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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-

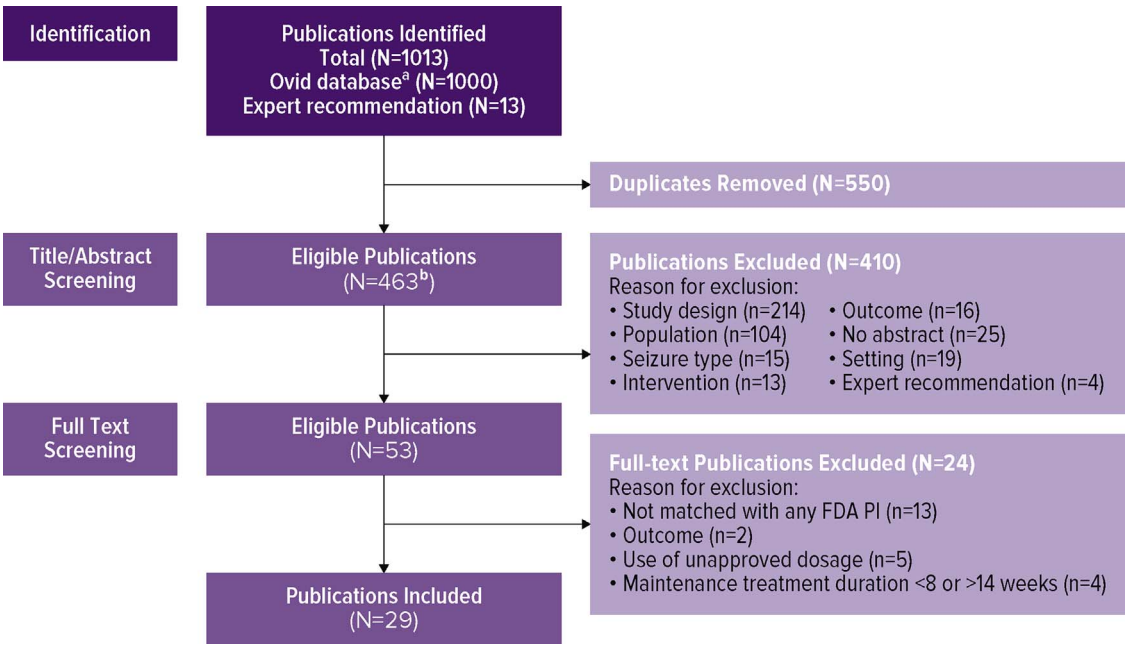

Fig. 1. PRISMA flow chart of search strategy to identify pivotal publications of adjunctive AED treatments for meta-analyses.
[a] Medline and Cochrane Library Databases were queried via Ovid on August 12, 2014.
[b] Published pivotal studies of which the authors were aware, but that did not appear in 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.

analysis for that outcome. AEDs were pooled by dosage and compared to placebo for both efficacy and safety outcomes.

2.5. Statistical analyses

Meta-analysis was conducted using a standard DerSimonian and Laird random-effects model (STATA version 13.0) to derive pooled effect estimates as odds ratios (OR) and associated 95% confidence intervals (DerSimonian and Laird, 1986). The effect on the analysis of within- and between-study heterogeneity was quantified by calculating I^2, which describes the percentage of effect size variability across studies that is due to heterogeneity rather than chance (Higgins et al., 2003).

Funnel plots of the log odds ratio (OR; effect estimate) versus their standard errors (study size or precision) were used to assess small study effects, where studies with smaller sample sizes have larger treatment effects (Egger et al., 1997; Sterne et al., 2011). Symmetry of the funnel plots was assessed visually and using Egger's test, with $P \leq 0.05$ suggesting asymmetry (ie, presence of small study effects).

3. Results

3.1. Systematic literature review

A total of 1013 publications were identified for potential inclusion. After removal of 550 duplicates and exclusion of another 410 based on title and/or abstract, full text of 53 eligible publications were obtained for more detailed screening (Fig. 1). Of these, 39 publications describing pivotal trials for 15 AEDs approved for refractory POS were identified (Anhut et al., 1994; Arroyo et al., 2004; Barcs et al., 2000; Ben-Menachem et al., 2007; Ben-Menachem and Falter, 2000; Ben-Menachem et al., 2010; Ben-Menachem et al., 1996; Beydoun et al., 2005; Bourgeois et al., 1993; Brodie et al., 2010; Cereghino et al., 2000; Chung et al., 2010; Dean et al., 1999; Elger et al., 2009; Faught et al., 2001; Faught et al., 1996; French et al., 2011; French et al., 2012; French et al., 2013; French et al., 2003; French et al., 1996; Guberman et al., 2002; Halasz et al., 2009; Kalviainen et al., 1998; Krauss et al., 2012; Matsuo et al., 1993; Messenheimer et al., 1994; Porter et al., 2007; Privitera et al., 1996; Sachdeo et al., 1997; Sackellares et al., 2004; Schmidt et al., 1993; Sharief et al., 1996; Shorvon et al., 2000; Tassinari et al., 1996; UK, 1990; US Gabapentin Study Group, 1993; Uthman et al., 1998; Willmore et al., 1996). Five of these studies were excluded due to use of unapproved dosages of study drug (Ben-Menachem et al., 1996; Faught et al., 2001; Privitera et al., 1996; Tassinari et al., 1996; Willmore et al., 1996), and 4 were excluded because the maintenance treatment duration was < 8 or > 14 weeks (Barcs et al., 2000; Bourgeois et al., 1993; Messenheimer et al., 1994; UK, 1990).

