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REVIEW

Tolerability of new antiepileptic drugs: a network meta-analysis

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Abstract
Objective The objective of this study was to perform a comparative assessment of tolerability of all licensed new antiepileptic drugs (AEDs) through a network meta-analysis (NMA) including all placebo-controlled double-blind clinical trials (RCTs) in all conditions in which these drugs have been tested.
Methods NMA with a frequentist approach was used to compare proportions of patients withdrawing because of adverse events (AEs). Analyses were conducted for all therapeutic doses pooled and specifically for high therapeutic doses. Patients treated with non-therapeutic doses of each drug were excluded.
Results A total of 195 RCTs were included in the current analysis, comprising a total of 28,013 patients treated with AEDs and 17,908 patients treated with placebo. RCTs included in the analysis were 8 for brivaracetam; 5 for eslicarbazepine; 22 for gabapentin; 7 for lacosamide; 14 for levetiracetam; 14 for lamotrigine; 6 for oxcarbazepine; 9 for perampanel; 50 for pregabalin; 5 for tiagabine; 36 for topiramate; 7 for zonisamide; 4 for gabapentin-extended formulation (ER); 2 each for levetiracetam-ER, lamotrigine-ER, and topiramate-ER; and 1 each for oxcarbazepine-ER and pregabalin-ER. Brivaracetam, gabapentin, gabapentin-ER, and levetiracetam had a significantly lower withdrawal rate compared to several other AEDs, while eslicarbazepine, lacosamide, oxcarbazepine, and topiramate had a higher withdrawal rate. Perampanel, lamotrigine, pregabalin, tiagabine, and zonisamide showed an intermediate pattern of tolerability. Additional analysis has been conducted through selection of highly recommended doses for each drug. This analysis has roughly confirmed results of head to head comparisons of the all-dose analysis, with some exceptions. A further analysis has been conducted after exclusion of RCTs in which patients were allocated to the therapeutic dose of the experimental drug without titration, and it failed to show clinically important differences.
Significance Relevant differences in short-term tolerability of AEDs have been observed between AEDs. Brivaracetam, gabapentin, and levetiracetam show the best tolerability profile while other AEDs are at higher risk for intolerable adverse effects.

Keywords Meta-analysis · Network meta-analysis · Adverse effects · Tolerability of antiepileptic drugs · Brivaracetam · Perampanel · Eslicarbazepine · Lacosamide

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Introduction

In recent years, several new antiepileptic drugs (AEDs) have been approved as add-on treatments in drug-resistant focal epilepsy patients [1, 2]. Although information on comparative efficacy and tolerability of these drugs is of strategic importance for the choice of the appropriate AED, registrative, double-blind, placebo-controlled studies do not give this information [1, 3].

Recently, a new meta-analytical technique, the so-called network meta-analysis (NMA), has been proposed as an objective way of comparing alternative treatments where direct treatment comparisons are not available [4, 5]. Up to now, several NMAs of efficacy and tolerability of AEDs including RCTs performed in patients with drug-resistant focal epilepsy provided different conclusions [6–11].

In this meta-analysis, assessment of short-term tolerability of all new AEDs has been performed through an NMA aimed at comparing the most robust outcome measure of tolerability (patients withdrawing because of adverse effects) in all double-blind, placebo-controlled RCTs performed in adults in which these drugs have been tested, including those performed in conditions other than epilepsy. The number of patients withdrawing because of adverse effects is not influenced by all sources of heterogeneity which hamper analysis of efficacy [11, 12]. Analyses were performed both for all doses pooled and specifically for high doses. A further analysis was conducted to assess the relative weight of titration rate.

Methods

We performed a systematic review of all placebo-controlled, double-blind RCTs assessing the use of licensed AEDs in all conditions in which these drugs have been studied in adults.

