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SPECIAL REPORT

# Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

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## Summary

**The purpose of this report was to update the 2006 International League Against Epilepsy (ILAE) report and identify the level of evidence for long-term efficacy or effectiveness for antiepileptic drugs (AEDs) as initial monotherapy for patients with newly diagnosed or untreated epilepsy. All applicable articles from July 2005 until March 2012 were identified, evaluated, and combined with the previous analysis (Glauser et al., 2006) to provide a comprehensive update. The prior analysis methodology was utilized with three modifications: (1) the detectable noninferiority boundary approach was dropped and both failed superiority studies and prespecified noninferiority studies were analyzed using a noninferiority approach, (2) the definition of an adequate comparator was clarified and now includes an absolute minimum point estimate for efficacy/effectiveness, and (3) the relationship table between clinical trial ratings, level of evidence, and conclusions no longer includes a recommendation column to reinforce that this review of efficacy/evidence for specific seizure types does not imply treatment recommendations. This evidence review contains one clarification: The commission has determined that class I superiority studies can be designed to detect up to a 20% absolute (rather than relative) difference in the point estimate of efficacy/effectiveness between study treatment and comparator using an intent-to-treat analysis. Since July, 2005, three class I randomized controlled trials (RCT) and 11 class III RCTs have been published. The combined analysis (1940–2012) now includes a total of 64 RCTs (7 with class I evidence, 2 with class II evidence) and 11 meta-analyses. New efficacy/effectiveness findings include the following: levetiracetam and zonisamide have level A evidence in adults with partial onset seizures and both ethosuximide and valproic acid have level A evidence in children with childhood absence epilepsy. There are no major changes in the level of evidence for any other subgroup. Levetiracetam and zonisamide join carbamazepine and phenytoin with level A efficacy/effectiveness evidence as initial monotherapy for adults with partial onset seizures. Although ethosuximide and valproic acid now have level A efficacy/effectiveness evidence as initial monotherapy for children with absence seizures, there continues to be an alarming lack of well designed, properly conducted epilepsy RCTs for patients with generalized seizures/epilepsies and in children in general. These findings reinforce the need for multicenter, multinational efforts to design, conduct, and analyze future clinically relevant adequately designed RCTs. When selecting a patient's AED, all relevant variables and not just efficacy and effectiveness should be considered.**

**KEY WORDS: Antiepileptic drug, Efficacy, Effectiveness, Monotherapy.**

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## Background

In 2006, the International League Against Epilepsy (ILAE) published a review (Glauser et al., 2006) aimed at providing an evidence-based answer to the following question: "For patients with newly diagnosed or untreated epilepsy, which AEDs have the best evidence for long term efficacy or effectiveness as initial monotherapy?" This restricted focus resulted from the inability to address all the other variables that affect initial antiepileptic drug (AED) selection in an evidence-based fashion. The ILAE subcommission of AED Guidelines decided to update its previous publication based on its impact coupled with the subsequent publication of new efficacy and effectiveness randomized controlled trials (RCTs) in patients with new-onset epilepsy.

## Purpose of this Evidence Review and Definition of Terms

The purpose of this review is to provide clinicians worldwide with an analysis of the existing AED efficacy/effectiveness evidence for initial monotherapy use in patients with epilepsy. The definitions, sources of data, and scope of this review are identical to those used in the previous review (Glauser et al., 2006). The ultimate judgment for therapy must be made in the light of all the clinical data presented by the patient and by the treatment options that are locally available for the patient and his/her clinician.

## Methods

### Description of analytical process

This update uses the previous report's methodology (Glauser et al., 2006) with three modifications. The first two of these modifications are needed to address analysis and adequate comparator issues resulting from trials published since the last review.

*Modification 1*

*The detectable noninferiority boundary (DNIB) approach is dropped, and both failed superiority studies and prespecified noninferiority studies are analyzed using a noninferiority approach.* After discussion, the commission determined that the DNIB approach is not adequate to rigorously demonstrate if a failed superiority study actually shows noninferiority between study treatments. As such, the commission has replaced the DNIB approach with an approach that applies the same standards of analysis to both prespecified noninferiority studies and failed superiority studies. This modification affects both the classification criteria for article evaluation (Table 1) and the rating scale of evidence for potentially relevant studies (Table 2). In Table 1, the fourth criterion (for superiority trials) has been changed and a fifth criterion (for noninferiority trials) has been added.