A total of 29 publications for 12 AEDs (eslicarbazepine, ezogabine, gabapentin, lacosamide, levetiracetam, perampanel, pregabalin, tiagabine, topiramate, vigabatrin, and zonisamide) met study selection criteria (Anhut et al., 1994; Arroyo et al., 2004; Ben-Menachem et al., 2007; Ben-Menachem and Falter, 2000; Ben-Menachem et al., 2010; Beydoun et al., 2005; Brodie et al., 2010; Cereghino et al., 2000; Chung et al., 2010; Dean et al., 1999; Elger et al., 2009; Faught et al., 1996; French et al., 2011; French et al., 2012; French et al., 2013; French et al., 2003; French et al., 1996; Guberman et al., 2002; Halasz et al., 2009; Kalviainen et al., 1998; Krauss et al., 2012; Porter et al., 2007; Sachdeo et al., 1997; Sackellares et al., 2004; Schmidt et al., 1993; Sharief et al., 1996; Shorvon et al., 2000; US Gabapentin Study Group, 1993; Uthman et al., 1998); the single eligible lamotrigine study was excluded from the meta-analysis because it did not report any of the outcomes assessed (Matsuo et al., 1993).

3.2. Study and patient characteristics

A risk of bias assessment of the AED studies included in the meta-analysis is shown in Supplemental Table 2. Funnel plots and Egger tests indicated that small study effects were present for the 50% responder rate ($P < 0.001$, Supplemental Fig. 1), but not for seizure freedom ($P = 0.12$, Supplemental Fig. 2) or discontinuation rate ($P = 0.49$, Supplemental Fig. 3).

Study design and baseline patient characteristics of the AED trials (N = 9265) are shown in Table 1 (More detailed description of study characteristics can be found in Supplemental Table 3). The duration of double-blind maintenance treatment (excluding baseline, titration, and withdrawal periods in most studies) was usually 12 weeks. Four studies had a shorter treatment period of 8 weeks and 5 had treatment periods of 13–14 weeks. All study designs employed parallel treatment groups. Mean patient age was 32–40 years, with a duration of epilepsy of 19–26 years. More than half of patients (53% to 89%) in all studies were taking ≥2 concomitant AEDs.

3.3. 50% responder rate

Compared with placebo, the pooled odds of achieving 50% responder status (≥50% reduction in seizure frequency by the end of double-blind treatment) were higher for all AED dosages assessed (Fig. 2). The overall pooled OR across all AEDs was 3.17 (95% CI: 2.76–3.64). Pooled ORs were 8.82 (95% CI: 2.77–28.11), 6.23 (95% CI: 1.46–26.20) and 8.08 (95% CI: 5.45–11.98) for tiagabine 56 mg/day, pregabalin 600 mg/day, and vigabatrin 3000 mg/day, respectively, and 1.62 (95% CI: 1.10–2.37) and 1.93 (95% CI: 1.28–2.92) for lacosamide 200 mg/day and ezogabine 600 mg/day, respectively.

There was little or no heterogeneity for the majority of AED doses, with higher I^2 values for perampanel 12 mg/day (58.1%), levetiracetam 3000 mg/day (61.3% for mg/day), and vigabatrin 3000 mg/day (74.4%) indicating heterogeneity of moderate to substantial importance.

3.4. Seizure freedom

The pooled odds of achieving seizure freedom were higher for all AEDs compared with placebo (Fig. 3), with an overall pooled OR across all AEDs of 3.41 (95% CI: 2.27–5.12). The odds of achieving seizure freedom were at least 7 times greater than placebo for patients receiving 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). Little or no heterogeneity was found ($I^2 = 0\%$ for all AEDs except lacosamide 400 mg/day, $I^2 = 17.3\%$).

3.5. Tolerability

The odds of discontinuation due to AEs were greater for patients treated with AEDs compared with those receiving placebo, except for the lowest dose of pregabalin (OR 0.77, 95% CI: 0.11–5.41, Fig. 4). The overall pooled OR across all AEDs was 2.63 (95% CI: 2.21–3.13).

The majority of AED doses had I^2 values of 0%, indicating little or no heterogeneity, with the exception of perampanel 12 mg/day ($I^2 = 58.1\%$), levetiracetam 3000 mg/day ($I^2 = 61.3\%$), and vigabatrin 3000 mg/day ($I^2 = 74.4\%$).

