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Measurement of seizure freedom in adjunctive therapy studies in refractory partial epilepsy: the levetiracetam experience

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ABSTRACT – *Purpose.* To assess the advantages and disadvantages of six methodologies used in calculating seizure freedom rates in placebo-controlled, adjunctive therapy trials of new antiepileptic drugs (AEDs) in partial epilepsy, and two methodologies for long-term follow-up studies. *Methods.* Data from levetiracetam trials were used to illustrate the impact of different methodologies on seizure freedom rates. Seizure-freedom data for several new AEDs were identified from the published medical literature using MEDLINE and from a recent comprehensive textbook. *Results.* Most randomized, placebo-controlled add-on clinical trials of new AEDs contain little or no information about seizure freedom. Importantly, the methodology used can profoundly affect results when calculating seizure-free rates. Seizure freedom data should be reported as well as the methodology used. The minimum duration for assessing seizure freedom should be the entire stable dose period in short-term trials and at least six months for long-term follow-up studies. It is proposed that the seizure freedom rates be calculated and reported with at least two different methodologies, one that considers patients withdrawing from treatment without having had a seizure as successes, and one that considers the same patients as failures. For an effective and well-tolerated AED, seizure freedom rates will be consistent across the two methodologies. *Conclusions.* Seizure freedom is the ultimate goal of AED therapy and should be reported for all clinical trials. Methodological differences among the few clinical studies reporting seizure freedom rates make it difficult to compare results across trials. Improved reporting of methodologies and seizure-free rates is warranted.

Keywords: epilepsy, seizure freedom, add-on therapy, antiepileptic drugs, levetiracetam, clinical trials

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Seizure freedom is the ultimate goal of epilepsy treatment: it reduces morbidity and mortality, prevents sudden death from epilepsy, and improves quality of life (Sander and Bell, 2004). Unfortunately, as recently shown in a comprehensive study of 1652 people with epilepsy, a large number of

patients (48.3% in this survey) failed to achieve seizure freedom during treatment with an antiepileptic drug (AED) (Moran *et al.*, 2004). This underscores the need for additional research and better treatment paradigms. Regulatory trials have some inherent limitations, such as less diverse populations than in the clinical setting, with fewer comorbid conditions and concomitant medications. They also tend to be only three to six months in duration. However, because of their randomized and placebo-controlled design, they are often the first objective report of a new drug's clinical efficacy and tolerability.

Calculating seizure freedom rates relative to a comparator is an ideal way to document efficacy of a new AED. However, adjunctive therapy trials designed to gain regulatory approval of new AEDs are usually conducted in patients resistant to mono- or polytherapy. Because this population is particularly refractory to drug therapy, only a few of these patients can be expected to become seizure-free. Although placebo-controlled add-on studies of new AEDs are not designed to compare complete seizure control rates, the proportion of patients achieving seizure freedom during the double-blind period and subsequent follow-up represents a clinically meaningful parameter and should be reported.

Seizure freedom may appear to be a dichotomous variable: a patient is either seizure-free, or a patient is not free of seizures. However, the duration of the period free of seizures is an important aspect of the measurement; seizure freedom for three years is a more profound effect than seizure freedom for three months. Therefore, with no standard definition, this metric varies widely among trials, and a consensus is not yet available. When comparing an AED in a double-blind way to placebo the duration of seizure freedom assessed should be the whole double-blind period (up-titration period included or not), which is usually around three months. For open-label studies the duration of evaluation can be much longer. In this paper, we use data from double-blind, placebo-controlled studies and long-term follow-up evaluations of levetiracetam (LEV). Pooled data were used because seizure freedom often has low statistical power due to its low event rate. This paper reports the assessment of the impact of different methodologies (*figure 1*) on seizure freedom results, compares these outcomes with available reports from the literature for other new AEDs, and proposes standard methods for reporting seizure-free data in future studies.

Review of published trials with new AEDs and seizure freedom

We conducted a literature search on MEDLINE in an attempt to obtain seizure freedom data for new AEDs in short-term add-on clinical trials. The search focused on gabapentin (GBP), lamotrigine (LTG), oxcarbazepine (OXC), pregabalin (PGB), tiagabine (TGB), topiramate (TPM), and zonisamide (ZNS), and included a search term for epilepsy. The search focused on double-blind randomized placebo-controlled add-on trials in adults with partial epilepsy. Information was also extracted from a recent comprehensive textbook (Levy *et al.* 2002). Only papers in English were included. The following studies were excluded as not meeting the search criteria: open-label or observer-blinded studies, monotherapy in newly diagnosed patients, presurgical evaluations, studies of children or healthy volunteers, studies in which primary generalized seizures were the only inclusion criterion, and comparative trials without a placebo control. Meta-analyses were not included, as none were based on seizure freedom (Chaisewikul *et al.*, 2002, Marson *et al.*, 2001). Studies that did not measure seizure frequency or that did not include efficacy as a primary outcome were also excluded. Thus, this analysis was limited to double-blind, placebo-controlled add-on trials which included seizure frequency as an efficacy parameter. We found 47 publications meeting these criteria (*table 1*).

Seizure freedom rates were reported in few of these publications, and when they were reported, were accompanied by little or no information describing the methodology for calculation. Overall, six of seven identified GBP publications, nine of 13 LTG publications, one of two OXC publications, two of four PGB publications, four of six TGB publications, and five of 13 TPM publications did not provide any data on seizure freedom. As confirmation of this lack of information, meta-analysis type reviews of several AEDs have reported odds ratios, relative risks, or number needed to treat for 50% responder rates, but none has reported these parameters based on seizure freedom (Chaisewikul *et al.*, 2002, Marson *et al.*, 2001).

Seizure freedom, defined as 100% reduction from baseline seizure frequency, is arguably the most (and arguably the only) meaningful clinical measure in determining an AED's efficacy. What changes is the treatment period (over the stable dose period, or over the titration and stable dose period or some other defined period) and the population (withdrawals may be counted as seizure-free or not seizure-free, and the intent-to-treat (ITT) population or only completers may be used). When one reviews the literature, one sees how the lack of a clear definition makes it difficult to interpret the reported data.

