FULL-LENGTH ORIGINAL RESEARCH

Prevention of generalized tonic–clonic seizures in refractory focal epilepsy: A meta-analysis

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Summary

Objectives: **Secondary generalized tonic–clonic seizures (SGTCS) are among the most severe forms of seizures, and the main risk factor for sudden unexpected death in epilepsy (SUDEP). Whether some antiepileptic drugs (AEDs) might be more efficacious than others on SGTCS in patients with drug-resistant focal epilepsy thus represents an important clinical issue for which no data are currently available.**

Methods: **We performed a meta-analysis of randomized controlled trials of adjunctive AED in which information on efficacy outcomes (i.e., responder rate and/or frequency per 28 days relative to baseline) were available both for all seizure types and for SGTCS. The primary analysis evaluated the efficacy of AEDs on all types of seizure and on SGTCS by comparing the responder rates for AED and for placebo.**

Results: **Responder rate was available both for all seizure types and for SGTCS in 13 of the 72 eligible trials, evaluating 7 AEDs. Only three AEDs—lacosamide, perampanel and topiramate—showed greater efficacy than placebo. However, confidence intervals of relative risks overlapped for all AEDs but pregabalin, which demonstrated significantly lower efficacy than lacosamide, perampanel, and topiramate. Moreover, there was a nonsignificant trend toward a lower relative risk of responder rate for SGTCS than for all seizure types, which appeared related to a greater response to placebo for this outcome.**

Significance: **Indirect comparison of AEDs using randomized placebo-controlled add-on trials does not support robust differences between AEDs to prevent SGTCS. Alternative designs for evaluation of therapeutic interventions in patients at risk for SGTCS-related complications are required.**

KEY WORDS: **Antiepileptic drugs, Generalized tonic–clonic seizures, Meta-analysis, Epilepsy, Sudden unexpected death in epilepsy.**

The presence and frequency of generalized tonic–clonic seizures (GTCS; either primary or secondary generalized [SGTCS]) were found to represent the strongest risk factors for sudden unexpected death in epilepsy (SUDEP),[1] with an odds ratio (OR) of >15 for patients with three or more GTCS per month.[2] SUDEP primarily affects young adults with uncontrolled seizures, with an incidence of about 0.4% per year.[1] Up to 20% of patients with childhood-onset drug-resistant epilepsy will die of SUDEP by the age of 45.[3] There is currently no effective treatment to prevent SUDEP, apart from reinforcing antiepileptic drug (AED) therapy.[1] Indeed, the only controlled data available in the field suggest that adding an AED to the baseline regimen might be protective.[4]

Over the last 20 years, the number of licensed AEDs has increased exponentially, making the process of drug selection difficult.[5] Furthermore, randomized head-to-head comparisons of available AEDs are lacking,[6] while systematic reviews and meta-analyses of placebo-controlled randomized trials have failed to demonstrate consistent differences.[7–11] However, these meta-analyses have assessed

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the impact of treatment on focal seizures with or without SGCTS, without specifically investigating SGTCS.

Why some focal seizures evolve to secondary generalization while others do not in the same individual remains poorly understood. Although the mechanisms underlying these two seizure types might not differ at their initiation phase, secondary generalization might reflect involvement of specific mechanisms, both at the cellular and network levels.[12–15] In vitro studies suggest that seizure initiation and propagation might be triggered by different alterations of synaptic transmission.[13,14] In patients, specific cortical and subcortical networks are thought to be involved during secondary generalization.[12,15,16] Based on these observations, one can speculate that some AEDs might be more efficacious than others to prevent secondary generalization, while they would not necessarily differ in their efficacy to prevent initiation of focal seizures. To address this issue, we undertook a meta-analysis of randomized controlled trials (RCTs) of adjunctive AED for which SGTCS outcome was available.

Materials and Methods

We performed a systematic review and meta-analysis of placebo-controlled double-blind adjunctive-therapy RCTs of licensed and investigational AEDs in adults with refractory focal epilepsy using methods similar to those we previously reported.[11] Our study met the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Two electronic databases (MEDLINE and Web of Science) were searched from 1960 to August 31, 2013 (Data S1). Additional RCTs were searched on the following: (1) registry websites; (2) the abstracts of the International and the European Congresses of the International League Against Epilepsy (ILAE), and the abstracts of the Annual Meetings of the American Epilepsy Society and the American Academy of Neurology; and (3) the references of all identified publications.

To qualify for inclusion, an RCT had to meet the following criteria: (1) efficacy as a primary endpoint; (2) information on number of arms and corresponding dosages; (3) a minimum baseline period of 4 weeks and a minimum treatment period of 6 weeks; (4) information on efficacy outcomes (i.e., responder rate and/or frequency per 28 days relative to baseline) available both for all seizure types (simple or complex focal seizures, with or without secondary generalizations) and for secondary generalized tonic–clonic seizures (SGTCS); and (5) results reported according to intention-to-treat (ITT) analysis.

Some AEDs have been evaluated as add-on therapy in patients with refractory primary GTCS.[17] Considering the variability of efficacy profile of AEDs across epilepsy syndromes,[5] pooling data obtained in focal epilepsies with those obtained in primary generalized epilepsies might be misleading. In this context, RCTs evaluating AEDs in patients with refractory primary GTCS were not included in the current study.

Data were independently extracted by two authors (CH and SR) using predefined data fields, including trials and patients' characteristics, interventions, and outcomes. The Cochrane Collaboration's tool for assessing risk of bias[18] was used to ascertain the validity of eligible RCTs.