4. Discussion

The current study is the first analysis to date to assess pooled data from AED pivotal trials. As the basis for FDA approval and the content of the package insert, pivotal trial data play an important role in shaping initial impressions of the relative efficacy and safety of AEDs.

Pooled data from more than 9000 patients in 29 pivotal trials of 11

Table 1
Study and patient characteristics of adjunctive AED trials included in meta-analyses.

Study	Treatment duration[a], wks	N	Treatment groups[b] (n)	Mean age[c], yrs	Male, %	Mean epilepsy duration[d], yrs	Number of concomitant AEDs (% patients)	
							1	≥ 2
Eslicarbazepine								
Elger et al. (2009)	12	402	ESC 400 (100), ESC 800 (98), ESC 1200 (102), PBO (102)	39	49	21	36	64
Ben-Menachem et al. (2010)	***14***	395	ESC 400 (96), ESC 800 (101), ESC 1200 (98), PBO (100)	37	49	24	19	78
Ezogabine								
Porter et al. (2007)	8	396	EZG 600 (99), EZG 900 (95), EZG 1200 (106), PBO (96)	37	52	20	29	71
Brodie et al. (2010)	12	538	EZG 600 (181), EZG 900 (178), PBO (179)	38	48	23	23	77
French et al. (2011)	12	305	EZG 1200 (153), PBO (152)	37	46	24	22	83
Gabapentin								
US Gabapentin Study Group (1993)	12	306	GBP 600 (53), GBP 1200 (101), GBP 1800 (54), PBO (98)	35	66	–	37	63
Anhut et al. (1994)	12	272	GBP 900 (111), GBP 1200 (52), PBO (109)	32	56	20	24	–
Lacosamide								
Ben-Menachem et al. (2007)	12	418	LCS 200 (107), LCS 400 (108), LCS 600 (106), PBO (97)	40	46	25	–	–
Halasz et al. (2009)	12	485	LCS 200 (163), LCS 400 (159), PBO (163)	38	52	22	13	85
Chung et al. (2010)	12	405	LCS 400 (204), LCS 600 (97), PBO (104)	38	49	25	18	81
Levetiracetam								
Ben-Menachem and Falter (2000)	12	286	LEV 3000 (181), PBO (105)	37	48	19	–	–
Cereghino et al. (2000)	14	294	LEV 1000 (98), LEV 3000 (101), PBO (95)	38	61	–	33	62
Shorvon et al. (2000)	12	324	LEV 1000 (106), LEV 2000 (106), PBO (112)	37	48	24	19	–
Perampanel								
French et al. (2012)	13	388	PER 8 (133), PER 12 (134), PBO (121)	36	48	24	15	85
Krauss et al. (2012)	13	706	PER 2 (180), PER 4 (172), PER 8 (169), PBO (185)	34	60	19	15	85
French et al. (2013)	13	386	PER 8 (129), PER 12 (121), PBO (136)	36	48	22	11	89
Pregabalin								
French et al. (2003)	12	453	PRB 50 (88), PRB 150 (86), PRB 300 (90), PRB 600 (89), PBO (100)	38	47	25	31	69
Arroyo et al. (2004)	***12***	287	PRB 150 (99), PRB 600 (92), PBO (96)	37	51	24	18	81
Beydoun et al. (2005)	***12***	312	PRB 600 (300 BID) (103), PRB 600 (200 TID) (111), PBO (98)	39	50	26	29	69
Tiagabine								
Sachdeo et al. (1997)	8	318	TGB 32 (16 BID) (106), TGB 32 (8 QID) (105), PBO (107)	34	58	21	–	–
Kalviainen et al. (1998)	12	154	TGB 30 (77), PBO (77)	36	58	24	–	–
Uthman et al. (1998)	12	297	TGB 16 (61), TGB 32 (88), TGB 56 (57), PBO (91)	34	42	23	–	–
Topiramate								
Faught et al. (1996)	12	181	TPM 200 (45), TPM 400 (45), TPM 600 (46), PBO (45)	37	79	–	35	65
Sharief et al. (1996)	8	47	TPM 400 (23), PBO (24)	34	85	–	–	–
Guberman et al. (2002)	***12***	263	TPM 200 (8-week TIT) (85), TPM 200 (4-week TIT) (86), PBO (92)	37	48	19	44	54
Vigabatrin								
French et al. (1996)	12	182	VGB 3000 (92), PBO (90)	34	44	–	–	–62
Dean et al. (1999)	12	174	VGB 1000 (45), VGB 3000 (43), VGB 6000 (41), PBO (45)	34	48	22	47	53
Zonisamide								
Schmidt et al. (1993)	***12***	139	ZNS 1.5–20 mg/kg/d (71), PBO (68)	35	58	23	–	–
Sackellares et al. (2004)	8	152	ZNS 1.5–20 mg/kg/d (78), PBO (74)	36	66	20	–	–

"–" indicates that the characteristic was not reported.
AED, antiepileptic drug; BID, two times per day; ESC, eslicarbazepine; EZG, ezogabine; FBM, felbamate; GBP, gabapentin; LCS, lacosamide; LTG, lamotrigine; LEV, levetiracetam; OXC, oxcarbazepine; PBO, placebo; PER, perampanel; PRB, pregabalin; QID, four times per day; TGB, tiagabine; TID, three times per day; TIT, titration period; TPM, topiramate; VPT, valproate; VGB, vigabatrin; wks, weeks; yrs, years; ZNS, zonisamide.