To determine if noninferiority existed, the analysis used (1) per-protocol study population data (for age/seizure type subgroups), (2) the lower limit of the 95% confidence interval for the study drug's efficacy/effectiveness outcome, and (3) a lower boundary based on the adequate comparator's point estimate of efficacy/effectiveness. Specifically, an acceptable lower cutoff value was determined by calculating 20% of the adequate comparator's efficacy/effectiveness point estimate and then subtracting this relative 20% value from the adequate comparator's efficacy/effectiveness point estimate. Once this lowest acceptable cutoff was established, the 95% lower confidence limit for the drug evaluated was calculated using a per-protocol study population (for age/seizure type subgroups). The study treatment was considered noninferior if its 95% lower confidence limit was above this lower acceptable cutoff. For example, if the adequate comparator's point efficacy was 55%, the study treatment would be considered noninferior if the lower limit of its 95% confidence interval for efficacy was >44% (since in this example 44% is the 20% lower boundary relative to the adequate comparator's point estimate for efficacy of 55%). If the failed superiority study did not provide per-protocol population data (for age/seizure type subgroups), the study was considered a class III study.

*Modification 2*

*The definition of an adequate comparator has been clarified and also now includes an absolute minimum point estimate for efficacy/effectiveness of 50% and thus a lower boundary of 40% for noninferiority comparisons.* An acceptable comparator for a specific seizure/epilepsy/age category is defined as a drug shown to be either.

**a** Superior to another drug, another dose of the same drug or another treatment modality or placebo for that seizure/epilepsy/age category in at least one class I predefined superiority trial or (if no class I studies exist) one class II predefined superiority trial.

OR

**b** Superior or noninferior to another drug previously established as an adequate comparator for that seizure/epilepsy/age category in at least one class I trial.

This absolute lower limit for an adequate comparator's point estimate and lower boundary prevents a series of noninferiority trials from identifying well-tolerated yet inefficacious AED(s) as adequate comparator(s).

Although not affecting the results of this update, these two modifications are included in Table 1 in anticipation that they will affect future versions of this review. A schematic diagram of how this modified scoring system works for efficacy and effectiveness studies is shown in Figure 1.

*Modification 3*

*The recommendations column in Table 3 has been removed.* This change was done to minimize the risk of a

**Table 1. Updated classification criteria for article evaluation**

| Criteria | Required | Comment/Example |
|---|---|---|
| Primary outcome variable | Clearly defined<br>Either effectiveness (patient retention) or efficacy (seizure freedom) | Ideal: Assessment of retention after a minimum of 48-week treatment for all seizure types<br>Ideal: Assessment of efficacy based on a minimum of 24-week seizure freedom for all seizure types |
| Minimal duration of treatment | Appropriate for assessing the primary outcome variable for the seizure type or epilepsy syndrome under consideration | Ideal: The minimal duration of treatment for seizure and epilepsy types addressed is 48 weeks |
| Potential for bias | Enrollment or treatment bias minimized by double blinding and description of treatment groups baseline characteristics | Ideal: Double-blind clinical trial design |
| For superiority trials: | A positive superiority trial is acceptable<br>OR<br>A superiority trial failing to identify a difference between treatments ("failed superiority trial") will be reanalyzed using the study's per-protocol study population (for age/seizure type subgroups). The study treatment's efficacy/effectiveness lower limit (95% confidence interval) will be compared to a lower boundary of efficacy/effectiveness relative to the adequate comparator's point estimate of efficacy/effectiveness | Ideal: A positive superiority trial or a failed superiority trial where the study treatment's efficacy lower limit (95% confidence interval) is above a lower cutoff relative to the adequate comparator's point estimate of efficacy/effectiveness. The cutoff uses a per-protocol study population (for age/seizure type subgroups) and is calculated by a 20% relative reduction from an adequate comparator efficacy/effectiveness point estimate. In a noninferiority analysis, the lower boundary for an adequate comparator's efficacy/effectiveness will never be <40% |
| For noninferiority trials: | Noninferiority trials will be analyzed using the study's per-protocol study population (for age/seizure type subgroups). The study treatment's efficacy/effectiveness lower limit (95% confidence interval) will be compared to a lower boundary of efficacy/effectiveness relative to the adequate comparator's point estimate of efficacy/effectiveness | Ideal: A noninferiority trial where the study treatment's efficacy/effectiveness lower limit (95% confidence interval) is above a 20% lower boundary relative to the adequate comparator's point estimate of efficacy/effectiveness using a per-protocol study population (for age/seizure type subgroups). In this noninferiority analysis, the lower boundary for an adequate comparator's efficacy/effectiveness will never be <40% |
| Statistical analysis | Appropriate statistical analysis presented or data presented allowing for statistical analysis | |

reader confusing the review's conclusion that an AED has evidence of seizure type–specific efficacy/effectiveness as an ILAE global recommendation of that AED for all patients with that seizure type. As stated above, the paucity of available evidence for all the other variables that affect initial AED selection limits this review's ability to make purely evidence-based treatment recommendations. Selection of the initial AED therapy for a person with newly diagnosed or untreated seizures requires integration of evidence and expert opinion for the patient-specific, AED-specific, and nation-specific variables that can impact overall response to therapy.