The primary end point was the responder rate (proportion of patients with ≥50% reduction in seizure frequency during the treatment period as compared to baseline). The responder rate for all types of seizure was calculated using the ITT population (defined as all randomized patients) as denominator and the number of responders as numerator, as defined by the standard last observation carried forward (LOCF) method.[11] The SGTCS responder rate was calculated using the number of randomized patients who demonstrated SGTCS during the baseline period as denominator and the number of patients with ≥50% reduction in SGTCS frequency during the treatment period as numerator, as defined by the LOCF method. Because a large majority of trials lacked information regarding the number of patients without SGTCS during baseline but who had a SGCTS during double-blind phase (see Table 1), such patients could not be included in the primary analyses. To evaluate the potential bias resulting from this approach, a sensitivity analysis was performed using the few trials providing data on patients with SGTCS during double-blind phase but not during baseline, who were counted as nonresponders. Another sensitivity analysis was performed by restricting data analysis to approved doses (defined as the doses recommended in the product information approved by the Food and Drug Administration [FDA] in the United States and/or European Medicines Agency [EMA] in Europe).

We evaluated the efficacy of AEDs on all types of seizure and on SGTCS by comparing the responder rate in the AED treatment group with that observed in the placebo group, using the logarithm of relative risk (RR) method. Treatment effect and heterogeneity tests were performed by setting a statistical significance level at <0.05 for treatment effect and a threshold of <0.10 for heterogeneity (Cochrane's Q-test). Heterogeneity was also assessed by the I^2 statistic, which is independent of the number of studies and quantifies heterogeneity on a scale of 0–100%. Very large heterogeneity between studies is denoted by I^2 values of ≥75%. In the absence of a clear explanation for heterogeneity, fixed-effect models for RR were planned. Funnel plots were used to investigate small study bias (e.g., publication bias).

An exploratory analysis was performed using the change in SGTCS frequency per 28 days relative to baseline rather than responder rate as efficacy end point. This endpoint was analyzed using effect size, consisting of a difference between each treated group and control arms in the change between treatment period and baseline, using the LOCF method. Data were then pooled by tested doses for each

Table 1. Characteristics of included studies

AED	RCT	Approved doses (mg/day)	Evaluated doses (mg/day)	Baseline characteristics: No. randomized patients AED	Placebo	Baseline characteristics: No. patients with SGTCs during baseline AED	Placebo	Baseline characteristics: Baseline monthly SGTCS frequency (median) AED	Placebo	No. patients with SGTCS during double-blind phase but without during baseline AED	Placebo	Responder rate (%): All seizure types AED	Placebo	Responder rate (%): SGTCS AED	Placebo	Median percent reduction from baseline in 28-day seizure frequency: All seizure types AED	Placebo	Median percent reduction from baseline in 28-day seizure frequency: SGTCS AED	Placebo
Carisbamate	Sperlling et al. (2010)	–	200;400	187; 192	186	78;80	75	na	na	na	na	25;33	18	na	na	−16; −27	−15	−28; −56[a]	−11
	Sperlling et al. (2010)		200;400	188; 185	189	95;81	84	na	na	na	na	23;24	21	na	na	−22; −21	−15	−36; −29	−28
	Halford et al. (2011)		800; 1,200	180; 182	185	56;64	70	na	na	9;17	8	28;37	26	na	na	−32[b]	−21	−18[a,b]	−11
Eslicarbazepine	Elger et al. (2009)	800–1,200	400;800; 1,200	100; 98; 102	102	na	na	3.2; 2.5; 1.5	2.5	na	na	25;32; 36	15	na	na	na	na	−16; −64; −20	−28
Lacosamide	Chung et al. (2010)	200–400	400;600	204; 97	104	84;47	45	3.3; 5	4	na	na	38;41	18	56; 70	33	−37; −38	−21	na	na
Levetiracetam	Shorvon et al. (2000)	1,000–3,000	1,000; 2,000	106; 106	112	28;21	24	na	na	2; na	8	21;35	6	na	na	−18; −27	−6	−37[a]; −28	−17
	Cereghino et al. (2000)		1,000; 3,000	98; 101	95	na	na	na	na	na	na	37;40	7	na	na	−37; −38	−7	−85[a]; −65[a]	−24
Oxcarbazepine	Barcs et al. (2000)	1,200	600; 1,200; 2,400	169; 178; 174	173	49;68; 60	51	3.5; 2; 2.4	3.5	na	na	27;41; 50	13	na	na	−26; −40; −50	−8	−71[a]; −86[a]; −94[a]	−13
Perampanel	French et al. (2012)	4–12	8;12	133; 134	121	51;52	56	3.4. 4.1	4.1	na	na	38;36	26	67; 60	38	−26; −35	−21	−56[a]; −40[a]	−16
	French et al. (2013)		8;12	129; 121	136	44;43	48	3.4; 3.8	3.5	na	na	33;34	15	50; 47	25	−31; −18	−10	−34[a]; −35[a]	−14
	Krauss et al. (2012)		2;4;8	180; 172; 169	185	68;71; 62	69	3.4. 3.7; 2.7	3.4	na	na	21;29; 35	18	44; 49; 63	45	−14; −23; −31	−11	−2[a]; −30[a]; −38[a]	−7

Continued

Table 1. Continued.