The AED with the most published seizure freedom data is TPM. Three publications reported pooled seizure freedom rates of 4% to 5% with TPM, as compared to 0% to 1% with placebo (Reife and Pledger, 1997, Reife *et al.*, 2000, Peeters *et al.*, 2003). In the Korean Topiramate Study, seizure freedom in the ITT population was reported to be significantly higher with TPM than placebo (7.9% *versus* 1.2%, $p = 0.04$). In all of these publications, no information was provided about how withdrawals were handled, about duration of seizure freedom, and whether or not the up-titration period was included (Korean Topiramate Study Group, 1999). TPM also had a higher reported

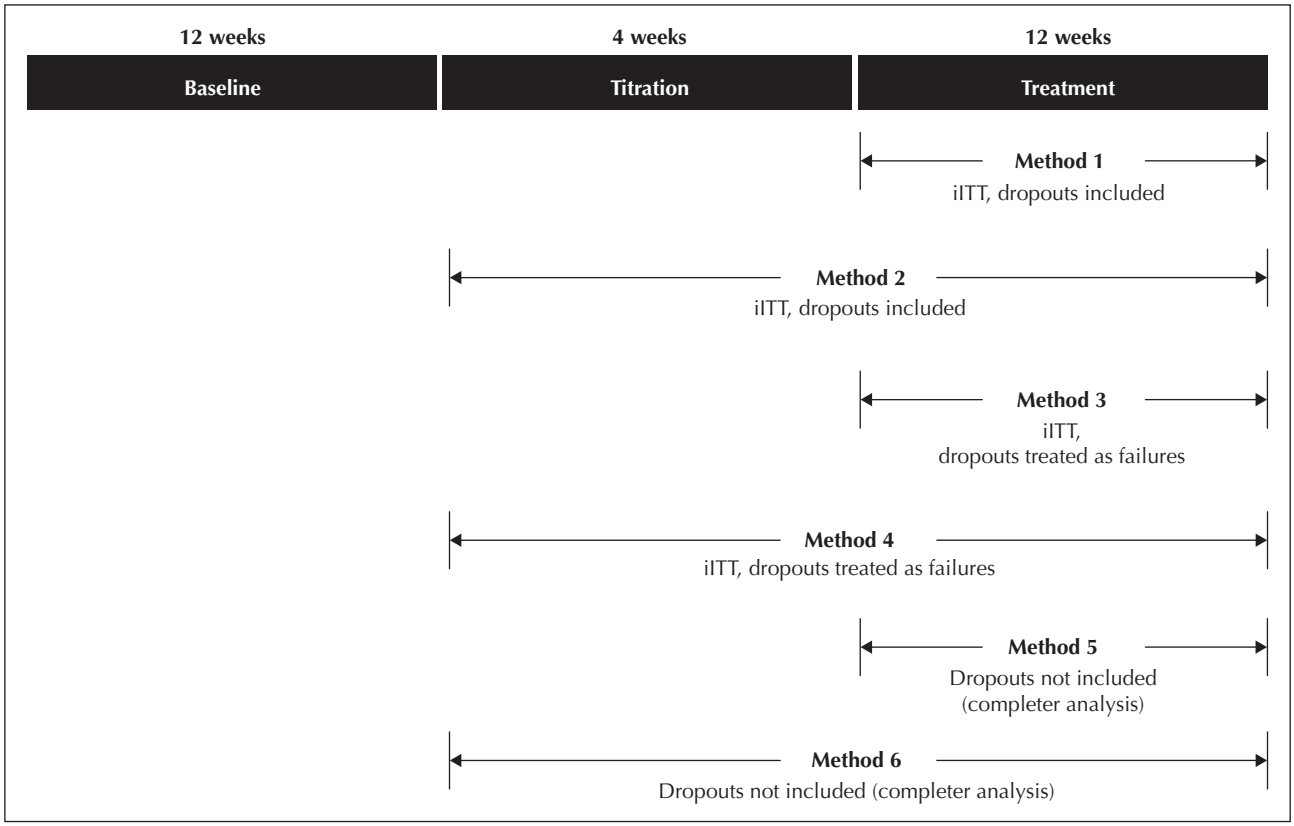

Figure 1. Summary of methods used in the analysis. iITT = inferential intent-to-treat.

seizure freedom rate than placebo in a study of add-on therapy to carbamazepine (6% *versus* 2%) (Guberman *et al.*, 2002). In this study, higher seizure freedom rates were reported, but only during a 4-week maintenance period, and the methodology used for the seizure freedom analysis was not described further. Two other publications reported zero patients out of 60 and two patients out of 47 being seizure-free with TPM, respectively (Tassinari *et al.*, 1996, Sharief *et al.*, 1996), and a third reported results for secondarily generalized seizures only in patients who had such seizures at baseline (Faught *et al.*, 1996). Obviously, the latter analysis provides higher seizure freedom rates than those considering all seizure types.

Seizure-free rates ranging from 3% to 22% were reported for OXC at doses of 600 to 2 400 mg/d as compared to 0.6% with placebo (Barcs *et al.*, 2000). However, it is very difficult to draw conclusions from this apparently high seizure freedom rate, because no information was provided about the methodology used to define seizure freedom. For example, 174 patients were randomly assigned to the highest dose of OXC, but 128 patients (74%) discontinued treatment. It is unclear how long the duration of the evaluation was and how seizure-free patients discontinuing treatment were considered in the seizure-freedom analysis.

Two ZNS publications reported seizure freedom rates of approximately 4% to 6% as compared to 1% to 3% for placebo (Faught *et al.*, 2001, Schmidt *et al.*, 1993). In one publication (Schmidt *et al.*, 1993), the analysis included the ITT population, but no information was given on the handling of withdrawals, whereas information about methodology was not provided in the other (Faught *et al.*, 2001). For TGB, one publication reported that two of 77 patients (2.6%) in the TGB group were seizure-free for the 12-week fixed-dose period, as compared to none of the 77 patients in the placebo group (Kalviainen *et al.*, 1998). In this publication and one other, information was provided on the number of seizure-free days, but this data cannot be used to calculate seizure freedom rates for the whole study (or stable dose) period (Kalviainen *et al.*, 1998, Ben-Menachem, 1995).

Two LTG studies reported seizure freedom during one month of treatment or during five consecutive weeks of double-blind treatment, but neither reported seizure-freedom rates for the entire study period (Matsuo *et al.*, 1993; Stolarek *et al.*, 1994). Seizure-free days were reported in a placebo-controlled crossover study, but none of the patients became seizure-free while receiving LTG (Sander *et al.*, 1990). In a publication on patients with simple partial seizures, more patients in the placebo group

Table 1. Summary of seizure freedom data for new antiepileptic drugs.

Drug	Publications (Total = 47)	Did not report seizure freedom rates (Total = 28)
Gabapentin	US Gabapentin Study Group, 1990	√
	Sivenius *et al.*, 1991	√
	Chadwick, 1991	√
	US Gabapentin Study Group No. 5, 1993	√
	Anhut *et al.*, 1994	√
	Fisher *et al.*, 2001	√
	Crawford *et al.*, 1987	
Lamotrigine	Binnie *et al.*, 1987	√
	Binnie *et al.*, 1989	√
	Jawad *et al.*, 1989	√
	Loiseau *et al.*, 1990	√
	Smith *et al.*, 1993	√
	Schapel *et al.*, 1993	√
	Messenheimer *et al.*, 1994	√
	Pellock, 1994	√
	Beran *et al.*, 1998	√
	Matsuo *et al.*, 1993	
	Stolarek *et al.*, 1994	
	Sander *et al.*, 1990	
	Boas *et al.*, 1996	
Oxcarbazepine	Schmidt and Sachdeo, 2000	√
	Barcs *et al.*, 2000	
Pregabalin	Brodie, 2004	
	French *et al.*, 2003	√
	Miller *et al.*, 2003	√
	Arroyo *et al.*, 2004	
Tiagabine	Richens *et al.*, 1995	√
	Loiseau, 1999	√
	Sachdeo *et al.*, 1997	√
	Uthman *et al.*, 1998	√
	Kalviainen *et al.*, 1998	
	Ben-Menachem, 1995	
Topiramate	Ben-Menachem *et al.*, 1996	√
	Privitera *et al.*, 1996	√
	Faught, 1997	√
	Ben-Menachem, 1997	√
	Yen *et al.*, 2000	√
	Reife and Pledger, 1997	
	Reife *et al.*, 2000	
	Peeters *et al.*, 2003	
	Korean Topiramate Study Group, 1999	
	Guberman *et al.*, 2002	
	Tassinari *et al.*, 1996	
	Sharief *et al.*, 1996	
	Faught *et al.*, 1996	
Zonisamide	Faught *et al.*, 2001	
	Schmidt *et al.*, 1993	

Table 2. Baseline demographic and clinical characteristics in the inferential intent-to-treat (ITT) population of patients included in placebo-controlled adjunctive therapy trials of levetiracetam (LEV) in refractory partial epilepsy.