There were no other changes or modifications to the level of evidence classification approach or the relationship between clinical trial ratings, level of evidence, and conclusions about efficacy/effectiveness as initial monotherapy (Table 3). There remain six levels, labeled A–F; the relationship between level of evidence and clinical trial rating is shown in Table 3. Levels A through D are defined by specific combinations of clinical trials ratings (based on the criteria in Table 1). AEDs with level A evidence have the highest supporting level of clinical trial evidence, followed sequentially by levels B, C, and D. For any AED, level E evidence indicated there are no published clinical trial reports of the AED's use as initial monotherapy for a specific seizure type/epilepsy syndrome. Level F indicates documented evidence of the AED's lack of efficacy and effectiveness or AED-associated seizure aggravation.

### *This evidence review contains one clarification*

#### *Clarification 1*

*The commission has determined that class I superiority studies be designed to detect a >20% absolute (rather than relative) difference in the primary outcome (i.e., efficacy/effectiveness) between study treatment and comparator using an intent-to-treat analysis.* The previous ILAE treatment report stated that superiority studies should be designed to a >20% relative difference (using 80% power and type I error set at $\leq 0.05$) in the primary outcome (i.e., efficacy/effectiveness) between study treatment and comparator using an intent-to-treat analysis. This new absolute difference standard has been detected in previously

**Table 2. Rating scale of evidence for potentially relevant studies**

| Class | Criteria |
|---|---|
| I | A prospective, randomized, controlled clinical trial (RCT) or meta-analysis of RCTs, in a representative population that meets all six criteria:<br>Primary outcome variable: efficacy or effectiveness<br>Treatment duration: ≥48 weeks<br>Study design: double blind<br>Design:<br>For superiority trials: superiority demonstrated<br>For noninferiority trials or failed superiority trials: the study treatment's efficacy/effectiveness lower limit (95% confidence interval) is above a 20% lower boundary relative to the adequate comparator's point estimate of efficacy/effectiveness using a per-protocol study population (for age/seizure type subgroups).<br>Study exit: Not forced by a predetermined number of treatment emergent seizures<br>Appropriate statistical analysis |
| II | An RCT or a meta-analysis meeting all the class I criteria except that<br>Treatment duration: ≥24 weeks but <48 weeks<br>OR<br>Design: For noninferiority trials or failed superiority trials: the study treatment's efficacy/effectiveness lower limit (95% confidence interval) is between the 21% and 30% lower boundary relative to the adequate comparator's point estimate of efficacy/effectiveness using a per-protocol study population (for age/seizure type subgroups) |
| III | An RCT or a meta-analysis not meeting the criteria for any class I or class II category. Examples include:<br>An open-label study<br>A study with a forced exit criterion<br>A failed double-blind superiority study, where data from the study's "per-protocol" population (for age/seizure type subgroups) is not provided<br>A prespecified noninferiority study or a failed double-blind superiority study, where the study treatment's efficacy/effectiveness lower limit (95% confidence interval) is below the 30% lower boundary relative to the adequate comparator's point estimate of efficacy/effectiveness using a per-protocol study population (for age/seizure type subgroups)<br>For noninferiority studies, lack of using an adequate comparator when one exists |
| IV | Evidence from nonrandomized, prospective, controlled or uncontrolled studies, case series, or expert reports |

successful class 1 superiority studies (Mattson et al., 1985; Chadwick, 1999; Glauser et al., 2010) and sets a practical and clinically relevant efficacy/effectiveness threshold for superiority trial design. This >20% absolute difference for class 1 superiority trials is in contrast to the up to 20% relative difference boundary for class 1 noninferiority studies. This difference in approach reflects two distinct yet complementary goals: using superiority trials to identify AEDs that have clinically significantly higher rates of efficacy/effectiveness compared to adequate comparators while limiting the risk that a series of noninferiority trials will identify as acceptable well-tolerated yet inefficacious AEDs.

For this update, articles were considered potentially relevant if they were published between July 4, 2005 (the cutoff for the previous report) and March 31, 2012, their primary outcome measure was efficacy or effectiveness, and the size of each seizure type subgroup was stated. For the 2005–2012 interval literature searches, lacosamide and rufinamide were added to the previous report's list of 36 AEDs. In addition, literature searches were conducted for potassium bromide and trimethadione initial monotherapy clinical trials published before March 31, 2012. As with the previous report, pharmaceutical companies were asked to supplement missing data from any publicly known RCTs and for any unpublished potentially relevant clinical trials.