AED	RCT	Approved doses (mg/day)	Evaluated doses (mg/day)	Baseline characteristics: No. randomized patients		Baseline characteristics: No. patients with SGTCs during baseline		Baseline characteristics: Baseline monthly SGTCS frequency (median)		No. patients with SGTCS during double-blind phase but without during baseline		Responder rate (%): All seizure types		Responder rate (%): SGTCS		Median percent reduction from baseline in 28-day seizure frequency: All seizure types		Median percent reduction from baseline in 28-day seizure frequency: SGTCS	
				AED	Placebo	AED	Placebo	AED	Placebo	AED	Placebo	AED	Placebo	AED	Placebo	AED	Placebo	AED	Placebo
Pregabalin	Lee et al. (2009)	150–600	150–600	119	59	45	25	na	na	na	na	46	32	62	80	−38	−20	−70[a]	−68
Rufinamide	Brodie et al. (2009)	–	3,200	156	157	47	54	1	1.6	18	20	28	19	na	na	−20	1.6	−38	−38
	Biton et al. (2011)		3,200	176	181	76	65	na	na	na	na	33	14	na	na	−13	−5	−40[a]	−25
Tiagabine	Kalviainen et al. (1998)	32–56	32	77	77	32	30	1.4	0.7	6	5	14	6	32	26	−13	0	−21.8	0
	Uthman et al. (1998)		16;32; 56	61; 88; 57	91	na	na	1.6; 1.8; 1.5	2	4;5; 3	3	8;19; 28	4	na	na	−13; −25; −33	−11	−43; −44; −47	−60
Topiramate	Privitera et al. (1996)	200–400	600;800; 1,000	48; 48; 47	47	12; 17; 11	17	na	na	na	na	44;39; 38	9	67;47; 54	35	−41; −41; −36	−1	−66; −44; −78	−40
	Korean study group (1999)		600	91	86	na	na	na	na	na	na	49	9	na	na	−51	−9	−100[a]	−40
	Sharief et al. (1996)		400	23	24	14	8	na	na	0	5	35	8	71	38	−41	−1	−84[a]	−9
	Faught et al. (1996)		200;400; 600	45. 45; 46	45	14; 15; 13	14	na	na	na	na	27:47; 46	18	71; 87.77	21	−30; −48; −45	−13	−62[a]; −100[a]; −89[a]	−1
	Ben-Menachem et al. (1996)		800	28	28	11	13	na	na	na	na	43	4	82	23	−36	18	−90[a]	−19
	Guberman et. (2002)		200	171	92	55	36	0	0	na	na	45	24	49	33	−44	−20	−50[a]	−1

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Table 1. Continued.

AED	RCT	Approved doses (mg/day)	Evaluated doses (mg/day)	Baseline characteristics						No. patients with SGTCS during double-blind phase but without during baseline		Responder rate (%)				Median percent reduction from baseline in 28-day seizure frequency			
				No. randomized patients		No. patients with SGTCs during baseline		Baseline monthly SGTCS frequency (median)				All seizure types		SGTCS		All seizure types		SGTCS	
				AED	Placebo	AED	Placebo	AED	Placebo	AED	Placebo	AED	Placebo	AED	Placebo	AED	Placebo	AED	Placebo
Vigabatrin	French et al. (1996)	1,000–3,000	3,000	93	90	31	29	na	na	na	na	43	19	48	52	−36	−10	na	na
Zonisamide	Schmidt et al. (1993)	100–500	400	73	71	8	7	na	na	na	na	26	13	25	57	−23	−3	−23	−61

[a]Arms in which the variability of the outcome could be extrapolated from published data (see Materials and Methods).
[b]Pooled data from all AED arms.

AED. This analysis required use of mean value and standard deviation of the outcome in each intervention group.[18] However, reports from RCTs preferentially provide median value for each study arm rather than mean value, and variability is usually not detailed. Although we could not assess whether the distribution of data was symmetrical, we considered median values as mean values. In addition, standard deviations were extrapolated from p-values for differences in means/medians between treatment arms and placebo using the approach proposed by the Cochrane Collaboration Group.[18] Meta-analyses were performed using the software EasyMA (M. Cucherat, Lyon, France).

Results

The search for RCTs of any AED in the adjunctive-therapy treatment of refractory focal epilepsy identified 6,078 publications. Exclusion of irrelevant and duplicate publications after review of the abstracts reduced the number of trials to 278. Of these, 206 were excluded for the reasons listed in Figure 1, leaving a total of 72 eligible trials.

Only 24 (33%) of these 72 eligible trials provided efficacy data for SGTCS and were included in further analyses. Fifty percent responder rates for SGTS were available in the original publication for 10 studies (14%) and could be retrieved from a post hoc study[19] for three additional trials evaluating perampanel.[20–22] Change in SGTCS frequency per 28 days relative to baseline was available in 22 studies (38.7%). However, variability of the SGTCS frequency change could not be extrapolated in 7 of them and, therefore, only 15 studies (21%) contributed to this outcome in the meta-analysis. Seven studies contributed to both outcomes (see Table 1). In contrast, three studies that provided median reduction from baseline in 28-day SGTCS frequency without information allowing extrapolation of variability and without SGTCS 50% responder rates, did not contribute to any outcome.[23–25]

Overall, the 24 included RCTs evaluated 12 AEDs, all but one (carisbamate) being currently licensed as adjunctive-therapy treatment for refractory focal epilepsy. All of them were second-generation AEDs, with no RCT having evaluated older generation AED meeting the eligibility criteria. The 13 RCTs providing the SGTCS responder rate evaluated 7 AEDs (lacosamide, perampanel, pregabalin, tiagabine, topiramate, vigabatrin, and zonisamide). The 15 studies that contributed to the exploratory analysis of median reduction from baseline in 28-day SGTCS frequency also evaluated 7 AEDs (carisbamate, levetiracetam, oxcarbazepine, perampanel, pregabalin, rufinamide, and topiramate).