	Placebo (n = 367)	LEV 1000 mg (n = 277)	LEV 2000 mg (n = 175)	LEV 3000 mg (n = 269)
Gender, n (%)				
Female	179 (48.8)	121 (43.7)	91 (52.0)	121 (45.0)
Male	188 (51.2)	156 (56.3)	84 (48.0)	148 (55.0)
Age, years: mean (± SD)	37.0 (11.4)	37.4 (11.1)	36.7 (11.9)	37.0 (11.2)
Age at epilepsy onset, years: mean (± SD)	15.2 (12.2)	14.1 (11.7)[a]	13.8 (11.3)	16.2 (13.0)
Duration of epilepsy, years: mean (± SD)	22.3 (11.7)	23.9 (12.3)[a]	23.4 (13.6)	21.4 (12.1)
Baseline seizure frequency/week: median (Q1-Q3)	2.0 (1.3-3.9)	2.6 (1.6-5.7)	2.6 (1.6-5.0)	1.9 (1.1-3.5)

[a] One subject was unevaluable for the age at epilepsy onset and duration of epilepsy.
For those two variables, the denominator in thus 276.

than in the LTG group became seizure-free (five of 26, or 19%, *versus* three of 30, or 10%) (Boas *et al.*, 1996). Incomplete information is also available about seizure freedom with GBP and PGB.

In one GBP publication, anecdotal information was provided for one patient who was reported to be seizure-free for the entire 2-month treatment period while receiving GBP (Crawford *et al.*, 1987).

One PGB publication considered three randomized, placebo-controlled, 12-week studies and reported that across the dose range of 150-600 mg/d, 3% to 17% of patients were seizure-free, but only for the last 28 days of treatment (Brodie, 2004). Additionally, a *post hoc* analysis was conducted on a restricted ITT population of patients who received > 28 days of treatment and completed > 75% of the daily seizure diary. Using this restricted ITT population, both the 300 and 600 mg/d dose were significantly more effective than placebo, with between 7% and 19% of patients reporting complete freedom from seizures over the 12-week period. No information about the way withdrawals were handled and about how many seizure-free patients withdrew from the studies was provided.

More recently, PGB was evaluated in an international multicenter, 12-week, double-blind placebo-controlled study (Arroyo *et al.*, 2004). The percentage of seizure-free patients was determined using Fisher's exact test. Again, the seizure-free period was defined as the last 28 days of treatment. This calculation showed 7% and 12% of patients in the 150-mg and 600-mg groups, respectively, to be seizure-free, compared with just 1% in the placebo group (p = 0.065 and p = 0.002 *versus* placebo, respectively).

Experience from levetiracetam trials: methodological issues in assessing rates of seizure freedom

The calculation of seizure freedom rates in clinical trials is subject to several pitfalls, mainly that the results can be biased by the methodology chosen. For this discussion, an inferential ITT population, including patients and data from three pivotal studies of add-on LEV in partial-onset epilepsy, is used. Data from three pivotal trials, two parallel-group studies (Cereghino *et al.*, 2000, Ben-Menachem and Falter, 2000) and a crossover study (Boon *et al.*, 2002, Shorvon *et al.*, 2000), conducted in Europe and the USA were analyzed and included in a data set of 1088 subjects (placebo, n = 367; LEV 1000 mg/d, n = 277; LEV 2000 mg/d, n = 175; and LEV 3000 mg/d, n = 269). Further details are shown in *table 2*. Inferential ITT was chosen consistent with previous methodology (Boon *et al.*, 2002). Specifically, the inferential ITT population includes patients from both parts of and with non-missing data for partial-onset seizure frequency per week in the baseline and stable dose periods (n = 1088, all three studies). Patients who withdrew from a study before entering a stable dose period were therefore excluded (placebo, n = 72; LEV, n = 103), but patients withdrawing during the stable dose period were included. Patients in the crossover study were randomly assigned to different treatments in each part of the study. Each patient is counted once under the relevant treatment in these analyses. Seizures reported during a stable dose period are attributed to the treatment administered during that period. This approach to counting patients from the crossover study results in treating each as if they were two independent subjects.

Baseline demographic and clinical characteristics described in *table 2* indicate the severity of the disease in the ITT population. Patients had epilepsy for a mean of > 20 years and had a median baseline seizure frequency per week ranging from 1.9 to 2.6 depending on the treatment arm.

Six different methods for calculating seizure freedom were applied to these data (*figure 1*). The first method (Method 1) defines seizure freedom as the absence of seizures during the stable dose period, irrespective of whether the patient completed the stable dose period or not. For this calculation, the denominator is the total number of subjects in the inferential ITT population for

that treatment group. According to this approach, completion status during the stable dose phase does not influence the definition of seizure freedom. In particular, patients who did not complete the stable dose period but did not have any seizures up to the time of withdrawal are considered to be seizure-free. The percentage of patients meeting the definition of seizure freedom by Method 1 was 0.8% in the placebo group, 4.7% in the LEV 1000-mg group, 6.3% in the LEV 2000-mg group, and 8.6% in the LEV 3000-mg group (*figure 2*).

A two-sided Fisher exact test was used to make inferential comparisons between each randomized LEV dose group and placebo (*table 3*). The seizure freedom odds ratios *versus* placebo ranged from 6.0 to 11.3 with LEV 1000 to 3000 mg as compared with placebo ($p = 0.003$ for LEV 1000 mg and $p < 0.001$ for LEV 2000 and 3000 mg). The inferential analysis underestimates the variability expected from a sample of the same size comprised of real independent subjects, in that the two parts of the crossover trial were counted as if they corresponded to two independent patients.

Table 4 describes gender differences, age, age at epilepsy onset, and duration of epilepsy in both seizure-free patients and patients not seizure-free (as per Method 1).

An alternative method (Method 2) defines seizure freedom as the absence of seizures during both the titration and stable dose periods for the inferential ITT population. Withdrawals are handled in the same way as with Method 1: seizure-free patients discontinuing during the stable dose period before the end of the study are counted as seizure-free. Therefore, the only difference is that the titration period is also included in the calculation. As shown in *table 3*, the number of seizure-free patients was lower with Method 2 than with Method 1 in each of the groups. Nevertheless, the data show that the odds ratio *versus* placebo for seizure freedom was about 11 with LEV 2000 mg and 3000 mg as compared with placebo ($p < 0.001$).