## Results

### Study and meta-analysis identification

The search strategies for this evidence review were identical to the 2006 report, except for publication dates searched (now up to March 31, 2012) and the addition of four AEDs (lacosamide, rufinamide, potassium bromide, or trimethadione). These computerized searches were last performed on March 31, 2012. The resulting studies were reviewed for relevance and placed into one of the eight seizure type or epilepsy syndrome categories. The reference lists of all included studies were reviewed to identify any additional relevant studies not identified by the above-mentioned searches. In total, 14 relevant RCTs were identified (Sobaniec et al., 2005; Steinhoff et al., 2005; Brodie et al., 2007; Coppola et al., 2007; Levisohn & Holland, 2007; Marson et al., 2007a,b,c; Saetre et al., 2007; Glauser et al., 2010; Ramsay et al., 2010; Eun et al., 2011; Fattore et al., 2011; Kwan et al., 2011; Baulac et al., 2012), some of which were included in multiple categories.

A search of the Cochrane library and medical literature yielded four additional completed and relevant published new meta-analyses (Gamble et al., 2006a,b; Muller et al., 2006; Koch & Polman, 2009) and one updated one (Posner et al., 2005). Additional information was requested and received about one pharmaceutical company sponsored and one National Institutes of Health sponsored RCT (Glauser et al., 2010). With these additional RCTs and meta-analyses, a total of 64 RCTs and 11 meta-analyses were included as sources in the development of this updated evidence review.

### Adults with partial onset seizures

*Overview of evidence*

Since the last report, a total of six RCTs (Steinhoff et al., 2005; Brodie et al., 2007; Marson et al., 2007a; Ramsay et al., 2010; Kwan et al., 2011; Baulac et al., 2012) and four new meta-analyses (Gamble et al., 2006a,b; Muller et al., 2006; Koch & Polman, 2009) examined the effi-

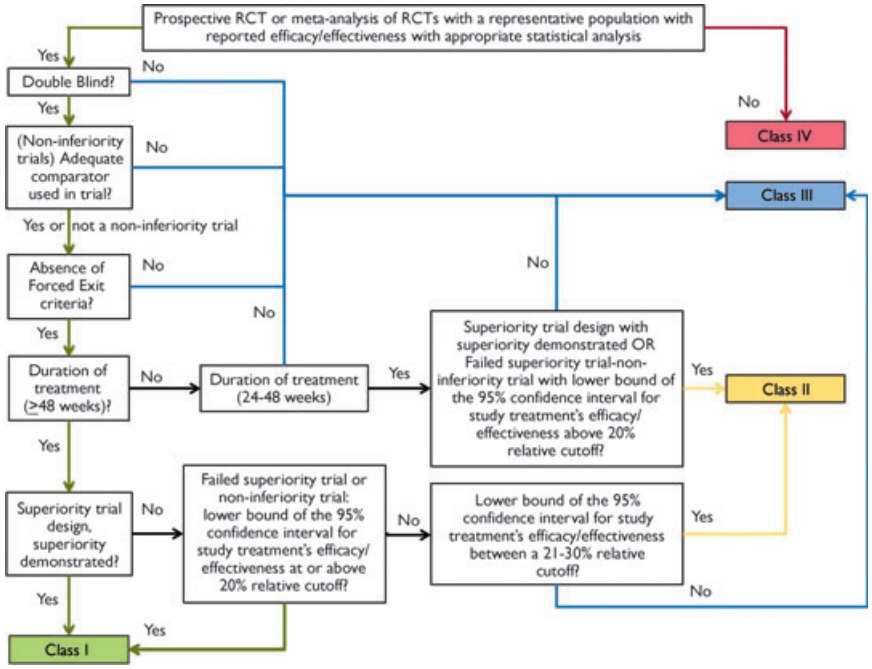


**Figure 1.**
Application of evidence rating criteria for efficacy/effectiveness studies.
*Epilepsia* © ILAE

**Table 3. Relationship between clinical trial ratings, level of evidence, and conclusions**

| Combination(s) of clinical trial ratings | Level of evidence | Conclusions |
|---|---|---|
| ≥ 1 Class I studies or meta-analysis meeting class I criteria sources OR ≥ 2 Class II studies | A | AED established as efficacious or effective as initial monotherapy |
| 1 Class II study or meta-analysis meeting class II criteria | B | AED probably efficacious or effective as initial monotherapy |
| ≥ 2 Class III double-blind or open-label studies | C | AED possibly efficacious or effective as initial monotherapy |
| 1 Class III double-blind or open-label study OR ≥ 1 Class IV clinical studies OR Data from expert committee reports, opinions from experienced clinicians | D | AED potentially efficacious or effective as initial monotherapy |
| Absence of directly applicable clinical evidence upon which to base a recommendation | E | No data available to assess if AED is effective as initial monotherapy |
| Positive evidence of lack of efficacy or effectiveness based on class I to IV studies OR Significant risk of seizure aggravation based on class I to IV studies | F | AED established as ineffective or significant risk of seizure aggravation |

cacy/effectiveness of initial monotherapy of adults with partial-onset seizures. Among the six RCTs, two were considered class I studies (Brodie et al., 2007; Baulac et al., 2012), whereas the other four met criteria for class III studies because of an open-label design (Steinhoff et al., 2005; Marson et al., 2007a), too brief treatment duration (Steinhoff et al., 2005; Ramsay et al., 2010), or lack of an adequate comparator (Kwan et al., 2011).