Validity of eligible RCTs was ascertained with the Cochrane Collaboration's tool for assessing risk of bias.[18] Study design was adequate in all but two RCTs, which did not provide complete information about sequence generation,

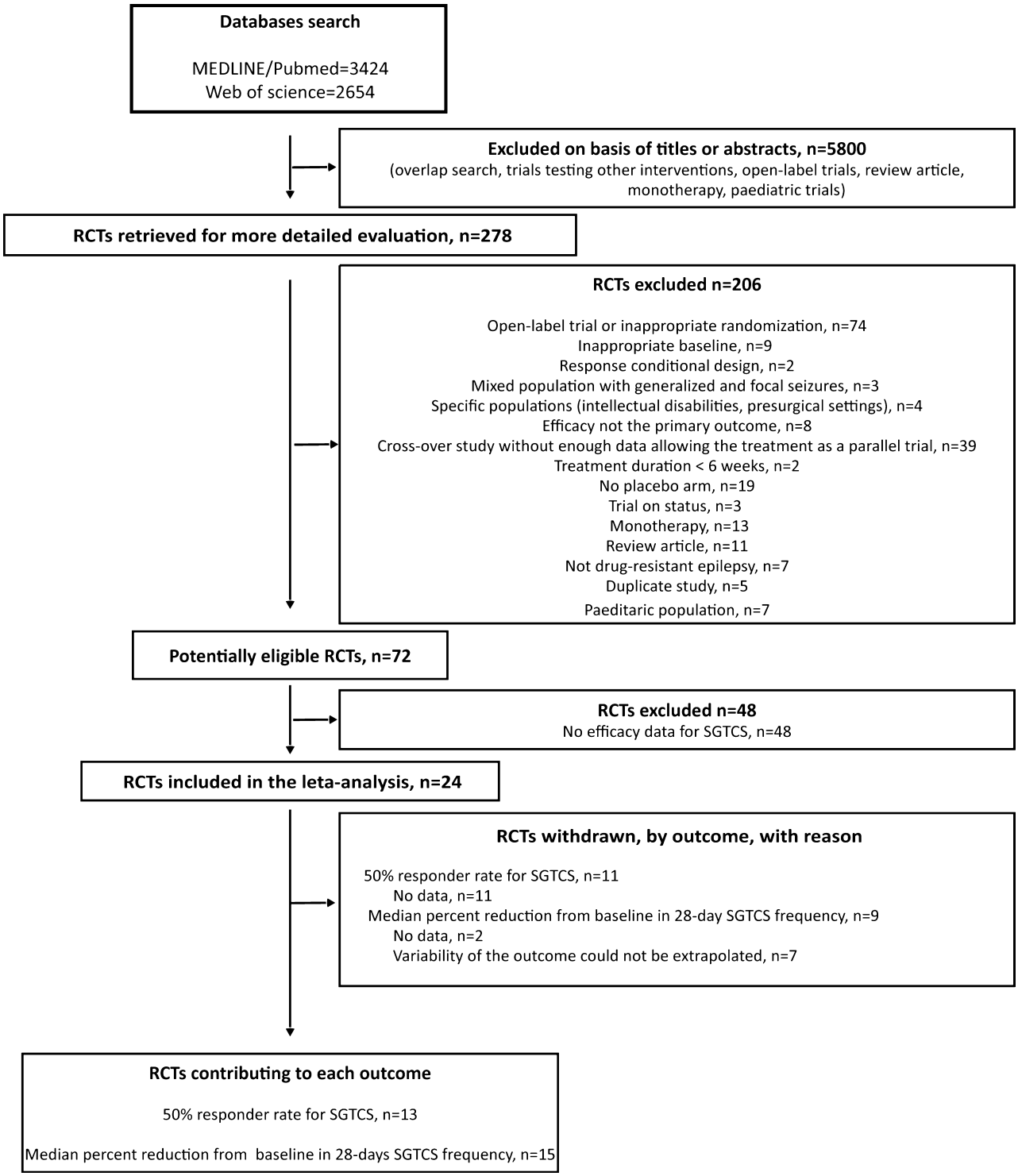

Figure 1.
Flow diagrams of trials.
Epilepsia © ILAE

allocation concealment, and blinding. Because efficacy data for SGTCS were available only for a minority of the 72 eligible RCTs, the possibility of reporting bias should be considered when interpreting the results.

The main characteristics and results of the 24 included studies are summarized in Table 1. A total of 7,823 patients were enrolled, one third of whom were allocated to placebo. Among included patients, 37.4 ± 10.4% demonstrated

SGTCS during baseline period (range 10.4–50.3%). Baseline SGTCS frequency was provided in only 10 studies. In the latter, the median baseline SGTCS frequency was typically ranging from 2 to 3.5 per month (see Table 1). Only 6 of the 24 trials provided the number of patients who did not have SGTCS during baseline, but had one during double-blind phase, including two that could contribute to our primary outcome (i.e., 50% responder rate) (Table 1). However, SGTCS frequency during the treatment period was not provided for these patients.

Meta-analysis and indirect comparisons of responder rates are presented in Figure 2. Only three of the seven AEDs included in the analysis (lacosamide, perampanel, and topiramate) showed significantly greater reduction of SGTC frequency than placebo. AEDs that failed to prove more efficacious than placebo were those tested with the smallest sample size, possibly accounting for the lack of significant difference as compared to placebo. With the exception of pregabalin, which demonstrated significantly lower efficacy than lacosamide, perampanel, and topiramate, confidence interval (CIs)s overlapped for all other AEDs, indicating that differences in point estimates were not statistically significant. Results remained similar when analyses were reprocessed using approved doses only (Fig. S1).

A nonsignificant trend toward a lower efficacy over SGTCS than over all seizure types was observed for all AEDs (Fig. 2). This lower effect size was related to greater response to placebo for SGTCS. Although responder rates were significantly greater for SGTCS than for all seizure types both in active treatment arms and in placebo groups, this variation was indeed greater with placebo than with AED. The mean ± standard deviation (SD) 50% responder rate with AEDs was 36.3 ± 9.0% for all seizure types and 56.7 ± 15.8% for SGTCS ($p < 0.001$ by Mann-Whitney *U*-test). In placebo groups, the mean ± SD 50% responder rate was 16.1 ± 8.3% for all seizure types and 39.3 ± 16.1% for SGTCS ($p < 0.001$ by Mann-Whitney *U*-test). Accordingly, 50% responder rates for SGTCS was 303 ± 164% higher than that for all seizure types in placebo arms, and 162 ± 45% higher in AEDs groups ($p = 0.016$ by Mann-Whitney *U*-test).