[a] Treatment duration does not include titration period, with the following exceptions indicated in bold italics: Ben-Menachem 2010 includes 2-week TIT from 800 mg/day to 1200 mg/day for 1200 mg/day group; Messenheimer 1994 included 3-week TIT and a 2-week taper; Arroyo 2004 includes 4- and 8-day TIT in the 150 mg/day and 600 mg/day pregabalin groups, respectively; Beydoun 2005 includes 8-day TIT, Guberman 2002 includes 8-week or 4-week TIT, Schmidt includes 4-week TIT.

[b] All dosages reported in mg/day, except ZNS, which was reported in mg/kg/d based on body weight.

[c] If mean age for the total study population was not reported, it was calculated as a weighted average using mean age of treatment groups.

[d] If duration of epilepsy for the total study population was not reported, it was calculated as a weighted average duration of epilepsy of treatment groups.

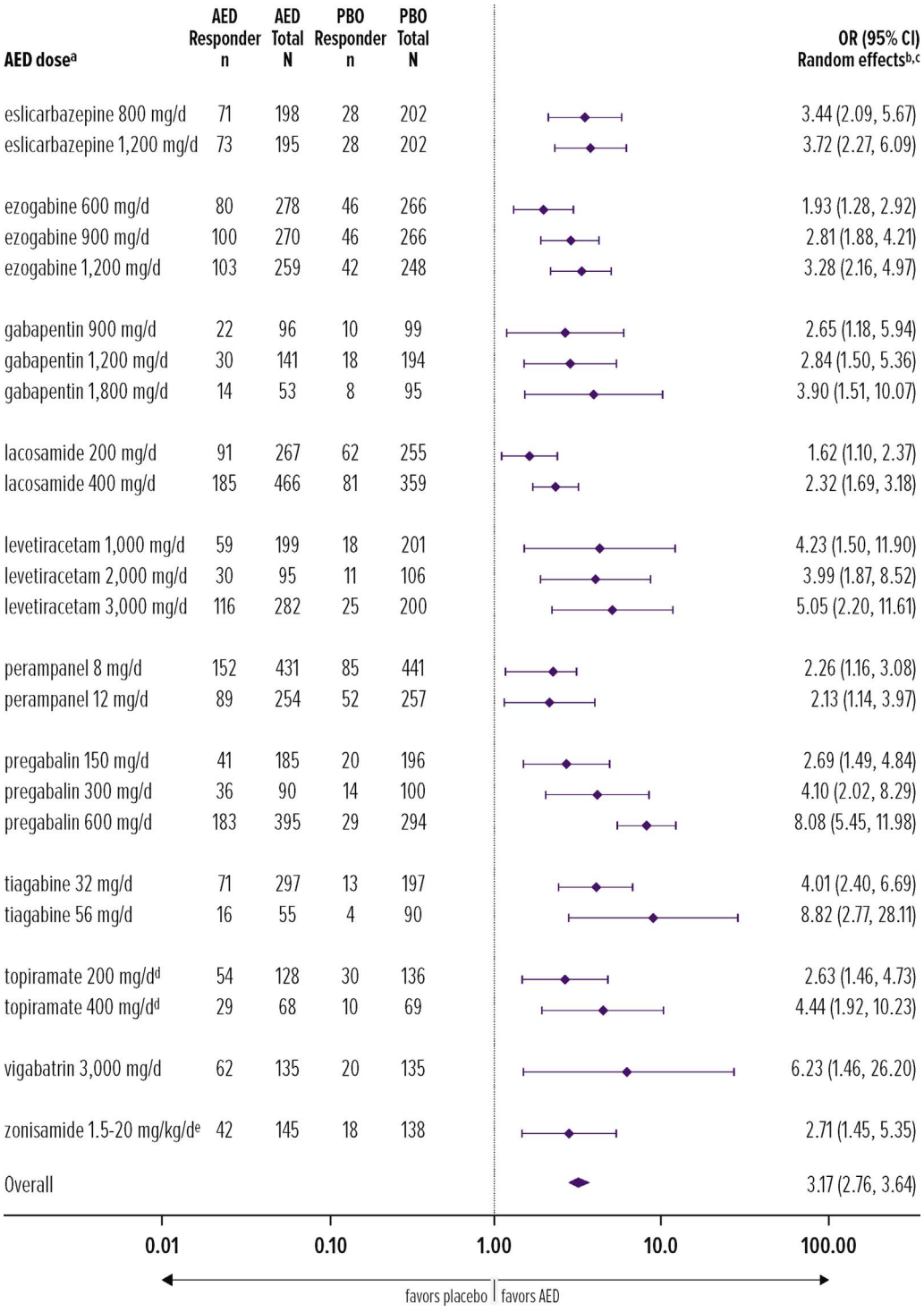

Fig. 2. Forest plot of the odds ratio of the 50% responder rate for pooled adjunctive AED dosages.