Method 2 is a more conservative approach: by including the titration period, it offers the advantage of measuring efficacy from the first day of treatment and thus determining whether a drug has a rapid onset of action. However, a disadvantage of Method 2 in analyzing LEV trials is that some patients received placebo during the first 2 weeks of the titration period. The patients who had a seizure while receiving placebo or a low, subtherapeutic LEV dose during titration are not considered seizure-free even when they had no seizures during the stable dose period. In the inferential ITT population, 112 out of 183 patients randomized to receive LEV 1000 mg/d during one of the periods of the crossover study received placebo during the first 2 weeks of the titration period (Boon *et al.*, 2002). In the other studies, there was no placebo during titration but the titration was done gradually, either to 333 mg/d, 666 mg/d, and then 1000 mg/d over 4 weeks (Cereghino *et al.*, 2000) or to 1000 mg/d, 2000 mg/d, and then 3000 mg/d (Cereghino *et al.*, 2000, Ben-Menachem and Falter, 2000). Consequently, the percentage of seizure-free patients in the other groups is also expected to be lower during titration than during the stable dose period, because patients received lower doses of LEV during titration. For placebo-controlled trials, this could be an argument for restricting the assessment of seizure freedom to the stable dose period (Method 1). In clinical trials directly

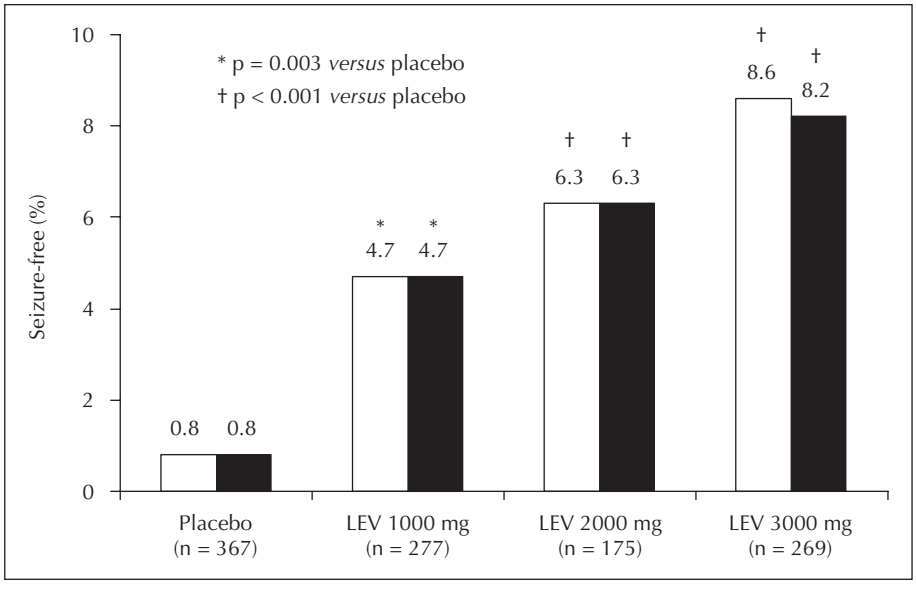

Figure 2. Seizure freedom rates in levetiracetam (LEV)-treated patients based on Method 1 (white bars) and Method 3 (grey bars). Results include both parts of the crossover trial.

Table 3. Seizure freedom estimates based on method of analysis in placebo-controlled adjunctive therapy trials of levetiracetam (LEV) in patients with refractory partial epilepsy.

Method	Placebo	LEV 1000 mg	LEV 2000 mg	LEV 3000 mg
Method 1[a]				
Seizure-free patients, % (n/total)	0.8 (3/367)	4.7 (13/277)	6.3 (11/175)	8.6 (23/269)
Odds ratio (95% CI)		6.0 (1.6–32.9)	8.1 (2.1-45.8)	11.3 (3.4-59.5)
p value *versus* placebo		0.003	<0.001	<0.001
Method 2[b]				
Seizure-free patients, % (n/total)	0.5 (2/367)	2.2 (6/277)	5.7 (10/175)	5.9 (16/269)
Odds ratio (95% CI)		4.0 (0.7–41.2)	11.1 (2.3–104.5)	11.5 (2.7–104.0)
p value *versus* placebo		0.081	<0.001	<0.001
Method 3[c]				
Seizure-free patients, % (n/total)	0.8 (3/367)	4.7 (13/277)	6.3 (11/175)	8.2 (22/269)
Odds ratio (95% CI)		6.0 (1.6–32.9)	8.1 (2.1-45.8)	10.8 (3.2-56.8)
p value *versus* placebo		0.003	<0.001	<0.001
Method 4[d]				
Seizure-free patients, % (n/total)	0.5 (2/367)	2.2 (6/277)	5.7 (10/175)	5.9 (16/269)
Odds ratio (95% CI)		4.0 (0.7–41.2)	11.1 (2.3–104.5)	11.5 (2.7–104.0)
p value *versus* placebo		0.081	<0.001	<0.001
Method 5[e]				
Seizure-free patients, % (n/total)	0.9 (3/343)	5.1 (13/257)	6.7 (11/163)	8.9 (22/247)
Odds ratio (95% CI)		6.0 (1.6–33.3)	8.2 (2.1–46.2)	11.1 (3.3–58.3)
p value *versus* placebo		0.003	<0.001	<0.001
Method 6[f]				
Seizure-free patients, % (n/total)	0.6 (2/343)	2.3 (6/657)	6.1 (10/163)	6.5 (16/247)
Odds ratio (95% CI)		4.1 (0.7-41.5)	11.1 (2.3-105.3)	11.8 (2.7-106.5)
p value *versus* placebo		0.079	<0.001	<0.001

[a] Method 1: Seizure freedom defined by absence of seizures during the stable dose period. Patients seizure-free at time of withdrawal are counted as seizure-free.

[b] Method 2: Seizure freedom defined by absence of seizures during the titration plus stable dose period for patients reaching the stable dose period. Patients seizure-free at time of withdrawal are counted as seizure-free.

[c] Method 3: Seizure freedom defined by absence of seizures during the stable dose period. Withdrawals are counted as not seizure-free.

[d] Method 4: Seizure freedom defined by absence of seizures during the titration plus stable dose period for patients reaching the stable dose period. Withdrawals are counted as not seizure-free.

[e] Method 5: Seizure freedom defined by absence of seizures during the stable dose period for completers, using completers as denominator.

[f] Method 6: Seizure freedom defined by absence of seizures during the titration plus stable dose period for completers, using completers as denominator.

comparing two or more AEDs, however, measuring seizure freedom from the first drug dose, including the titration period (Method 2), will reveal differences between a drug reaching therapeutic doses quickly and a drug needing to be uptitrated slowly. The clinical relevance of stopping seizures as soon as possible is evident.