The impact of excluding patients who had SGTCS during double-blind phase but not during baseline on the RRs of the 50% responder rate was evaluated in two trials.[26,27] In one study,[26] whether such patients were excluded or not from the analysis resulted in similar RRs (1.25, 95% CI 0.62–2.53 vs. 1.23 95% CI 0.59–2.55, respectively). In the other study,[27] the RR was significantly greater when counting these patients as nonresponders than when excluding them from the analysis (3.09 95% CI 1.09–8.0 vs. 1.90 95% CI 0.73–4.94, respectively). Another four studies provided the number of patients who had SGTCS during the double-blind phase but not during baseline, but without providing the 50% responder rate[23,25,28,29] (Table 1). However, we could compare the proportion of such patients between the active treatment and placebo groups. This proportion was greater in the placebo group in two studies (i.e., 7.1% vs. 1.9%,[29] and 12.7% vs. 11.5%[23]), whereas the opposite was observed in the two other studies (4.3% vs. 5% and 9.3% in the two active treatment arms,[28] and 3.3% vs. 6.6%, 5.7% and 5.3% in the three active treatment arms[25]).

Exploratory analysis of median reduction from baseline in 28-day SGTCS frequency showed similar results (Fig. 3). All evaluated AEDs but perampanel 2 mg/day and 4 mg/day pregabalin, rufinamide and topiramate 600 mg/day demonstrated significantly greater efficacy than placebo. However, CIs overlapped for all AEDs and

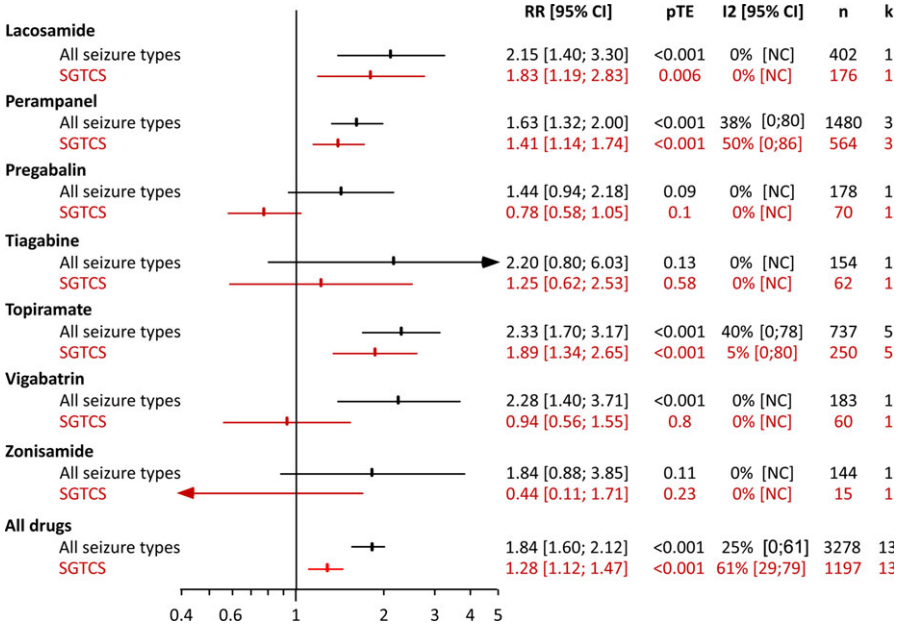

Figure 2.
Relative risk for responder rate for SGTCS and for all seizure types among patients enrolled in placebo-controlled adjunctive therapy RCTs of AEDs in refractory focal epilepsy. All doses combined. p TE, value of the treatment effect test, I^2, point estimates of Higgins I^2 with confidence interval; n, total number of patients; k, total number of trials.