[a] 50% responder rate was not reported as an outcome in the single eligible lamotrigine study; therefore, lamotrigine was not included in these analyses.

[b] Pooled odds ratios and 95% CI were calculated using DerSimonian & Laird random effects method.

[c] Computed I^2 were 0% across all studies, with the following exceptions: levetiracetam 3000 mg/day (I^2 = 61.3%), perampanel 12 mg/day (I^2 = 58.1%), topiramate 200 mg/day (I^2 = 10.8%), vigabatrin 3000 mg/day (I^2 = 74.4%), and zonisamide (I^2 = 16.4%). I^2 values of 25%, 50%, and 75% are considered low, moderate, and high risk of heterogeneity, respectively.

[d] The maintenance treatment period for the 8-week (N = 85) TIT group in Guberman 2002 (topiramate) was < 8 weeks; therefore, data from the 8-week TIT patient group were excluded from this analysis.

[e] The FDA approved dose for zonisamide is 100–600 mg/day. The dosages reported in the pivotal trials were based on body weight and reported in mg/kg/d.

AED, antiepileptic drug; CI, confidence interval; OR, odds ratio; PBO, placebo.

adjunctive AEDs for refractory POS indicate that AED-treated patients were more likely to respond than those treated with placebo. Patients receiving tiagabine, pregabalin, and vigabatrin had pooled odds of 8.82 (95% CI: 2.77–28.11), 6.23 (95% CI: 1.46–26.20) and 8.08 (95% CI: 5.45–11.98), respectively, of experiencing a ≥50% reduction in seizures, and patients receiving levetiracetam, vigabatrin, and ezogabine, had pooled odds of 11.00 (95% CI: 2.08–58.06), 7.41 (95% CI: 1.31–41.84), and 7.09 (95% CI: 0.36–58.06), respectively, of achieving seizure freedom. Patients were more likely to discontinue any AED than placebo, with the exception of low-dose pregabalin.

These findings are similar to those of previous meta-analyses, all of which demonstrated improved pooled efficacy of AEDs versus placebo (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). Of those that assessed similar outcomes and/or overlapping AEDs with this study, one study found that topiramate, oxcarbazepine, and pregabalin had the highest 50% responder rates, and levetiracetam, vigabatrin, valproate, and gabapentin had the best combination of short-term efficacy and tolerability (Bodalia et al., 2013). In another, topiramate, levetiracetam, pregabalin, and oxcarbazepine had the highest efficacy and lowest risk of