The following drugs have been included in the analysis: brivaracetam (BRV), eslicarbazepine (ESL), gabapentin (GBP), lacosamide (LCM), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), perampanel (PER), pregabalin (PGB), tiagabine (TGB), topiramate (TPM), and zonisamide (ZNS). Extended release (ER) formulations of AEDs were considered as different AEDs and were included in the analysis, even though some of them are not yet available in clinical practice.

Studies were identified through MEDLINE (PubMED interface) and EMBASE up to April 2016. This study was done according to the preferred reporting items for systematic reviews and meta-analysis guidelines [13]. See PRISMA checklist in S1. Feasibility of NMA has been assessed through a stepwise algorithm recently proposed [14].

Eligibility criteria

All double-blind placebo-controlled RCTs exploring efficacy of the above cited AEDs in any condition they have been studied and reporting patients withdrawing because of adverse events (AEs) as an outcome, with a parallel or cross-over design, and a duration of double-blind phase of at least 4 weeks, were included. For details of inclusion/exclusion criteria, see S2.

Data abstraction

For each RCT, two authors assessed eligibility and risk of bias, and extracted data. Cochrane Collaboration's tool for assessing risk of bias [15] was used to ascertain the validity of eligible RCTs. For each study, the number of patients treated with placebo, and with the active drug at different doses, and the number of patients withdrawing because of AEs in all study arms were extracted.

Data analysis

NMA with a frequentist approach was used to compare proportions of patients withdrawing because of AEs while on treatment, using the netmeta R package version 8.0 (available at: http://CRAN.R-project.org/package=netmeta) to calculate point estimates of odds ratios (ORs) with 95% confidence intervals (CIs) and generate head-to-head comparisons and forest plots using random- or fixed-effect models comparing the effect estimates of different AEDs relative to placebo [16]. The R package netmeta employs graph theory methodology proposed by Rücker [17]. A meta-analytic graph consists of vertices (treatments) and edges (randomized comparisons). The resulting consistent treatment effects induced in the edges can be estimated via the Moore-Penrose pseudoinverse of the Laplacian matrix [17]. *P* rank scores were generated to determine probability scores to rank which AEDs result in the lowest proportion of withdrawals due to AEs. *P* scores are based solely on the point estimates and standard errors of the network estimates. They measure the extent of certainty that a treatment is better than another treatment, averaged over all competing treatments. The *P* score of treatment *i* is defined as the mean of all $1 - P[j]$ where $P[j]$ denotes the one-sided *P* value of accepting the alternative hypothesis that treatment *i* is better than one of the competing treatments *j*. Thus, if treatment *i* is better than many other treatments, many of these *P* values will be small and the *P* score will be large. Vice versa, if treatment *i* is worse than most other treatments, the *P* score is small. The *P* score of treatment *i* can be interpreted as the mean extent of certainty that treatment *i* is better than another treatment. Heterogeneity across individual studies was assessed by using the Cochran *Q* (chi-squared) and Higgins I^2 statistics which quantified the percent of total variation due to between-study heterogeneity [18]. As the heterogeneity

among studies was low (see results), data were analyzed using a fixed-effect model.

For each AED, all these analyses have been performed after the exclusion of studies or arms of studies in which patients were treated with doses outside the range of therapeutic doses. These were doses which, according to the summary of product characteristics (SPC) [19] of each drug, were under the therapeutic dose or above the high therapeutic dose. For some AEDs, these doses are not clearly specified in the SPC. In such cases, doses were considered as not therapeutic when these were found not significantly effective in pivotal RCTs of drug-resistant epilepsy.

For the ER formulations, we considered that therapeutic doses were the same as for the immediate-release formulations (see Table 1 in S2).

Two analyses have been performed. In the first analysis, all patients treated with a drug dose within the range of effective doses were summed ("all-dose analysis"). A secondary analysis was restricted to studies or arms of studies in which patients were treated with the highest of recommended doses according to the SPC ("high-dose analysis").