Seizure freedom rates may be significantly impacted by all methods that allow investigators to define as seizure-free those patients who did not complete the entire treatment period. This could result in artificially inflated seizure-free rates: for example, with Method 1, which considers all patients who discontinue prematurely while being seizure-free as "successes", there is clearly a bias in favor of poorly tolerated AEDs, because patients would not have necessarily remained seizure-free had they not withdrawn. A highly conservative approach to circumvent this problem is to consider all patients who did not have seizures during the stable dose phase but did not complete such phase as "failures"; *i.e.*, these patients are not considered to be seizure-free (Method 3). In the case of LEV, however, using the inferential ITT population, Methods 1 and 3, both assessing the stable dose period, yielded almost identical results. In the placebo and 1000 and 2000 mg LEV groups, no seizure-free patients withdrew. In the 3000 mg LEV group, only one seizure-free patient withdrew before the end of the stable dose period. Assuming that this patient had remained seizure-free (Method 1), the percentage of seizure-free patients would be 8.6%

Table 4. Demographic and clinical characteristics in the inferential intent-to-treat (ITT) population included in placebo-controlled adjunctive therapy trials of levetiracetam (LEV) in patients with refractory partial epilepsy, classified according to their seizure freedom status in the trial (calculated according to Method 1[a]).

	Placebo n = 367	LEV 1000 mg n = 277	LEV 2000 mg n = 175	LEV 3000 mg n = 269
Gender: female/male (%/%)				
Seizure-free	33.3/66.7	46.2/53.8	45.5/54.5	34.8/65.2
Not seizure-free	48.9/51.1	43.6/56.4	52.4/47.6	45.9/54.1
Age, years: mean (±SD)				
Seizure-free	30.7 (9.5)	35.1 (9.6)	31.2 (13.7)	41.8 (11.8)
Not seizure-free	37.0 (11.4)	37.6 (11.2)	37.1 (11.7)	36.6 (11.1)
Age at epilepsy onset, years: mean (±SD)				
Seizure-free	21.2 (14.7)	18.4 (12.8)	12.0 (7.2)	19.9 (15.0)
Not seizure-free	15.2 (12.2)	13.8 (11.6)	13.9 (11.5)	15.8 (12.8)
Duration of epilepsy, years: mean (±SD)				
Seizure-free	10.0 (7.2)	17.0 (12.1)	19.6 (16.9)	22.4 (12.6)
Not seizure-free	22.4 (11.6)	24.2 (12.3)	23.6 (13.4)	21.3 (12.0)
Baseline seizure frequency per week: mean (±SD)				
Seizure-free	1.4 (0.7)	2.1 (1.3)	2.6 (2.3)	1.4 (1.1)
Not seizure-free	5.3 (13.9)	6.6 (12.5)	5.7 (10.2)	5.2 (15.1)

[a] Method 1: Seizure freedom defined by absence of seizures during the stable dose period. Patients seizure-free at time of withdrawal are counted as seizure-free.

(*figure 2*), whereas considering this patient as a failure (Method 3) would yield a seizure freedom rate of 8.2% (*table 3*). Obviously, the difference between these two rates would be much larger for a drug (or dose) with higher withdrawal rates due to poor tolerability. The finding of similar results obtained with Methods 1 and 3 provides indirect evidence that all drug doses were well tolerated.

A fourth method is the most conservative of all, in that it defines seizure freedom as the absence of seizures during both the titration and the stable dose period (as in Method 2), and considers seizure-free non-completers as failures, as in Method 3. For LEV, using the inferential ITT population, Method 2 and Method 4 yielded identical seizure freedom results (*table 3*). This finding is consistent with the comparison between Methods 1 and 3.

A fifth approach (Method 5) disregards the inferential ITT population and considers as denominator only the population of patients who complete the stable dose period. In this method, the number of seizure-free patients is the same as determined using Method 3 (*i.e.*, only completers with no seizures during the stable dose phase are considered seizure-free), but the number of patients used in the denominator becomes smaller because only completers are considered. In studies with large numbers of patient discontinuations, the reduction in the denominator can have a significant impact on seizure-free rates. This method can be seriously biased, because it uses the subset of subjects who finish the trial, and excludes those who may have withdrawn because of lack of efficacy or low tolerability. If Method 5 is used, then an analysis based on Method 3 should also be provided: if there is a large difference between the two methods, the analysis suggests that the drug is poorly tolerated. In the LEV trials, the largest difference in seizure-free rates between Method 5 and Method 3 was seen in the 3000-mg group (*table 3*), but was very minor (8.9% *versus* 8.2%, respectively). In fact, the number of patients who discontinued was 24 in the placebo group, 20 in the LEV 1000-mg group, 12 in the LEV 2000-mg group, and 22 in the LEV 3000-mg group. An approach similar to Method 5, using completers in the denominator, can also be applied by defining as seizure-free only those patients who complete the trial without seizures during both the titration and the stable dose period (Method 6). In this case, consistency of results should be sought by comparing Method 6 with Method 4.

Assessing seizure-free rates during long-term follow-up

Long-term follow-up after the double-blind add-on phase can only be performed in an open-label setting for obvious ethical reasons. Some methodological pitfalls in assessing seizure freedom during follow-up are similar to those described for short-term trials, such as the handling of withdrawals and, more importantly, the selective drop-out of non-responders. Other methodological issues are specific to the design of the long-term follow-up. Patients enter these studies at different time points, and usually the studies contain a clearly defined cut-off point, often coinciding with the marketing approval of the drug. Patients will thus receive treatment for variable durations, making