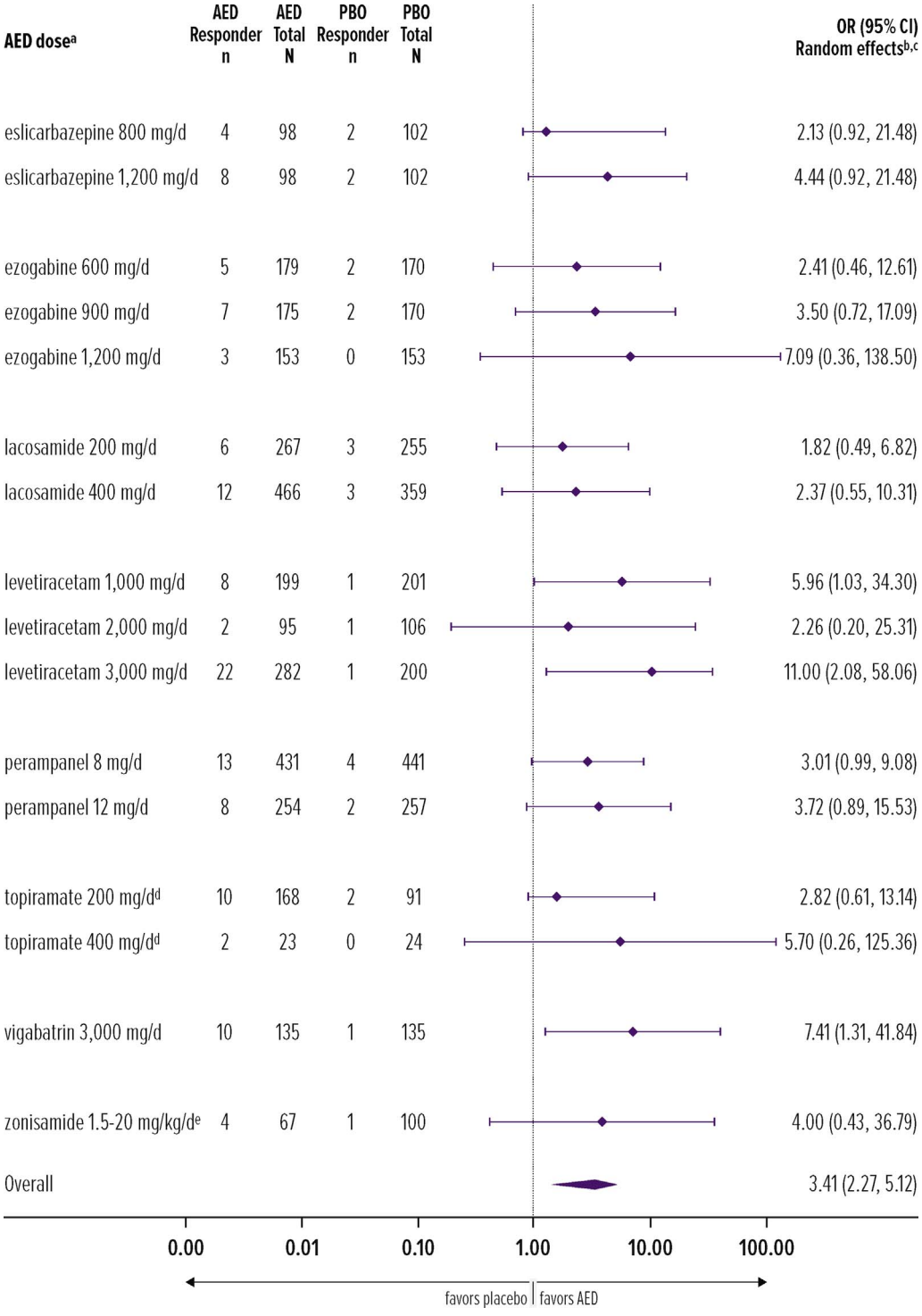

Fig. 3. Forest plot of the odds ratio of seizure freedom for pooled adjunctive AED dosages.

[a] Seizure freedom was not reported as an outcome in the eligible gabapentin, lamotrigine, and tiagabine studies; therefore, they were not included in these analyses.

[b] The pooled odds ratios and 95% CI were calculated using DerSimonian & Laird random effects method.

[c] Computed I^2 were 0% across all studies, with the following exception: lacosamide 400 mg/day (I^2 = 17.3%). An I^2 value of ≤25% is considered low risk of heterogeneity.

[d] The seizure freedom analysis includes both the 4-week and 8-week TIT treatment groups from Guberman 2002 because the outcome for the treatment groups was not reported separately.

[e] The FDA approved dose for zonisamide is 100–600 mg/day. The dosages reported in the pivotal trials were based on body weight and reported in mg/kg/d.

AED, antiepileptic drug; CI, confidence interval; OR, odds ratio; PBO, placebo.

adverse events (Zhao et al., 2017). An indirect comparison of 50% responder rates favored topiramate (OR), and topiramate and levetiracetam (number needed to treat, NNT), over other AEDs (Costa et al., 2011), and another favored levetiracetam (Otoul et al., 2005). Variation in the findings of the studies likely result from several factors, including differences in AEDs assessed, methodology, and inclusion criteria.

While this study provides useful information to aid clinicians in treatment decisions for patients with refractory POS, the following limitations should be noted. As with all random-effects meta-analysis, the precision of pooled effect estimates (OR) is dependent on sample size; therefore pooled effect estimates for studies with a smaller sample size may be less precise (ie, have a wider 95% CI). For inclusion in this analysis, studies must have met been placebo-controlled, pivotal RCTs for adjunctive treatment of refractory POS, used approved dosages of AEDs, and had an 8- to 14-week maintenance period. In addition, studies must have reported 50% responder rate, seizure freedom, and discontinuation rate due to AE as outcomes. Pivotal studies that led to the approval of felbamate (Bourgeois et al., 1993) and oxcarbazepine (Barcs et al., 2000) did not meet the inclusion 8- to 14-week inclusion criterion and were excluded from the analysis. The single pivotal valproate study allowed valproate dosages that exceeded the approved