Finally, further secondary analyses were performed excluding patients who received full-maintenance doses without prior titration (all-dose analysis and high-dose analysis after the exclusion of studies or arms of studies in which patients were randomized to the active treatment without titration).

Results

Characteristics of eligible trials

Flowcharts of the identified studies and relative references are reported for each AED in supplementary material S3.

From 231 RCTs, after exclusion of RCTs exploring only doses not included in the range of therapeutic doses ($n = 36$), a total of 195 RCTs were included in the analysis (8 for BRV, 5 for ESL, 22 for GBP, 7 for LCM, 14 for LEV, 14 for LTG, 6 for OXC, 9 for PER, 50 for PGB, 5 for TGB, 36 for TPM, 7 for ZNS). Six AEDs had corresponding ER formulations. These were GBP (4 studies); LEV, LTG, and TPM (2 studies each); and OXC and PGB (1 study each). The main features of the 195 RCTs included in the analysis are reported in S4. AEDs were explored in several diseases which have been grouped in seven main conditions (epilepsy, pain, movement disorders, obesity and binge eating disorders, psychiatric disorders, substance abuse, and miscellanea) (see S5).

A total of 28,013 patients were treated with therapeutic drug doses of experimental drugs and were included in the analysis with 17,908 placebo-treated patients. For each drug, the number of patients treated with the experimental drug and with placebo were, respectively, 1369 and 722 for BRV, 1086 and 560 for ESL, 2587 and 1958 for GBP, 847 and 394 for GBP-ER, 1401 and 655 for LCM, 1089 and 805 for LEV, 116 and 116 for LEV-ER, 1277 and 84 for LTG, 199 and 197 LTG-ER, 854 and 523 for OXC, 122 and 121 for OXC-ER, 1794 and 1203 for PER, 8110 and 5175 for PGB, 113 and 110 for PGB-ER, 1011 and 637 for TGB, 5239 and 3228 for TPM, 178 and 182 for TPM-ER, and 623 and 472 for ZNS. Twenty RCTs were crossover studies, and for these studies, both phases of the study were considered. Network geometry is given in Fig. 1.

Sample size of patients treated with the active drug and with placebo varied across trials from a minimum of 20 and 16 patients, respectively, to a maximum of 680 and 261 patients.

Mean duration of all double-blind periods (titration plus maintenance) (mean ± SD) was 13.9 ± 8.4 weeks (range 4–60). The duration of the titration period was also highly variable among all RCTs (from no titration up to 16 weeks).

Most of the trials had a low risk of bias (see S6).

Quantitative data synthesis

A total of 18 pairwise comparisons were available for each AED for all-dose analysis and 14 for the high-dose analysis. For three extended release formulations (LTG-ER, PGB-ER,

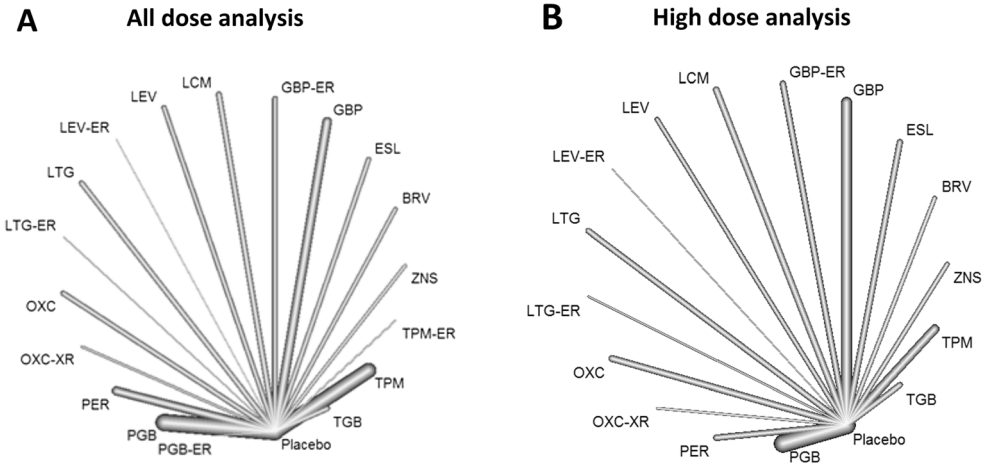

Fig. 1 Network configuration. The greater the *line thickness*, the higher the evidence (i.e., number of studies, number of patients)

