving clinicians to make treatment choices based on initial impressions, anecdotal evidence, and pre-existing treatment patterns.

In the absence of head-to-head clinical trial data, systematic reviews and meta-analyses of pooled data from RCTs provide a useful tool for informing treatment choices (Benbadis et al., 2014; Faught, 2012; Lathyris et al., 2010; Mohanraj and Brodie, 2003). Previous meta-

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analyses have compared the efficacy of AEDs approved for refractory POS using data from studies selected using various criteria, such as AEDs assessed, trial duration, publication date, and/or outcomes assessed (Beyenburg et al., 2010; Bodalia et al., 2013; Brigo et al., 2016a; Brigo et al., 2016b; Campos et al., 2016; Costa et al., 2011; Cramer et al., 1999; Gao et al., 2013; Hsu et al., 2013; Khan et al., 2013; Lattanzi et al., 2016; Li et al., 2014; Marson et al., 2001; Marson et al., 1997; Martyn-St James et al., 2012; Otoul et al., 2005; Rheims et al., 2011; Tian et al., 2015; Zhao et al., 2017).

This systematic literature review and meta-analysis examines the relative efficacy of AEDs approved by the US Food and Drug Administration (FDA) for adjunctive treatment of refractory POS, including refractory complex partial seizures (rCPS), using data from the published pivotal AED trials. Pivotal trial data, which are the basis for FDA approval, and for the content of the package insert, help shape clinicians' initial impression of the relative efficacy and safety of AEDs; therefore this meta-analysis provides practical information to aid clinicians in treatment decisions for patients with refractory POS.

2. Material and methods

2.1. Systematic literature search

A systematic literature search of Medline and Cochrane Central Register of Controlled Trials (CENTRAL) databases was conducted via Ovid in August 2014, to identify English-language studies that served as the basis for FDA approval of current AEDs for adjunctive treatment of refractory POS, including rCPS. Search terms are summarized in Supplemental Table 1. In addition, published pivotal studies of which the authors were aware, but that did not appear in the search results, were added to the list of publications. A PRISMA flow chart of the search strategy (Moher et al., 2009), which adhered to standard processes described in the Cochrane Handbook for Systematic Reviews of Interventions (2011), is shown in Fig. 1.

2.2. Study selection

Two independent reviewers screened abstracts and full-text articles of publications that met the following selection criteria: 1) Phase III randomized, double-blind, placebo-controlled, parallel-group design, with an 8- to 14-week maintenance period; 2) enrolled patients age ≥16 years with refractory POS, including rCPS; 3) patients received either placebo or an adjunctive AED approved for POS between 1993 and 2013; and, 4) patients received FDA-approved dosage of adjunctive AED. Eligible studies were those that met these selection criteria and could be matched to pivotal studies reported in FDA prescribing information documents.

2.3. Data collection and risk of bias assessment

To insure consistency of data collection for each study, the following information from the eligible studies was entered into a structured Excel data table: study characteristics (i.e., sample size, duration of titration and maintenance periods), patient characteristics (i.e., age, sex, seizure etiology, disease duration and comorbidities), treatment regimen, concomitant AEDs, and clinical outcomes (percentage of reduction in seizure frequency from baseline, 50% responder rate, seizure frequency, seizure freedom, and discontinuation due to adverse events).

An assessment form from the Cochrane Handbook was used to assess the quality of selection, performance, detection, attrition, and reporting biases of each eligible study as low, unclear and high risk of bias (2011).

2.4. Outcome measures

Efficacy outcomes analyzed were responder rate (proportion of patients with ≥50% reduction in seizure frequency from baseline to the end of the double-blind treatment period) and seizure freedom (proportion of patients that were seizure-free during double-blind treatment). The safety outcome was rate of discontinuation due to adverse events (AEs) during double-blind treatment. If a given outcome was not reported in an eligible study, the study was not included in the meta-

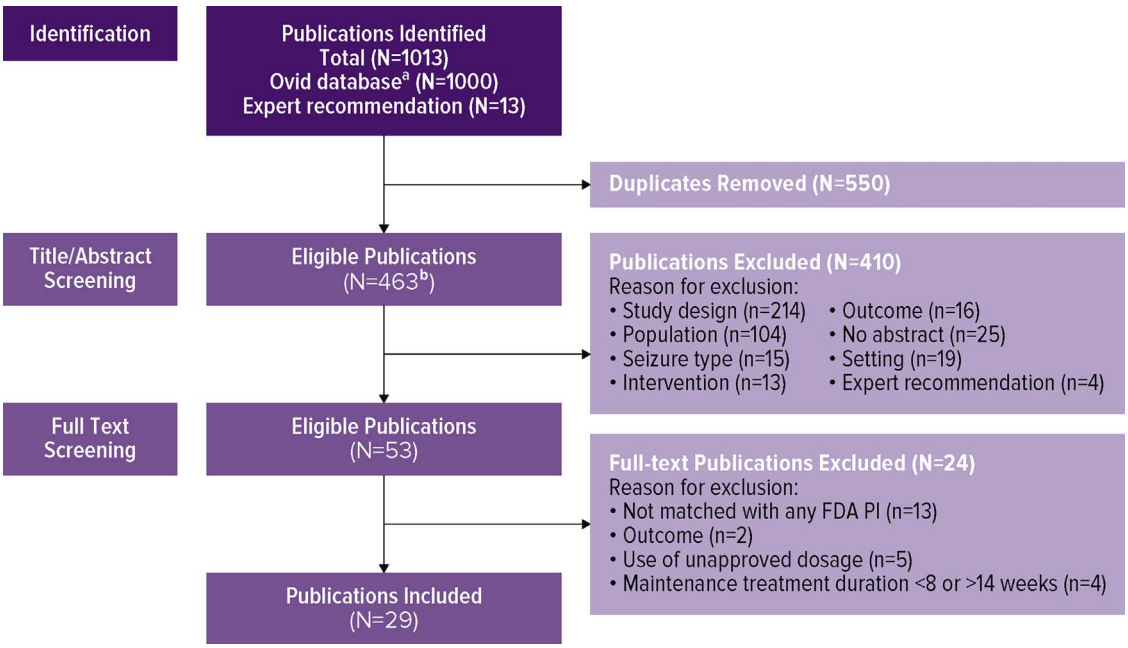

Fig. 1. PRISMA flow chart of search strategy to identify pivotal publications of adjunctive AED treatments for meta-analyses.
[a] Medline and Cochrane Library Databases were queried via Ovid on August 12, 2014.
[b] Published pivotal studies of which the authors were aware, but that did not appear in the search results, were added to the list of publications.
AED, anti-epileptic drug; FDA, Food and Drug Administration; PI, prescribing information, PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.