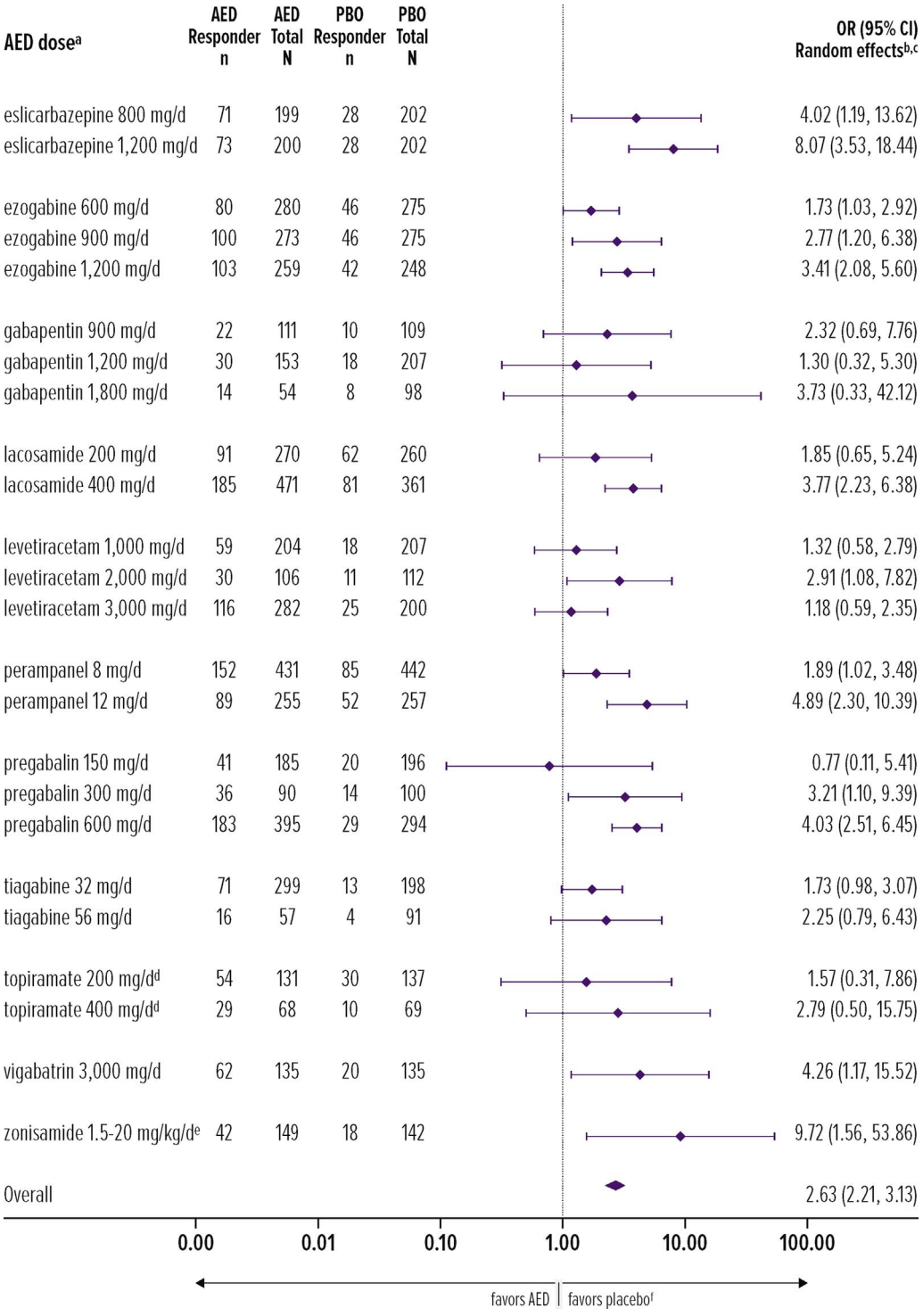

Fig. 4. Forest plot of the odds ratio for the discontinuation rate due to AEs for pooled adjunctive AED dosages.

[a] Discontinuation rate was not reported as an outcome in the single eligible lamotrigine study; therefore, lamotrigine was not included in these analyses.

[b] The pooled odds ratios and 95% CI were calculated using DerSimonian & Laird random effects method.

[c] Computed I^2 were 0% across all studies, with the following exceptions: levetiracetam 3000 mg/day (I^2 = 61.3%), perampanel 12 mg/day (I^2 = 58.1%), topiramate 200 mg/day (I^2 = 10.8%), vigabatrin 3000 mg/day (I^2 = 74.4%), and zonisamide (I^2 = 16.4%). I^2 values of 25%, 50%, and 75% are considered low, moderate, and high risk of heterogeneity, respectively.

[d] The maintenance treatment period for the 8-week (N = 85) TIT group in Guberman 2002 (topiramate) was < 8 weeks; therefore, data from the 8-week TIT patient group were excluded from this analysis.

[e] The FDA approved dose for zonisamide is 100–600 mg/day. The dosages reported in the pivotal trials were based on body weight and reported in mg/kg/d.

[f] Treatment discontinuation due to AEs is an unfavorable outcome; therefore, an OR > 1 indicates that patients receiving AEDs are more likely to discontinue treatment than patients on PBO.

AE, adverse event; AED, antiepileptic drug; CI, confidence interval; OR, odds ratio; PBO, placebo.

dosage (Willmore et al., 1996) and was therefore excluded. Of the two published pivotal lamotrigine studies, one did not meet the 8- to-14 week maintenance duration criterion (Messenheimer et al., 1994); the other did not report the outcomes assessed (Matsuo et al., 1993).

Brivaracetam, a recent addition to the AEDs approved for refractory POS, was not approved at the time this analysis was conducted; therefore the three pivotal trials of brivaracetam were not included (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014). In a pooled analysis of the three trials (Ben-Menachem et al., 2016), there were significantly more 50% responders after 12 weeks of maintenance treatment in the brivaracetam 50, 100, or 200 mg/d groups than placebo, and discontinuation due to TEAEs was higher in brivaracetam (6.7%) than placebo (3.9%) patients.