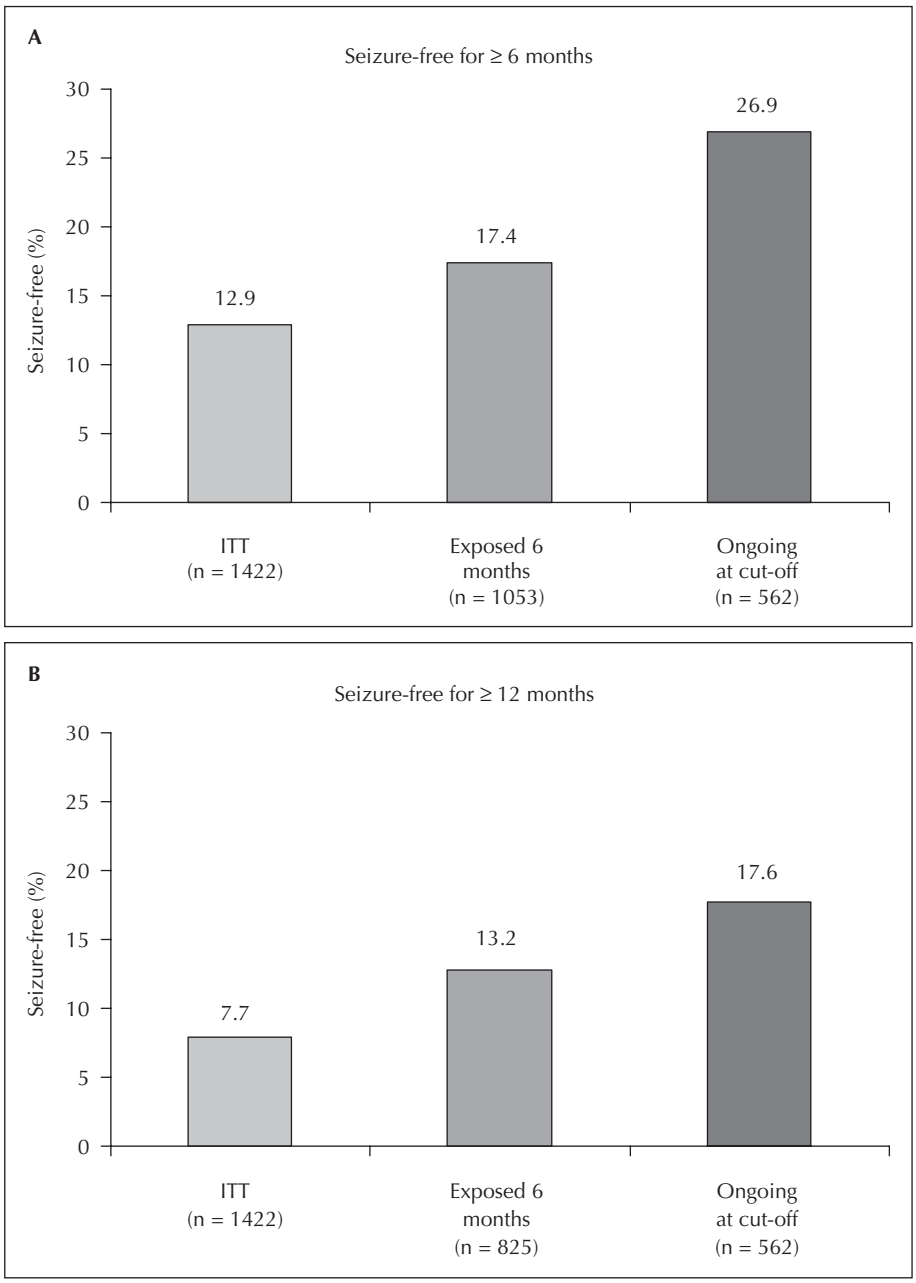

Figure 3. Seizure-free rates with add-on levetiracetam for any 6-month or 12-month period during long-term follow-up (Radtke and Bennett, 2000). Data are shown for the intent-to-treat (ITT) population of 1422 patients, the subgroups treated for at least 6 and 12 months, and the subgroup continuing to receive levetiracetam at the cut-off point of follow-up.

the analysis of seizure freedom more complicated and comparisons between different AEDs particularly difficult. Two general methodologies can be used in calculating seizure freedom in long-term follow-up studies. Seizure freedom can be measured over a specified time period, such as 6 or 12 months, either by determining the patients who were seizure-free "during the last 6 (or 12) months" of treatment or by considering the patients who were seizure-free "for at least 6 (or 12) months" (at any period in the study). By definition, seizure freedom rates will be smaller or at best equal with the "last x month" approach as compared with the "at least x month" strategy. *figure 3* shows data for patients exposed to add-on LEV during long-term pre-marketing follow-up (Radtke and Bennett, 2000). Various populations were evaluated, including the ITT population of 1422 patients, the populations who

were exposed to LEV for at least 6 and 12 months, and the population in whom treatment was ongoing at the trial cut-off date. Six-month seizure-free rates (patients seizure-free for at least six months at any time during follow-up) ranged from 12.9% (ITT population) to 26.9% (ongoing population), and similarly, 12-month seizure-free rates ranged from 7.7% to 17.6%.

The ITT population also included patients who were exposed for less than six months or one year, respectively. Patients may have a shorter follow-up because they discontinue treatment, or because the study cut-off date has been reached after less than six months/one year. In this case, the denominator was reduced from 1422 (ITT) to 1053 (exposed for at least six months) or 825 (exposed for at least one year). Thus, the ITT population included patients who by definition could not be counted as seizure-free, because they did not reach the minimum duration of exposure required to be considered as seizure-free. The seizure freedom rate will thus be profoundly affected by whether the study population (denominator) is defined on an ITT basis or as the subgroup exposed to treatment for a specific number of months, making ITT a particularly conservative method for this kind of analysis. However, the ITT method is the most conservative, compared with an analysis of subjects exposed for at least a certain period of time, particularly if subjects were unable to reach the minimum exposure period due to low drug efficacy or intolerable adverse effects.

The method by which withdrawals are handled in long-term studies can also have a considerable impact on seizure freedom rates. The most conservative approach considers all seizure-free patients who discontinue as failures, similar to Method 3 in short-term trials. However, this approach may underestimate the real efficacy of the drug, because patients discontinue for several different reasons, and some would likely have remained seizure-free for a longer period had they remained in the study. In a prolonged follow-up, some patients may remain seizure-free over long time periods, prompting physicians to withdraw one drug or stop all drug therapy. An alternative approach is to consider all withdrawals while seizure-free as successes and include such patients in the calculation of seizure-free rates, similar to Method 1 in the short-term trials. This approach, however, gives an advantage to an effective but poorly tolerated drug with significant numbers of discontinuations due to adverse effects. Such patients would not necessarily have remained seizure-free had they not withdrawn from the study.

As described above, although the ITT approach is associated with the least bias, it is necessary to indicate how the early discontinuations are handled in an ITT population. The following theoretical examples illustrate how these factors influence the seizure freedom results for three different AEDs. Each drug is administered to a theoretical cohort of 100 patients.

Drug A (efficacious and well tolerated AED)

For such a drug, a realistic assumption could be that, in an ITT population of 100 patients, 70 continue treatment with drug one for at least six months; two are seizure-free and discontinue, and 15 patients are seizure-free and still on drug at the end of the follow-up. Using the ITT population, the seizure freedom rate is 17% (17/100) if withdrawals are considered as successes and 15% (15/100) if withdrawals are considered as failures. If the population is defined as the patients exposed for at least 6 months, then the seizure freedom rate is 21% (15/70).

Drug B (efficacious but poorly tolerated AED)

For such a drug, a realistic scenario can be assumed whereby, in an ITT population of 100 patients, 50 continue treatment with the drug for at least six months; 10 are seizure-free but withdraw from treatment, and 15 are seizure-free and still on the drug at the end of the trial. Using the ITT population, the seizure freedom rate is 25% (25/100) if withdrawals are considered as successes and 15% (15/100) if withdrawals are considered as failures. If the population is defined as patients exposed for at least six months, then the seizure freedom rate is 30% (15/50).

Drug C (well tolerated but less efficacious AED)

Here, a reasonable scenario could be that, in an ITT population of 100 patients, 70 continue treatment with drug three for at least six months, one patient is seizure-free and discontinues, and five patients are seizure-free and still on the drug at the end of the trial. Using the ITT population, the seizure freedom rate is 6% (6/100) if withdrawals are considered as successes and 5% (5/100) if withdrawals are considered as failures. If the population is defined as patients exposed for at least 6 months, then the seizure freedom rate is 7% (5/70).
Based on the above examples, it is clear that the seizure freedom rate for a poorly tolerated drug (drug B) is grossly overestimated when withdrawals are considered as successes in the ITT population or when the denominator is defined as the population exposed to drug for at least six months.

Discussion

This review has shown that the literature contains little information on seizure freedom rates with AEDs used as add-on therapy, and even less information about how these rates were determined. Moreover, as reported in this article, lack of uniformity in defining seizure freedom and, more importantly, failure to define seizure freedom in many publications, do not allow any meaningful comparison to be made. Some methods for calculating seizure freedom give highly inflated estimates, particularly with poorly tolerated drugs when last observation carried

forward analysis is used, *i.e.*, when seizure-free patients withdrawing from treatment are counted as successes.