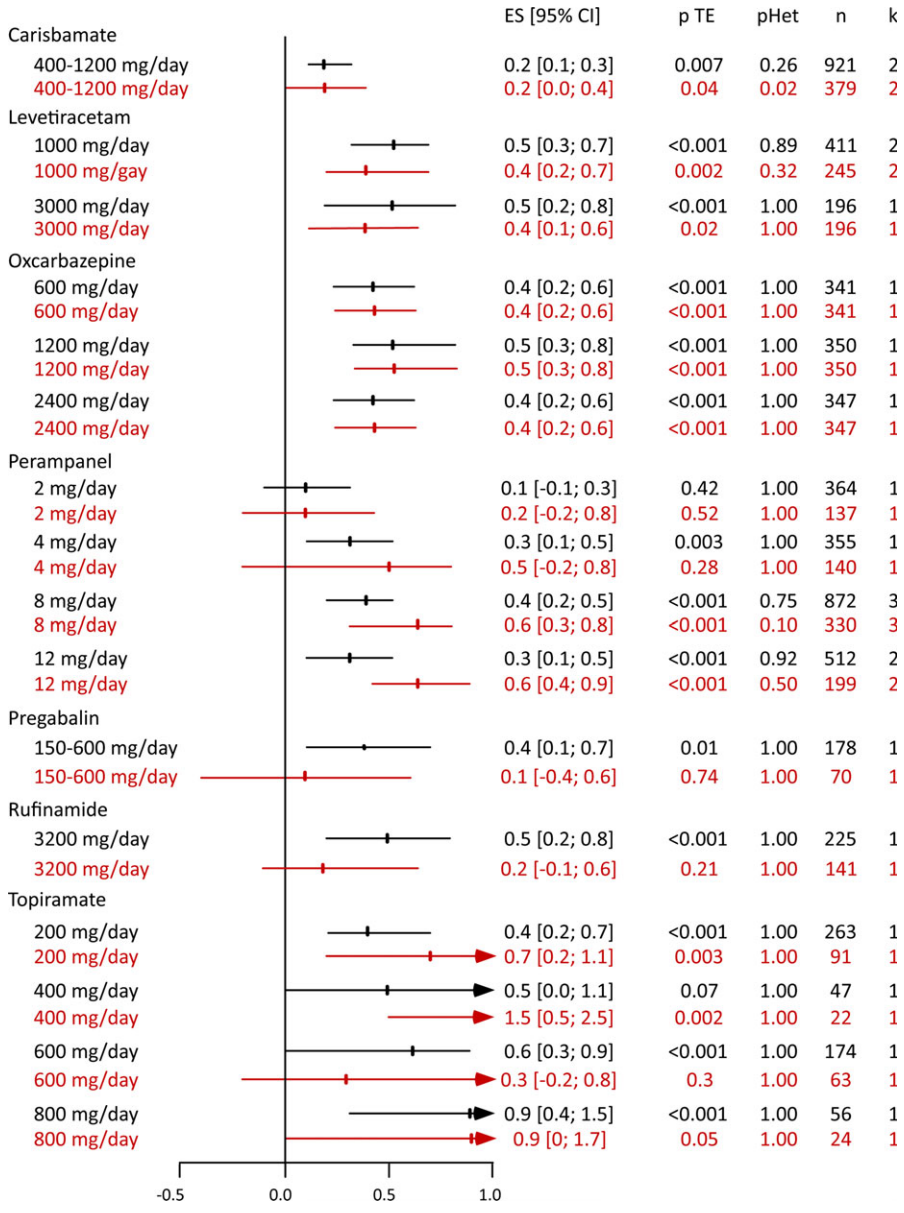

Figure 3.
Effect size for median reduction from baseline in 28-day seizure frequency for SGTCS and for all seizure types among patients enrolled in placebo-controlled adjunctive therapy RCTs of AEDs in refractory focal epilepsy. p TE, value of the treatment effect test, p Het, value of the heterogeneity test; n, total number of patients; k, total number of trials.

for all doses, indicating that differences in point estimates were not statistically significant.

Discussion

About a third of patients with drug-resistant focal epilepsy have SGTCS.[30] In these patients, occurrence of SGTCS represents the main risk factor for SUDEP,[2] which these seizures appear to trigger in most instances.[31] There is currently no effective treatment to prevent SUDEP,[32] apart from reinforcing the AED regimen.[4] In this context, prevention of SGCTS might be an important parameter for treatment choice in patients with refractory epilepsy. All AEDs licensed for add-on therapy in drug-resistant focal epilepsy are considered to prevent both focal seizures and SGTCS. However, whether some AEDs might be more efficacious than others on SGCTS remains unknown. The present work, which aimed at addressing this issue, demonstrated the following: (1) although efficacy data on SGTCS are collected during phase III RCTs, this specific outcome is rarely provided in trial's reports; (2) one third of patients included in regulatory trials have SGTCS during the baseline period, with low baseline SGTCS frequency, further complicating interpretation of data; (3) there is a nonsignificant trend toward a lower relative risk of 50% responder rate for SGTCS than for all seizure types, which appears related to a greater response to placebo for this outcome; and (4) although the available data do not support robust differences between AEDs to prevent SGTCS in adult patients with drug-resistant focal epilepsy, preferential use of the AEDs

that demonstrated greater efficacy than placebo for this outcome might be proposed.

These results primarily highlight the limitations of the current RCT design for evaluating AEDs efficacy on SGTCS. The main objectives of phase III add-on RCTs are to evaluate efficacy and safety of new AEDs within a representative sample of patients with drug-resistant focal epilepsy, taking into account the recommendations of regulatory authorities in terms of trial design and outcomes.[6] Accordingly, no specific emphasis has been put on SGTCS in add-on RCTs inclusion criteria. In this context, the proportion of patients with focal seizures and SGTCS included in these studies remains limited to about one third. Moreover, the monthly SGTCS rate is highly variable and often low in patients with drug-resistant focal epilepsy who are eligible for inclusion in phase III trials. The infrequent and irregular occurrence of SGTCS raises important statistical issues. Specifically, these characteristics result in higher variance for this outcome than for all seizure types. Thus study power, which depends on the variance of the outcome and the sample size, is inappropriate for testing the efficacy of AEDs on SGTCS only in classic phase III RCTs, resulting in increased risk of type II error. As shown in Table S1, all RCTs but one demonstrated study power <50% to detect a treatment difference of 25% for SGTCS, the effect size usually assumed in phase III RCTs. In contrast, 20 of 24 studies had ≥80% power and 23 of 24 had ≥50% power to detect the same effect size for all seizure types. As shown in Table S2, a sample of 161 patients with SGTCS in each treatment arm would have been required for 80% power to detect a treatment difference of 25% in percentage change in SGTCS frequency between placebo and active treatment arm. In this context, we cannot exclude that treatment efficacy on SGTCS was falsely undetected in negative trials. Although the meta-analysis process might partly compensate low power of individual studies, the precision of the effect size evaluation remains impacted by the number of underpowered studies included in the meta-analysis.[33,34]

The recommended primary efficacy outcome differs across regulatory authorities, with the FDA recommending the use of median reduction from baseline in 28-day seizure frequency and the EMA recommending the use of the 50% responder rate.[35] For methodologic reasons, previous meta-analyses of phase III RCTs focused on only 50% responder rate.[7–11] The primary objective of our study was to evaluate the level of information for SGTCS in add-on RCTs; we analyzed both 50% responder rate and median reduction from baseline in 28-day SGTCS frequency. This approach allowed us to provide a more accurate picture of the quality of reporting of SGTCS-related outcomes in publications. However, data variability being available in a minority of studies, analyses of median reduction from baseline in 28-day SGTCS frequency should be interpreted with caution. Specifically, extrapolation of means values from median values in the absence of formal evaluation of data distribution might have introduced significant bias. On the other hand, the similarity of the qualitative results between the two outcomes (i.e., 50% responder rates and median reduction from baseline in 28-day SGTCS frequency) suggests that this methodologic bias was limited.