Combined with the previous 33 RCTs from the last report, carbamazepine (CBZ) remains the most frequently studied (n = 23), followed by phenytoin (PHT) (n = 12) and valproate (VPA) (n = 11) (Sommerfeld-Ziskin, 1940; Mikkelsen et al., 1981; Shakir et al., 1981; Gibberd et al., 1982; Turnbull et al., 1982; Ramsay et al., 1983, 2010; Loiseau et al., 1984; Callaghan et al., 1985; Mattson et al., 1985; Turnbull et al.,1985; Dam et al., 1989; Feksi et al., 1991; Rastogi et al., 1991; Mattson et al., 1992; Placencia et al., 1993; Richens et al., 1994; Brodie et al., 1995; Heller et al., 1995; Kalviainen et al., 1995; Reunanen et al., 1996; Tanganelli & Regesta, 1996; Bill et al., 1997; Christe et al., 1997; Chadwick et al., 1998; Chadwick, 1999; Steiner et al., 1999; Nieto-Barrera et al., 2001; Brodie et al., 2002a,b; Gilliam et al., 2003; Privitera et al., 2003; Pharmaceutical, 2004; Arroyo et al., 2005). The number of studies for each AED and their distribution by RCT class of evidence is shown in Table S1.

*Summary of new evidence*

In this update, only two AEDs (levetiracetam [LEV] and zonisamide [ZNS]) had new class I or class II evidence

regarding efficacy or effectiveness in adults with partial-onset seizures. Seven AEDs (CBZ, lamotrigine [LTG], oxcarbazepine [OXC], pregabalin [PGB] PHT, topiramate [TPM], and gabapentin [GBP]) had additional class III evidence regarding efficacy or effectiveness in adults with partial-onset seizures.

*CBZ, LEV, ZNS (Class I, n = 2).* A 2007 noninferiority trial compared LEV to controlled-release CBZ in 579 adults with epilepsy (Brodie et al., 2007). For the subset of patients with partial-onset seizures, the 6-month seizure-free rate was 73.3% for the 202 per-protocol patients on the CBZ arm (20% relative lower bound 58.6%) compared to a 6-month seizure-free rate of 72.5% for the 207 per-protocol patients on the LEV arm (one-sided 95% lower bound confidence interval [CI] 66.4%). These results met this evidence review's criteria for a successful noninferiority trial. The initial target LEV dose was 500 mg twice daily and the controlled-release initial target CBZ dose was 200 mg twice daily. The study protocol allowed dosage adjustments based on clinical response, with three different target dose levels.

A 2012 noninferiority trial compared ZNS with controlled-release CBZ monotherapy in 583 untreated adults with new-onset partial epilepsy (Baulac et al., 2012). Following initiation (ZNS 100 mg/day, CBZ 200 mg/day) and uptitration (to 300 and 600 mg/day, respectively), patients entered a 26–78 week flexible dosing period according to response/tolerability. Primary outcome measure was proportion of patients achieving seizure-freedom for 26 weeks. Overall, 57.1% patients randomized to ZNS and 63.8% to CBZ group completed the trial. On per-protocol primary analysis, 26 week seizure-freedom rates were 79.4% for ZNS (one sided 95% lower bound confidence interval 73.2%) versus 83.7% for CBZ (20% relative lower bound 67.0%). These results met this evidence review's criteria for a successful noninferiority trial.

*CBZ, LTG, OXC, PGB, PHT, TPM, and GBP (Class III, n = 4).* A 2007 large-scale, open-label RCT compared CBZ, GBP, LTG, OXC, and TPM in 1,721 patients with partial-onset seizures (Marson et al., 2007a). LTG was superior to CBZ, GBP, and TPM for time to treatment failure. CBZ was superior to GBP for time to 12-month remission. A per-protocol analysis, at 2 and 4 years, suggested noninferiority of LTG compared with CBZ in the proportion achieving a 12-month remission. A 2005 open-label superiority RCT compared LTG and CBZ as 24-week monotherapy in patients 12 years and older with newly diagnosed partial-onset epilepsy (Steinhoff et al., 2005). The seizure-free rate for the 88 LTG patients was similar to that for the 88 CBZ patients. A 2010 double-blind noninferiority RCT compared TPM (n = 132) and PHT (n = 127) monotherapy in patients 12–65 years of age with new-onset epilepsy (Ramsay et al., 2010). At day 28, the estimated seizure-free rate, modeled using survival analysis, was 81% for TPM versus 90.3% for PHT. Pregabalin (n = 330) and LTG (n = 330) were compared in a double-blind, noninferiority design with primary efficacy endpoint being proportion of patients who remained seizure free for 6 or more continuous months during a 52-week efficacy assessment phase. PGB was inferior to LTG on both intention-to-treat (52% vs. 68%, estimated true difference in proportion, −0.16 with 95% CI from −0.24 to −0.09) and per-protocol analyses, (difference −0.16 with 95% CI from −0.24 to −0.08) (Kwan et al., 2011). However, LTG is not considered an adequate comparator in this seizure type and the study is class III rather than class I.