and TPM-ER), there were no data for the high-dose analysis. For LTG, it was not possible to isolate patients treated with high doses and only the all-dose analysis has been performed (see Fig. 2).

It was found that all ER formulations do not show a significant difference in respect to placebo, both with the all-dose analysis and with the high-dose analysis. This finding, with the exception of GBP-ER, was likely to be related to their wide CIs. Also BRV, both at all doses and at high doses, and LEV, only at high doses, did not show significant differences compared with placebo. All other AEDs showed a significantly lower tolerability compared to placebo. Increased OR values for the high-dose analysis in respect to full-dose analysis were found for ESL, LCM, OXC, PER, PGB, TPM, and ZNS.

Head-to-head comparisons both for all-dose analyses and for high-dose analyses are shown in S7.

In Table 1, only those comparisons which displayed significant findings are indicated for each AED. It is shown that BRV, GBP, GBP-ER, and LEV have a significantly lower withdrawal rate compared with several other drugs, while ESL, LCM, OXC, and TPM showed a worse performance. Perampanel, LTG, PGB, TGB, and ZNS show an intermediate pattern of tolerability. Non-significant findings were observed for head-to-head comparisons of all ER formulations (with the exception of GBP-ER), and this was likely due to the wide CI.

Rank analysis, which indicates the probability score that a drug is associated to the lowest withdrawal rate, is shown in Fig. 3 both for all-dose analysis and for high-dose analysis.

Finally, we performed a further analysis excluding those studies or arms of studies in which patients were randomized without titration. This study design was adopted with 7 AEDs for a total of 25 RCTs. In 5 of these studies, the experimental drug was BRV, in 9 it was GBP, in 1 LEV, in 1 LEV-ER, in 1 PER, in 7 PGB, and in 1 ZNS. Briefly, with this analysis LEV tolerability was slightly further improved and this drug appeared significantly better tolerated not only as compared with ESL and OXC (as shown in the general all-dose analysis above reported) but also in comparison with TPM. In the case of BRV, IC became very wide and all findings related to this drug became non-significant. Also in the case of PER, wider IC caused the loss of a significant better profile of PER in respect to ESL at high doses. For the AEDs PGB, GBP, LEV-ER, and ZNS, no changes were observed compared with the general all-dose analysis above reported. Detailed data are reported in S8.

There was no significant heterogeneity/inconsistency among comparisons investigated. Namely, I^2 of the proportions was 9.5% (Q = 185.5; P value =0.168) for all doses and 16.9% (Q = 138.4; P value =0.067) for high-dose analyses.

Discussion

This analysis of comparative tolerability of 18 new AEDs has assessed the number of patients withdrawing because of AEs, which is considered a robust tolerability outcome measure, in a population of almost 46,000 patients recruited in 195 RCTs, and several significant and consistent findings have been detected (see Fig. 2, Table 1, and S7). Figure 3 shows that drug tolerability has a probability score of being associated with the lowest withdrawal rate (placebo) which ranges from about 80% for GBP to about 10% for OXC.