It has been shown that the 50% responder rate in regulatory trials is also significantly impacted by methodologic issues, including the method used to define responders (i.e., LOCF vs. completer methods) or the evaluation period (i.e., whole treatment vs. maintenance periods).[11] For SGTCS, only data obtained using the LOCF method were available, which could lead to an overestimation of the 50% responder rates,[11] and did not allow comparison of the seizure-free rate across AEDs.[36] In addition, studies evaluating lacosamide and perampanel[20–22,37] provided data for SGTCS on the maintenance period, whereas the other studies used the whole treatment period as the evaluation period. This might have negatively impacted the comparability of the studies. Because relative risk of 50% responder rate appears significantly lower when response is assessed over the maintenance period compared with the entire treatment period,[11] this bias might have lowered the SGTCS responder rate of lacosamide and perampanel rather than increasing differences with the other AEDs.

Another potential bias in the interpretation of the SGTCS 50% responder rate is the lack of information in reports of most RCTs regarding the number of patients with SGTCS during the treatment period but not during baseline (see Table 1), hampering the inclusion of these patients in our primary analyses. These patients being by definition nonresponders, their noninclusion might have resulted in overestimating the 50% responder rate. However, the magnitude of this potential bias remains unclear. In the six studies where we could assess this outcome, the proportion of randomized patients without SGTCS during baseline who had a SGTCS during the double-blind phase was greater, similar, or lower in the placebo group than in the active treatment groups.

It has been shown that interpretation and comparison of add-on RCTs results is affected by a progressive increase of the response to placebo.[11,38] Although the exact mechanisms underlying this evolution remain to be determined, it has been suggested that nonpharmacologic phenomena might be predominant, including the Hawthorne effect and regression to the mean.[11] Similar hypotheses might be proposed to explain the unusually high response to placebo for SGCTS observed in the current study. Specifically, it might be speculated that regression to the mean might be greater for SGTCS than for complex focal seizures, inasmuch as patients with SGCTS during the treatment period but not during baseline could not be included in our analyses. According to the impact of SGTCS on quality of life, patients might thus be more prone to be included in phase III RCTs when they experience aggravation of SGTCS frequency. In addition, tapering of an ongoing AED might

sometimes be required before inclusion within the trial, a modification that might result in transient occurrence and/or increased rate of SGTCS.

With the exception of pregabalin, which demonstrated significantly lower efficacy than lacosamide, perampanel, and topiramate, we did not observe significant difference across AEDs for the prevention of SGTCS. However, all previous factors drastically limited the representativeness of the dataset and the interpretability of our results. Our results must therefore be interpreted with caution. Whether they reflect true equivalent efficacy of new AEDs on SGTCS or just the paucity of available informative data remains an open question. Similarly, whether the observation that only three (i.e., perampanel, lacosamide, or topiramate) of the seven AEDs for which SGTCS responder rates were available demonstrated significant superiority over placebo might support their preferential use in patients with SGTCS is questionable. Overall, phase III RCTs are not designed and powered to appropriately evaluate SGTCS. Rather than reflecting lack of interest into this seizure type, this situation likely derives from the difficulty to enroll patients with frequent SGTCS in placebo-controlled trials. Appropriate evaluation of SGTCS in RCTs using the current design would require the inclusion of patients with 3–4 SGTCS per month, or running the trial for a very long time, raising feasibility issues. This reinforces the need to develop alternative designs for the evaluation of new therapeutic interventions in epilepsy,[39] especially in at-risk patients with seizure-related complications and/or comorbidities.[40]

Disclosure or Conflict of Interest

Claire Hemery reports no disclosures. Philippe Ryvlin has received speaker or consultant fees from Pfizer, Sanofi-Aventis, GlaxoSmithKline, Jansen-Cilag, UCB pharma, Eisai, and Valeant. Sylvain Rheims has received speaker fees from UCB pharma, consultant fees from Eisai, and funding for attending scientific congress from GlaxoSmithKline and Cyberonics. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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References