*Meta-analyses.* Four recent meta-analyses examined AED efficacy and effectiveness for adults with partial-onset seizures (Gamble et al., 2006a,b; Muller et al., 2006; Koch & Polman, 2009). Two of these meta-analyses examined LTG versus CBZ (Gamble et al., 2006a,b), whereas the others focused on OXC versus PHT (Muller et al., 2006) and OXC versus CBZ (Koch & Polman, 2009). The meta-analyses had similar end points: time to withdrawal, number of patients achieving 6 or months or more seizure freedom, and time to first seizure. Most data used in these meta-analyses were from class III studies. The meta-analyses found that "OXC is significantly better than PHT for time to treatment withdrawal, but suggest no overall difference between OXC and PHT for other outcomes" (Muller et al., 2006), "OXC and CBZ appear to be similarly effective and well tolerated" with "no overall difference in time to treatment withdrawal" between them (Koch & Polman, 2009), and that "LTG is significantly less likely to be withdrawn than CBZ, but results for time to first seizure suggest a nonsignificant trend that CBZ may be superior in terms of seizure control" (Gamble et al., 2006a,b). The authors identify significant methodologic flaws in the underlying clinical trials that limit the direct applicability of the results to clinical practice.

*Conclusions*

**1** There are four adequate comparators for this category: CBZ, LEV, PHT, and ZNS.

**2** CBZ, LEV, PHT, and ZNS are established (level A); VPA is probably (level B); GBP, LTG, OXC, phenobarbital (PB), TPM, and vigabatrin (VGB) are possibly (level C); whereas clonazepam (CZP) and primidone (PRM) are potentially (level D) efficacious/effective as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures.

## Children with partial-onset seizures

*Overview of evidence*

Since the last review, two RCTs (Sobaniec et al., 2005; Eun et al., 2011) and four new meta-analyses (Gamble et al., 2006a,b; Muller et al., 2006; Koch & Polman, 2009)

examined initial monotherapy of children with partial-onset seizures. Both RCTs were considered class III studies because of an open-label design, too short treatment duration (Sobaniec et al., 2005; Eun et al., 2011), and a forced exit criteria (Sobaniec et al., 2005). Combined with the previous 18 RCTs (Sommerfeld-Ziskin, 1940; Mikkelsen et al., 1981; Shakir et al., 1981; Loiseau et al., 1984; Callaghan et al., 1985; Feksi et al., 1991; Rastogi et al., 1991; Placencia et al., 1993; Verity et al., 1995; de Silva et al., 1996; Guerreiro et al., 1997; Canadian Study Group for Childhood Epilepsy, 1998; Pal et al., 1998; Zamponi & Cardinali, 1999; Nieto-Barrera et al., 2001; Gilliam et al., 2003; Wheless et al., 2004; Glauser et al., 2007) from the last report, CBZ remains the most frequently studied (n = 12) followed by VPA (n = 7) and PHT (n = 6). The number of studies for each AED and their distribution by RCT class of evidence is shown in Table S2.

*Summary of new evidence*

In this update, no AED has new class I or class II evidence regarding efficacy or effectiveness in children with partial-onset seizures. Three AEDs (CBZ, VGB, and ZNS) had additional class III open-label RCT evidence regarding efficacy or effectiveness in children with partial-onset seizures.

*CBZ, VGB, ZNS (Class III open label [OL], n = 2).* In a class III 24-week, open-label RCT comparing CBZ (n = 28) to VGB (n = 26) in children with new-onset partial seizures, efficacy was similar between the two AEDs (Sobaniec et al., 2005). An open-label ZNS high-dose (6–8 mg/kg/day, n = 59) versus low-dose (3–4 mg/kg/day, n = 65) RCT in children with newly diagnosed epilepsy (81% with partial seizures) found similar 6-month seizure-free rates between the two groups (Eun et al., 2011). There was inadequate information provided about the outcome of the remaining 19% of subjects for further inclusion in this review (Eun et al., 2011).