Several previous NMAs, performed with the aim to compare both efficacy and tolerability of AEDs used as add-on drugs in focal epilepsies, came to non-significant or contradictory results [6–9]. There are several factors which have limited the validity of these analyses [10]. These are the small number of subjects which are often included in the meta-analyses, with consequent wide confidence intervals and lack of significant results and, most importantly, the heterogeneity of casistics and methods of analysis of efficacy data among different RCTs [10, 11]. However, some heterogeneity sources which limit the validity of assessment of efficacy do not apply to the assessment of tolerability [10, 11]. In fact, date of publication [11, 12, 20] and different techniques of analysis (last

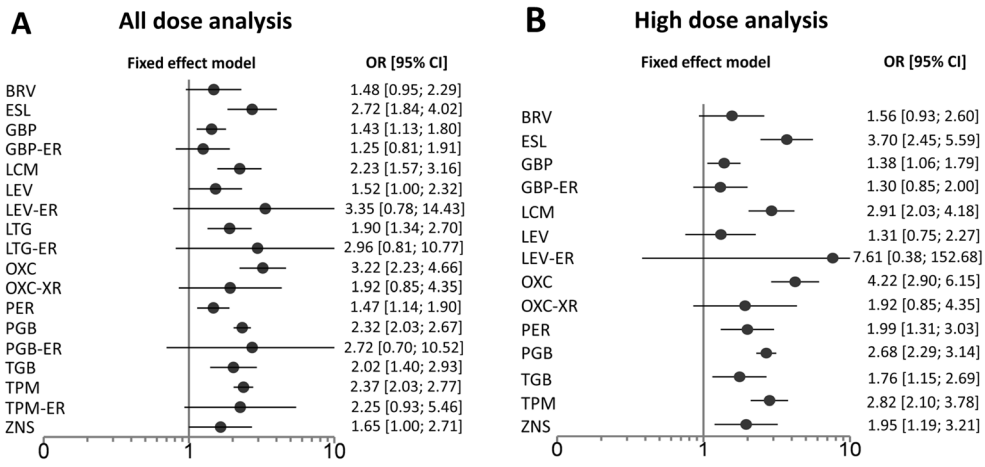

Fig. 2 Funnel plot. Odds ratio (OR) with 95% confidence intervals (ICs) of all comparisons of each antiepileptic drug with placebo

Table 1 Summary of the most important findings of this meta-analysis

Antiepileptic drug	Analysis	Significantly better than	Significantly worse than
Brivaracetam	All doses	Eslicarbazepine, oxcarbazepine, topiramate	
	High doses	Eslicarbazepine, lacosamide, oxcarbazepine, pregabalin, topiramate	
Eslicarbazepine	All doses		Gabapentin, gabapentin-ER, perampanel
	High doses		Brivaracetam, gabapentin, gabapentin-ER, levetiracetam, perampanel, tiagabine
Gabapentin	All doses	Eslicarbazepine, lacosamide, oxcarbazepine, pregabalin, topiramate	
	High doses	Eslicarbazepine, lacosamide, oxcarbazepine, pregabalin, topiramate	
Gabapentin-ER	All doses	Eslicarbazepine, lacosamide, oxcarbazepine, pregabalin, topiramate	
	High doses	Eslicarbazepine, lacosamide, oxcarbazepine, pregabalin, topiramate	
Lacosamide	All doses		Gabapentin, gabapentin-ER
	High doses		Brivaracetam, gabapentin, gabapentin-ER, levetiracetam
Levetiracetam	All doses	Eslicarbazepine, oxcarbazepine	
	High doses	Eslicarbazepine, lacosamide, oxcarbazepine, pregabalin, topiramate	
Lamotrigine	All doses	Oxcarbazepine	
Oxcarbazepine	All doses		Brivaracetam, gabapentin, gabapentin-ER, levetiracetam, lamotrigine, perampanel, zonisamide
	High doses		Brivaracetam, gabapentin, gabapentin-ER, levetiracetam, perampanel, pregabalin, tiagabine, zonisamide
Perampanel	All doses	Eslicarbazepine, oxcarbazepine, pregabalin, topiramate	
	High doses	Eslicarbazepine, oxcarbazepine	
Pregabalin	All doses		Gabapentin, gabapentin-ER, perampanel
	High doses	Oxcarbazepine	Brivaracetam, gabapentin, gabapentin-ER, levetiracetam
Tiagabine	All doses		
	High doses	Eslicarbazepine, oxcarbazepine	
Topiramate	All doses		Brivaracetam, gabapentin, gabapentin-ER, perampanel
	High doses		Brivaracetam, gabapentin, gabapentin-ER, levetiracetam
Zonisamide	All doses	Oxcarbazepine	
	High doses	Oxcarbazepine	