Physicians can choose among many different AEDs when selecting treatment for their patients. A variety of criteria enter into the decision-making process, including the efficacy and tolerability of the drug as well as various individual patient characteristics, such as seizure history, pre-existing drug therapy, and comorbidities. At least for adjunctive therapy trials, no direct comparisons between AEDs have been conducted that allow efficacy and tolerability of the drugs to be compared. Moreover, methodological differences among studies make it problematic to differentiate between AEDs.

If we believe that no seizures and no adverse side effects is the ultimate goal of epilepsy treatment (Langfitt and Meador, 2004), then seizure freedom is a very important parameter, and how it is calculated is a vital piece of information in order to evaluate, compare, and apply the data to a particular patient.

Newly diagnosed epilepsy is treated with old or new AEDs, and up to two thirds of these patients may achieve remission with monotherapy (Kwan and Brodie, 2000). Patients who are refractory to mono- or polytherapy may be included in clinical trials of new AEDs, with the goal of achieving regulatory approval for use in add-on therapy. Because this patient population is particularly refractory to AED treatment, high seizure-freedom rates cannot be expected, and seizure freedom often is not reported.

No one can deny, however, that seizure freedom is the single most important determinant of quality of life, and even a modest probability of achieving seizure freedom may well justify trying a new AED in a patient with severely refractory epilepsy. Because of this, information on comparative seizure freedom rates in adjunctive therapy and follow-up studies of new AEDs is clinically meaningful, and it should be reported at all times. For some of the recently introduced AEDs, seizure freedom rates during adjunctive therapy use in severely refractory epilepsy have been modest, but not always negligible. In particular, 6-month seizure freedom rates in long-term follow-up studies of LEV were as high as 26%, depending on the calculation method used. If the ITT calculation method is applied (*e.g.*, ITT analysis in the entire population of 1422 patients included in follow-up studies), the seizure freedom rate was still close to 13%, which is clinically important in a population of patients who had already failed a wide range of drugs.

To be able to comparatively assess the value of the many available AEDs, it would be important to perform a meta-analysis of seizure freedom rates in all studies performed so far with each of the AEDs. Regrettably, a lack of published seizure freedom information makes such a meta-analysis impossible at the present time.

Conclusion

Little emphasis has been placed on seizure freedom in adjunctive therapy studies. Inasmuch as seizure freedom is the ultimate goal of AED therapy, a standardized methodology may need to be developed to ensure seizure freedom rates are reported consistently for all clinical studies, even when such rates are very low or even zero. Direct comparisons between new AEDs remain to be done. In the meantime, indirect comparisons would be a useful, albeit limited alternative; however, they are difficult to conduct because seizure freedom rates are only reported for some AEDs or some trials, leading to potential reporting bias, and because the methods used to calculate them are not always reported and, when they are, differ across studies. Therefore, such comparisons need to be made cautiously. Transparency in the methodology used to assess seizure freedom is mandatory in order to make such indirect comparisons valid. A whole range of different methodologies is available. It is our recommendation that the minimum duration for assessing seizure freedom should be the entire stable dose period in short-term double-blind clinical trials, and the last six months for long-term follow-up studies regardless of the status of the patient's treatment. At a minimum, the methodology used should be described and at least two different methodologies should be presented, one that considers seizure-free withdrawals as successes, and one that considers them as failures. In the end, it is the number of patients that remain seizure-free throughout the study that may be the most valid measurement. The ultimate goal of antiepileptic treatment is complete seizure control without unacceptable side effects, so reporting seizure freedom is very important, and as such, should not be misrepresented. □

References

Anhut H, Ashman P, Feuerstein TJ, Sauermann W, Saunders M, Schmidt B. Gabapentin (Neurontin) as add-on therapy in patients with partial seizures: a double-blind, placebo-controlled study. *Epilepsia* 1994; 35: 795-801.

Arroyo S, Anhut H, Kugler AR, *et al.* Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures. *Epilepsia* 2004; 45: 20-7.

Barcs G, Walker EB, Elger CE, *et al.* Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy. *Epilepsia* 2000; 41: 1597-607.

Ben-Menachem E. International experience with tiagabine add-on therapy. *Epilepsia* 1995; 36(suppl. 6): S14-S21.

Ben-Menachem E. Clinical efficacy of topiramate as add-on therapy in refractory partial epilepsy: the European experience. *Epilepsia* 1997; 38(suppl. 1): S28-S30.

Ben-Menachem E, Falter U, for the European Levetiracetam Study Group. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. *Epilepsia* 2000; 41: 1276-83.

Ben-Menachem E, Henriksen O, Dam M, *et al.* Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. *Epilepsia* 1996; 37: 539-43.

Beran RG, Berkovic SF, Dunagan FM, *et al.* Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalized epilepsy. *Epilepsia* 1998; 39: 1329-33.

Binnie CD, Beintema DJ, Debets RM, *et al.* Seven day administration of lamotrigine in epilepsy: placebo-controlled add-on trial. *Epilepsy Res* 1987; 1: 202-8.

Binnie CD, Debets RM, Engelsman M, *et al.* Double-blind crossover trial of lamotrigine (Lamictal) as add-on therapy in intractable epilepsy. *Epilepsy Res* 1989; 4: 222-9.

Boas J, Dam M, Friis ML, Kristensen O, Pedersen B, Gallagher J. Controlled trial of lamotrigine (Lamictal®) for treatment-resistant partial seizures. *Acta Neurol Scand* 1996; 94: 247-52.

Boon P, Chauvel P, Pohlmann-Eden B, Otoul C, Wroe S. Dose-response effect of levetiracetam 1000 and 2000 mg/d in partial epilepsy. *Epilepsy Res* 2002; 48: 77-89.

Brodie MJ. Pregabalin as adjunctive therapy for partial seizures. *Epilepsia* 2004; 45(suppl. 6): 19-27.

Cereghino JJ, Biton V, Abou-Khalil B, Dreifuss F, Gauer LJ, Leppik I. Levetiracetam for partial seizures. Results of a double-blind, randomized clinical trial. *Neurology* 2000; 55: 236-42.

Chadwick D. Gabapentin. *Epilepsy Res* 1991; 3(suppl): 183-6.

Chaisewikul R, Privitera MD, Hutton JL, Marson AG. Levetiracetam add-on for drug-resistant localization related (partial) epilepsy. *Cochrane Database Syst Rev* 2002; 1; (CD001901).

Crawford P, Ghadiali E, Lane R, Blumhardt L, Chadwick D. Gabapentin as an antiepileptic drug in man. *J Neurol Neurosurg Psychiatry* 1987; 50: 682-6.

Faught E. Efficacy of topiramate as adjunctive therapy in refractory partial seizures: United States trial experience. *Epilepsia* 1997; 38(suppl. 1): S24-S27.

Faught E, Ayala R, Montouris GG, Leppik IE. Zonisamide 922 Trial Group. Randomized controlled trial of zonisamide for the treatment of refractory partial-onset seizures. *Neurology* 2001; 57: 1774-9.