*Meta-analysis.* Four recent meta-analysis examined AED efficacy and effectiveness in children with new-onset epilepsy. One meta-analysis examined OXC versus PHT monotherapy for epilepsy and included a class I study described previously (Guerreiro et al., 1997). Based on an analysis that included adults, adolescents, and children, the authors concluded: "For patients with partial-onset seizures OXC is significantly less likely to be withdrawn, but current data do not allow a statement as to whether OXC is equivalent, superior, or inferior to phenytoin in terms of seizure control" (Muller et al., 2006). Two meta-analyses examined LTG versus CBZ monotherapy for epilepsy and included studies involving children; however, the total number of children studied was too small to draw any definitive conclusions (Gamble et al., 2006a,b). The last meta-analysis examined CBZ versus OXC. Only one trial used adequate outcome measures of efficacy, but children were not included in that study. Therefore, no conclusions concerning efficacy could be made comparing CBZ and OXC in children (Koch & Polman, 2009).

*Conclusions*

**1** The only adequate comparator for this category is OXC.
**2** OXC is established (level A); CBZ, PB, PHT, TPM, VPA, and VGB are possibly (level C); and clobazam (CLB), CZP, LTG, and ZNS are potentially (level D) efficacious/effective as initial monotherapy for children with newly diagnosed or untreated partial-onset seizures.

### Elderly adults with partial-onset seizures

*Overview of evidence*

Since the last review, only one RCT (Saetre et al., 2007) has examined initial monotherapy of elderly adults with partial-onset seizures. The RCT was considered a class III study because of too short a treatment duration. Combined with the previous four RCTs from the last report (Brodie et al., 1999; Nieto-Barrera et al., 2001; Privitera et al., 2003; Rowan et al., 2005), CBZ remains the most frequently studied (n = 5) followed by LTG (n = 4), GBP (n = 1), TPM (n = 1), and VPA (n = 1). The number of studies for each AED and their distribution by RCT class of evidence is shown in Table S3.

*Summary of evidence*

In this update, no AED has new class I or class II evidence regarding efficacy or effectiveness in elderly adults with partial-onset seizures. Two AEDs (CBZ, LTG) had additional class III double-blind RCT evidence regarding efficacy or effectiveness in elderly adults with partial-onset seizures (Saetre et al., 2007).

*CBZ, LTG (Class III DB, n = 1).* In a class III 40-week, double-blind RCT comparing CBZ (n = 92) to LTG (n = 93) in adults 65 years or older with new-onset partial seizures, there was no difference noted in effectiveness between LTG and sustained-release CBZ, but a trend was seen for higher seizure-free rates for CBZ and better tolerability for LTG (Saetre et al., 2007).

*Conclusions*

**1** The only adequate comparators for this category remain GBP and LTG.
**2** GBP and LTG are established (level A); CBZ is possibly (level C); and TPM and VPA are potentially (level D) efficacious/effective as initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures.

### Adults with generalized-onset tonic–clonic seizures

*Overview of evidence*

Since the last review, four RCTs (Steinhoff et al., 2005; Brodie et al., 2007; Marson et al., 2007b; Ramsay et al., 2010) and four new meta-analyses (Gamble et al., 2006a,b; Muller et al., 2006; Koch & Polman, 2009) examined initial monotherapy of adults with generalized-onset tonic–clonic

seizures. The four recent RCTs were considered class III studies because of either an open-label design (Steinhoff et al., 2005; Marson et al., 2007b), too brief treatment duration (Steinhoff et al., 2005; Ramsay et al., 2010), or lack of an adequate comparator (Brodie et al., 2007).

Combined with the previous 23 RCTs from the last report, CBZ, VPA, and PHT were the most commonly studied AEDs (n = 12 each) (Sommerfeld-Ziskin, 1940; Shakir et al., 1981; Gibberd et al., 1982; Turnbull et al., 1982, 1985; Ramsay et al., 1983, 1992; Callaghan et al., 1985; Dam et al., 1989; Feksi et al., 1991; Rastogi et al., 1991; Placencia et al., 1993; Richens et al., 1994; Brodie et al., 1995, 2002a; Heller et al., 1995; Kalviainen et al., 1995; Reunanen et al., 1996; Bill et al., 1997; Christe et al., 1997; Steiner et al., 1999; Privitera et al., 2003; Arroyo et al., 2005; Ramsay et al., 2010). The number of studies for each AED and their distribution by RCT class of evidence is shown in Table S4.

*Summary of evidence*

In this update, no AED had class I or class II evidence regarding efficacy or effectiveness in adults with generalized-onset tonic–clonic seizures. Six AEDs (CBZ, LEV, LTG, PHT, TPM, and VPA) had additional class III double-blind and open-label RCT evidence regarding efficacy or effectiveness in adults with generalized-onset tonic–clonic seizures.