For each AED, only significant results of each comparison with all other antiepileptic drugs are reported. For explanation, see text

observation carried forward analysis) [11] heavily influence the assessment of efficacy, while they do not affect the withdrawal rate [11, 12].

Furthermore, analysis of AED tolerability may be easier to accomplish and can be conducted in a wider population of patients since also studies in conditions different from epilepsy can be included [20, 21].

Three critical points may affect the results of this comparative analysis.

The first point is related to the AED dose. It is known that short-term adverse events, which may lead to drug withdrawal, are critically influenced by dose [21–24]. Therefore, equieffective doses of drugs should be compared. Unfortunately, equieffective doses of AEDs are unknown; furthermore, in several RCTs, they have been tested also at doses which are now considered as ineffective or higher than the range of effective doses. For this reason, we excluded from our analysis doses outside the range of therapeutic doses. Results of full-dose analysis show that BRV, GBP, GBP-ER, LEV, LTG, PER, and ZNS were significantly better tolerated than one or more of the remaining AEDs, while ESL, LCM, OXC, PGB, and TPM showed a significantly worse tolerability compared to other drugs. TGB was neither better nor worse than other AEDs.

To explore the specific role of high doses in inducing intolerable adverse events, a further analysis has been performed only with high recommended doses. A worsened tolerability was observed with the high-dose analysis for the AEDs ESL,

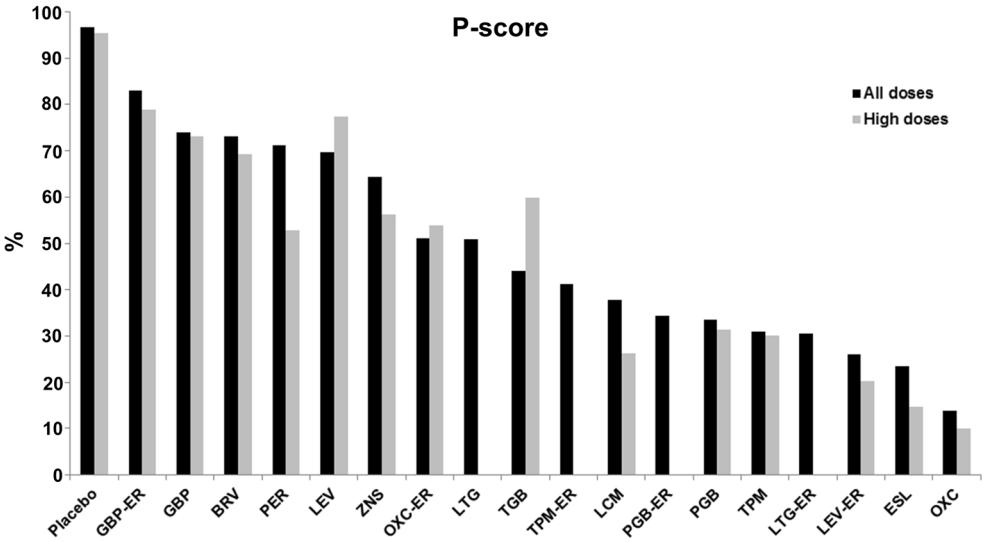

Fig. 3 *P* rank scores of all assessed antiepileptic drugs. *P* rank scores indicate the probability scores to rank which treatments result associated to the lowest withdrawal rate

PER, LCM, and OXC and, to a lesser degree, for ZNS, PGB, and TPM (Figs. 2 and 3). Tolerability of BRV and GBP was not apparently influenced by the dose. In the case of LEV, an apparent mild improvement of tolerability at high doses confirms a lack of a dose-effect relationship for the adverse effects of this drug [25]. From a general point of view, results of these analyses show that, although drug tolerability is often worsened at high doses, this dose-effect does not have a major impact in the overall picture of relative comparability of AEDs. It seems that drug tolerability, within the range of therapeutic doses, is more dependent on the selected drug than on drug dose.