1. Shorvon S, Tomson T. Sudden unexpected death in epilepsy. *Lancet* 2011;378:2028–2038.
2. Hesdorffer DC, Tomson T, Benn E, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. *Epilepsia* 2012;53:249–252.
3. Sillanpaa M, Shinnar S. Long-term mortality in childhood-onset epilepsy. *N Engl J Med* 2010;363:2522–2529.
4. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. *Lancet Neurol* 2011;10:961–968.
5. Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. *Lancet Neurol* 2011;10:446–456.
6. Marson AG, Williamson PR. Interpreting regulatory trials in epilepsy. *Curr Opin Neurol* 2009;22:167–173.
7. Beyenburg S, Stavem K, Schmidt D. Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and meta-analysis. *Epilepsia* 2010;51:7–26.
8. Marson AG, Kadir ZA, Hutton JL, et al. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. *Epilepsia* 1997;38:859–880.
9. Marson AG, Hutton JL, Leach JP, et al. Levetiracetam, oxcarbazepine, remacemide and zonisamide for drug resistant localization-related epilepsy: a systematic review. *Epilepsy Res* 2001;46:259–270.
10. Otoul C, Arrigo C, van Rijckevorsel K, et al. Meta-analysis and indirect comparisons of levetiracetam with other second-generation antiepileptic drugs in partial epilepsy. *Clin Neuropharmacol* 2005;28:72–78.
11. Rheims S, Perucca E, Cucherat M, et al. Factors determining response to antiepileptic drugs in randomized controlled trials. A systematic review and meta-analysis. *Epilepsia* 2011;52:219–233.
12. Blumenfeld H, Varghese GI, Purcaro MJ, et al. Cortical and subcortical networks in human secondarily generalized tonic-clonic seizures. *Brain* 2009;132:999–1012.
13. Pinto DJ, Patrick SL, Huang WC, et al. Initiation, propagation, and termination of epileptiform activity in rodent neocortex in vitro involve distinct mechanisms. *J Neurosci* 2005;25:8131–8140.
14. Trevelyan AJ, Sussillo D, Yuste R. Feedforward inhibition contributes to the control of epileptiform propagation speed. *J Neurosci* 2007;27:3383–3387.
15. Yoo JY, Farooque P, Chen WC, et al. Ictal spread of medial temporal lobe seizures with and without secondary generalization: an intracranial electroencephalography analysis. *Epilepsia* 2014;55:289–295.
16. Jobst BC, Williamson PD, Neuschwander TB, et al. Secondarily generalized seizures in mesial temporal epilepsy: clinical characteristics, lateralizing signs, and association with sleep-wake cycle. *Epilepsia* 2001;42:1279–1287.
17. Rheims S, Ryvlin P. Pharmacotherapy for tonic-clonic seizures. *Expert Opin Pharmacother* 2014;15:1417–1426.
18. Higgins JPT, Altman DG. *Cochrane handbook for systematic reviews of interventions version 5.1.0*. 2011. Available at:http://www.cochrane-handbook.org/. Accessed August 20, 2014.
19. Steinhoff BJ, Gauffin H, McKee P, et al. Efficacy of perampanel, a selective AMPA antagonist, in complex partial and secodarily generalized seizures: a pooled analysis of phase III studies in patients with treatment-resistant partial-onset seizures. *Epilepsia* 2012;53:122.
20. French JA, Krauss GL, Biton V, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. *Neurology* 2012;79:589–596.
21. French JA, Krauss GL, Steinhoff BJ, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. *Epilepsia* 2013;54:117–125.
22. Krauss GL, Serratosa JM, Villanueva V, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. *Neurology* 2012;78:1408–1415.
23. Brodie MJ, Rosenfeld WE, Vazquez B, et al. Rufinamide for the adjunctive treatment of partial seizures in adults and adolescents: a randomized placebo-controlled trial. *Epilepsia* 2009;50:1899–1909.
24. Elger C, Halasz P, Maia J, et al. Efficacy and safety of eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures: a randomized, double-blind, placebo-controlled, parallel-group phase III study. *Epilepsia* 2009;50:454–463.
25. Uthman BM, Rowan AJ, Ahmann PA, et al. Tiagabine for complex partial seizures: a randomized, add-on, dose-response trial. *Arch Neurol* 1998;55:56–62.
26. Kalviainen R, Brodie MJ, Duncan J, et al. A double-blind, placebo-controlled trial of tiagabine given three-times daily as add-on therapy for refractory partial seizures. Northern European Tiagabine Study Group. *Epilepsy Res* 1998;30:31–40.

27. Sharief M, Viteri C, Ben-Menachem E, et al. Double-blind, placebo-controlled study of topiramate in patients with refractory partial epilepsy. *Epilepsy Res* 1996;25:217–224.
28. Halford JJ, Ben-Menachem E, Kwan P, et al. A randomized, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of adjunctive carisbamate treatment in patients with partial-onset seizures. *Epilepsia* 2011;52:816–825.
29. Shorvon S, Lowenthal A, Janz D, et al. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. *Epilepsia* 2000;41:1179–1186.
30. Brodie M, Barry SJ, Bamagous G, et al. Patterns of treatment response in newly diagnosed epilepsy. *Epilepsia* 2011;52:10.
31. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol* 2013;12:966–977.
32. Shorvon S, Tomson T. Sudden unexpected death in epilepsy. *Lancet* 2011;378:2028–2038.
33. Thorlund K, Imberger G, Walsh M, et al. The number of patients and events required to limit the risk of overestimation of intervention effects in meta-analysis–a simulation study. *PLoS ONE* 2011;6:e25491.
34. Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. *PLoS ONE* 2013;8:e59202.
35. EMA. European medicines agency: guideline on clinical investigation of medicinal products in the treatment of epileptic disorders. 2010. Available at:http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500070043. Accessed April 4, 2014.
36. Gazzola DM, Balcer LJ, French JA. Seizure-free outcome in randomized add-on trials of the new antiepileptic drugs. *Epilepsia* 2007;48:1303–1307.
37. Chung S, Sperling MR, Biton V, et al. Lacosamide as adjunctive therapy for partial-onset seizures: a randomized controlled trial. *Epilepsia* 2010;51:958–967.
38. Guekht AB, Korczyn AD, Bondareva IB, et al. Placebo responses in randomized trials of antiepileptic drugs. *Epilepsy Behav* 2010;17:64–69.
39. Friedman D, French JA. Clinical trials for therapeutic assessment of antiepileptic drugs in the 21st century: obstacles and solutions. *Lancet Neurol* 2012;11:827–834.
40. Ryvlin P, Nashef L, Tomson T. Prevention of sudden unexpected death in epilepsy: a realistic goal? *Epilepsia* 2013;54 (Suppl. 2):23–28.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Relative risk for responder rate for SGTCS and for all seizure types among patients enrolled in placebo-controlled adjunctive therapy RCTs of AEDs in refractory focal epilepsy.

Table S1. Study power according to the evaluated outcome and the expected size of the treatment effect.

Table S2. Required sample size according to effect size and study power.

Data S1. Study search strategy and PRISMA checklist.

Data S2. Additional references.