Faught E, Wilder BJ, Ramsay RE, *et al.* Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. Topiramate YD Study Group. *Neurology* 1996; 46: 1684-90.

Fisher RS, Sachdeo RC, Pellock J, Penovich PE, Magnus L, Bernstein P. Rapid initiation of gabapentin: a randomized, controlled trial. *Neurology* 2001; 56: 743-8.

French JA, Kugler AR, Robbins JL, Knapp LE, Garofalo EA. Dose-response trial of pregabalin adjunctive therapy in patients with partial seizures. *Neurology* 2003; 60: 1631-7.

Guberman A, Neto W, Gassmann-Mayer C. EPAJ-119 Study Group. Low-dose topiramate in adults with treatment-resistant partial-onset seizures. *Acta Neurol Scand* 2002; 106: 183-9.

Jawad S, Richens A, Goodwin G, Yuen WC. Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. *Epilepsia* 1989; 30: 356-63.

Kalviainen R, Brodie MJ, Duncan J, Chadwick D, Edwards D, Lyby K. A double-blind, placebo-controlled trial of tiagabine given three times daily as add-on therapy for refractory partial seizures. North European Tiagabine Study Group. *Epilepsy Res* 1998; 30: 31-40.

Korean Topiramate Study Group. Topiramate in medically intractable partial epilepsies: double-blind placebo-controlled randomized parallel group trial. *Epilepsia* 1999; 40: 1767-74.

Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; 342: 314-9.

Langfitt J, Meador K. Want to improve epilepsy care? Ask the patient. *Neurology* 2004; 62: 6-7.

In: Levy RH, Mattson RH, Meldrum BS, Perucca E, eds. *Antiepileptic Drugs*. Baltimore: 5th ed. Lippincott Williams & Wilkins, 2002.

Loiseau P. Review of controlled trials of gabitril (tiagabine): a clinician's viewpoint. *Epilepsia* 1999; 40(suppl. 9): S14-S19.

Loiseau P, Yuen AW, Duche B, Menager T, Arne-Bes MC. A randomised double-blind placebo-controlled crossover add-on trial of lamotrigine in patients with treatment resistant partial seizures. *Epilepsy Res* 1990; 7: 136-45.

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: 259-70.

Matsuo F, Bergen D, Faught E, *et al.* Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. U.S. Lamotrigine Protocol 0.5 Clinical Trial Group. *Neurology* 1993; 43: 2284-91.

Messenheimer J, Ramsay RE, Willmore LJ, *et al.* Lamotrigine therapy for partial seizures: a multicenter, placebo-controlled, double-blind, cross-over trial. *Epilepsia* 1994; 35: 113-21.

Miller R, Frame B, Corrigan B, *et al.* Exposure-response analysis of pregabalin add-on treatment of patients with refractory partial seizures. *Clin Pharmacol Ther* 2003; 73: 491-505.

Moran NF, Poole K, Bell G, *et al.* Epilepsy in the United Kingdom: seizure frequency and severity, anti-epileptic drug utilization and impact on life in 1652 people with epilepsy. *Seizure* 2004; 13: 425-33.

Peeters K, Adriaenssen I, Wapenaar R, Neto W, Pledger G. A pooled analysis of adjunctive topiramate in refractory partial epilepsy. *Acta Neurol Scand* 2003; 108: 9-15.

Pellock JM. The clinical efficacy of lamotrigine as an antiepileptic drug. *Neurology* 1994; 44(suppl. 8): S29-S35.

Privitera M, Fincham R, Penry J, *et al.* Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600-, 800-, and 1,000-mg daily dosages. *Neurology* 1996; 46: 1678-83.

Radtke R, Bennett B. Calculating seizure-free rates after long-term AED exposure: impact of methodology using levetiracetam premarketing experience [abstract]. *Epilepsia* 2000; 41(suppl. 7): 121-2; [Abstract 2.127].

Reife RA, Pledger GW. Topiramate as adjunctive therapy in refractory partial epilepsy: pooled analysis of data from five double-blind, placebo-controlled trials. *Epilepsia* 1997; 38(suppl. 1): S31-S33.

Reife R, Pledger G, Wu SC. Topiramate as add-on therapy: pooled analysis of randomized controlled trials in adults. *Epilepsia* 2000; 41(suppl. 1): S66-S71.

Richens A, Chadwick DW, Duncan JS, *et al.* Adjunctive treatment of partial seizures with tiagabine: a placebo-controlled trial. *Epilepsy Res* 1995; 21: 37-42.

Sachdeo RC, Leroy RF, Krauss GL, *et al.* Tiagabine therapy for complex partial seizures. A dose-frequency study. The Tiagabine Study Group. *Arch Neurol* 1997; 54: 595-601.

Sander JW, Bell GS. Reducing mortality: an important aim of epilepsy management. *J Neurol Neurosurg Psychiatry* 2004; 75: 349-51.

Sander JW, Patsalos PN, Oxley JR, Hamilton MJ, Yuen WC. A randomised double-blind placebo-controlled add-on trial of lamotrigine in patients with severe epilepsy. *Epilepsy Res* 1990; 6: 221-6.

Schapel GJ, Beran RG, Vajda FJ, *et al.* Double-blind, placebo-controlled, crossover study of lamotrigine in treatment resistant partial seizures. *J Neurol Neurosurg Psychiatry* 1993; 56: 448-53.

Schmidt D, Sachdeo R. Oxcarbazepine for treatment of partial epilepsy: a review and recommendations for clinical use. *Epilepsy Behav* 2000; 1: 396-405.

Schmidt D, Jacob R, Loiseau P. Zonisamide for add-on treatment of refractory partial epilepsy: a European double-blind trial. *Epilepsy Res* 1993; 15: 67-73.

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: 217-24.

Shorvon SD, Löwenthal A, Janz D, Bielen E, Loiseau P, for the European Levetiracetam Study Group. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. *Epilepsia* 2000; 41: 1179-86.

Sivenius J, Kalviainen R, Ylinen A, Riekkinen P. Double-blind study of gabapentin in the treatment of partial seizures. *Epilepsia* 1991; 32: 539-42.

Smith D, Baker G, Davies G, Dewey M, Chadwick DW. Outcomes of add-on treatment with lamotrigine in partial epilepsy. *Epilepsia* 1993; 34: 312-22.

Stolarek I, Blacklaw J, Forrest G, Brodie MJ. Vigabatrin and lamotrigine in refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1994; 57: 921-4.

Tassinari CA, Michelucci R, Chauvel P, *et al.* Double-blind, placebo-controlled trial of topiramate (600 mg daily) for the treatment of refractory partial epilepsy. *Epilepsia* 1996; 37: 763-8.

US Gabapentin Study Group. Gabapentin in partial epilepsy. *Lancet* 1990; 335: 1114-7.

US Gabapentin Study Group No. 5. Gabapentin as add-on therapy in refractory partial epilepsy: a double-blind, placebo-controlled, parallel-group study. *Neurology* 1993; 43: 2292-8.

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.

Yen DJ, Yu HY, Guo YC, Chen C, Yiu CH, Su MS. A double-blind, placebo-controlled study of topiramate in adult patients with refractory partial epilepsy. *Epilepsia* 2000; 41: 1162-6.