A second critical point is titration. Several studies show that titration speed may have a relevant role for the appearance of dose-dependent adverse events [21–24, 26–28]. However, titration speeds were very different in the different selected RCTs and we could only assess the effect of titration excluding studies or arms of studies in which patients were randomized without any titration. In this subanalysis, LEV tolerability resulted mildly improved, while for the other 6 AEDs which had RCTs excluded from the analysis, no changes (GBP, LEV-ER, PGB, ZNS) or inconsistent results (BRV, PER) were found, mainly because of wider ICs (see S8).

It can be speculated that titration in RCTs is set at different speeds which depend on the characteristics of each drug (as assessed in phase 1 and 2 studies) and represents a compromise between the need to minimize intolerable AEs and that of avoiding unnecessary long double-blind periods.

A third critical point is represented by the fact that drug tolerability in RCTs can be affected by several factors unrelated to the experimental drug, such as tolerability of background treatments (in add on studies), the disease for which these drugs have been studied, and different times and geographical areas in which studies have been done [12, 29]. However, although some of these factors have a major impact on efficacy, tolerability seems to be less influenced by them. In fact, in a meta-analysis of all double-blind RCTs conducted in patients with focal epilepsy, proportions of placebo-treated patients withdrawing because of adverse effects were only mildly influenced by the condition explored [29]. A further meta-analysis of all double-blind studies performed with PGB showed that risk difference of patients who withdrew because of adverse effects was not affected by the condition explored [30]. In the case of other AEDs, concomitant treatments may influence tolerability as it has been shown with LCM [31]. Finally, we cannot exclude that efficacy of the experimental agent in a specific condition may influence tolerability, since patients experiencing no or marginal improvements would be more prone to find their AEs as intolerable.

As regards ER formulations of six AEDs, due to the small number of patients recruited, no significant findings were observed for any of these AEDs with the exception of GBP-ER which had an excellent tolerability, very similar to that of its immediate-release formulation.

In conclusion, this comparative meta-analysis constitutes an objective assessment of relative short-term tolerability of AEDs. It is known that frequency and severity of drug-related adverse effects are influenced both by biological and by psychological factors and that their assessment is highly dependent on the clinical and/or experimental setting [12]. Therefore, these effects can be precisely assessed only in placebo-controlled studies and, due to the lack of large comparative controlled studies, this indirect comparison may constitute the only way to approach the problem. It can be expected that, for each of the AEDs tested, different percentages of patients treated with high or therapeutic doses, different percentages of patients randomized to optimal or suboptimal speed titrations, and finally different percentages of patients with different conditions or concomitant treatments may have influenced results of this comparative analysis. However, we

are convinced these aspects cannot offset the detected differences in short-term tolerability between these AEDs.

BRV, GBP, and LEV show the best tolerability profile while other AEDs are at higher risk for intolerable adverse effects. Incidentally, those AEDs which had a better tolerability profile (BRV and GBP) were also those for which no titration had been adopted in several of their studies, which is consistent with their excellent tolerability pattern.

Contributions of authors GZ proposed the project, wrote the protocol, carried out the review, and wrote the article. FG and UB made all analyses. VF performed literature search. GZ, FG, FSG, VF, and SG extracted data for a subset of included articles, cross-checked the results, and assessed eligibility and risk of bias. All authors commented on or edited sections of the article.

Compliance with ethical standards

Ethics statement 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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