Other factors that may influence treatment choice, such as the incidence of AEs, were not assessed in this analysis due to the limitations of available data (ie, inconsistencies in the assessment and/or reporting of AEs in the studies). The RCTs included in the trial were limited to those that were 8–14 weeks in duration; however, variation in duration of exposure to target dose, due to variation in duration of titration, treatment, and or maintenance periods (see Supplemental Table 3), may have affected the study outcomes. In addition, while 8–14 weeks' duration is typically the duration required to meet regulatory criteria,

the extrapolation of these results to longer-term use must be approached with caution given the increased potential for AEs during longer-term use of some AEDs (Zaccara et al., 2006). Finally, including only studies that served as the basis for FDA approval (and possibly excluding pivotal trials for other regulatory bodies outside the US) may limit the applicability of these results outside the US.

Despite the relative similarity of study design of the RCTs included in the present meta-analysis, as well as the generally low levels of heterogeneity indicated by the I^2 values, there is always some level of inconsistency due to variability in factors such as treatment duration, outcomes assessed, patient age, severity of illness, medical history, seizure type(s), prior and current AEDs, comorbid conditions, and concomitant medications. It is worth noting that the studies were conducted over at least 16 years, during which time the management of epilepsy, availability of services, and conduct and reporting of RCTs has changed. More recent trials may include more refractory or drug-resistant patients than earlier studies, while other trials may have enrolled less medically refractory patients–either by intention (per study design) or on an unconscious basis–based on investigators' preconceived expectations of the safety or efficacy of the study drug. Though there is currently no direct metric for the degree of "medical refractoriness," it has been argued that the average number of previously failed AEDs or number of seizures during baseline period could be useful in this regard (Asadi-Pooya et al., 2017). However, these factors are not reported consistently and therefore could not be assessed in this study. Finally, by design, this meta-analysis included only pivotal trials that were conducted prior to FDA approval and market release; therefore, the dosing strategies in the trials may not reflect the dosing typically used in the clinical setting following approval.

When making treatment decisions for patients with refractory POS, clinicians must consider the many factors that contribute to treatment success for an individual patient, such as efficacy, safety, tolerability, formulation and timing of dosing, titration schedule, comorbid conditions, and concomitant medications. In the absence of trials that directly assess the relative efficacy and safety of AEDs (ie, head-to-head clinical trials), treatment choices are often guided by clinicians' initial impressions, anecdotal experience, and pre-existing practice patterns rather than evidence-based medicine. However, clinicians' widely held beliefs regarding relative efficacy and/or toxicity of AEDs may actually be at odds with the body of published evidence. Four of the 5 AEDs identified in this study as having high ORs for ≥50% seizure reduction or seizure freedom − ezogabine, pregabalin, tiagabine, and vigabatrin − are not among the most commonly prescribed AEDs for refractory POS, due to a perceived lack of efficacy (tiagabine, pregabalin) or side effects (vigabatrin: visual field loss; ezogabine: eye and skin discoloration, vision changes, and urinary retention). This study indicates that further investigation into the relative efficacy of AEDs with perceived lower efficacy, such as tiagabine and pregabalin, is warranted. In addition, careful assessment of the risk benefit ratio of the known efficacy of vigabatrin against the low risk of potential peripheral vision loss (Krauss et al., 2016) is in order.

These limitations highlight the real need for a set of design, conduct, and reporting standards to increase uniformity and reduce heterogeneity of AED RCTs, thereby maximizing the validity, confidence, and quality of subsequent meta-analyses, the importance of which should not be underestimated given that head-to-head trials are not likely to be conducted in the future. Following is a list of suggestions for future short-term AED trials:

- Study design: in the absence of an active control, trials should have a placebo-controlled, double-blind, and parallel design, with a treatment duration of at least 8 weeks (excluding lead-in, titration, or follow-up periods). Duration of 8 weeks is generally required for FDA approval; however, a longer duration of 12–14 weeks in these short-term trials would be preferred (ideally with the option to participate in a longer-term, open-label trial upon completion)
- Patient population: mean age, duration of epilepsy, age at epilepsy onset, number of previously failed AEDs, number of concomitant AEDs at baseline, and incidence of common comorbidities should be uniformly collected and reported for each treatment group
- Efficacy outcomes: 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) should be reported for each treatment group
- Safety/tolerability outcomes: incidence of most commonly reported (≥5 percent of patients) treatment-emergent AEs (eg, asthenia, ataxia, dizziness, headache, nervousness, somnolence, nausea, vomiting), as well as incidence of discontinuations due to AEs, should be reported for both treatment groups.

As long as regulatory authorities require clinical trials to demonstrate drug efficacy relative to placebo only, the dearth of head-to-head clinical trials will persist, leaving clinicians to make treatment choices based on initial impressions and anecdotal evidence, which may be at odds with evidence from studies such as this one. Thus, other methods must be used to make comparisons among emerging AEDs. Despite their limitations, meta-analyses are useful resources for measuring relative risks and benefits of available AEDs to optimize treatment and effectively manage patients' symptoms.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eplepsyres.2017.10.004.

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