*CBZ, LEV, LTG, PHT, TPM, and VPA (Class III, n = 4).* A 2007 noninferiority trial compared LEV to controlled release CBZ in 579 adults with epilepsy (Brodie et al., 2007). For the subset of patients with generalized-onset seizures, the 6-month seizure-free rate was 69.7% for the 33 per-protocol patients on the CBZ arm compared to a 6-month seizure-free rate of 76.7% for the 23 per-protocol patients on the LEV arm. However, CBZ is not an adequate comparator for this seizure type, which makes the study a class III trial for this seizure type. A 2007 large scale, open-label RCT compared LTG, VPA, and TPM in 716 patients with generalized-onset and unclassifiable seizures (Marson et al., 2007b). There were a large number of patients with either symptomatic/cryptogenic partial epilepsy or unclassifiable epilepsy. In the subgroup of patients with idiopathic generalized epilepsy, VPA was better than LTG and TPM in time-to-treatment failure and better than LTG but similar to TPM for time to 12-month remission. A 2005 open-label superiority RCT compared LTG and VPA as 24-week monotherapy in patients 12 years and older with newly diagnosed generalized-onset epilepsy (Steinhoff et al., 2005). The seizure-free rate for the 33 LTG patients was similar to that for the 30 VPA patients. A 2010 double-blind noninferiority RCT compared TPM (n = 132) and PHT (n = 127) monotherapy in patients 12–65 years of age with new-onset epilepsy (Ramsay et al., 2010). At day 28, the estimated seizure-free rate, modeled using survival analysis, was 81% for TPM versus 90.3% for PHT.

*Meta-analyses.* Three recent meta-analyses examined AED efficacy and effectiveness for adults with generalized-onset tonic–clonic seizures. Two of these meta-analyses examined LTG versus CBZ (Gamble et al., 2006b), whereas the others focused on OXC versus PHT (Muller et al., 2006) and OXC versus CBZ (Koch & Polman, 2009). Although the LTG versus CBZ meta-analyses contained trials involving adults with generalized-onset tonic–clonic seizures, the authors concluded that the analyses are: "primarily relevant to patients with a partial onset to their seizures for whom CBZ is considered the standard treatment of choice" (Gamble et al., 2006a,b). The OXC versus PHT meta-analysis found: "no significant advantage for either drug for patients with generalized onset seizures" (Muller et al., 2006), whereas the OXC versus CBZ was uninformative on this seizure type (Koch & Polman, 2009). Most data used in these meta-analyses were from class III studies.

*Conclusions*

**1** There are no adequate comparators for this category.

**2** CBZ, LTG, OXC, PB, PHT, TPM, and VPA are possibly (level C) and GBP, LEV, and VGB are potentially (level D) efficacious/effective as initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic–clonic seizures.

**3** Class IV evidence suggests that CBZ and PHT may precipitate or aggravate generalized-onset tonic–clonic seizures (Guerrini et al., 1998; Genton, 2000; Somerville, 2009).

### Children with generalized-onset tonic–clonic seizures

*Overview of evidence*

Since the last review, no new published RCTs have involved this seizure type. The previous report identified 14 class III RCTs for this seizure type (Sommerfeld-Ziskin, 1940; Shakir et al., 1981; Callaghan et al., 1985; Feksi et al., 1991; Rastogi et al., 1991; Placencia et al., 1993; Verity et al., 1995; de Silva et al., 1996; Thilothammal et al., 1996; Guerreiro et al., 1997; Pal et al., 1998; Wheless et al., 2004; Glauser et al., 2007). The continued lack of class I and class II RCTs for children with generalized-onset tonic–clonic seizures implies an ongoing marked deficiency in adequately powered, seizure-type specific published studies. There are no changes to the previous reports data, analysis, or conclusions. No AEDs reach the highest levels of evidence (level A or B) for efficacy/effectiveness for children with generalized-onset tonic–clonic seizures. There is no adequate comparator for this category.

*Conclusions*

**1** There are no adequate comparators for this category.

**2** CBZ, PB, PHT, TPM, and VPA are possibly (level C) and OXC is potentially (level D) efficacious/effective for

children with newly diagnosed or untreated generalized-onset tonic–clonic seizures.

**3** Class IV evidence suggests that CBZ and PHT may precipitate or aggravate generalized-onset tonic–clonic seizures (Guerrini et al., 1998; Genton, 2000; Somerville, 2009).

### Children with absence seizures

*Overview of evidence*

The previous review identified six class III RCTs (Callaghan et al., 1982; Sato et al., 1982; Martinovic, 1983; Trudeau et al., 1996; Frank et al., 1999; Coppola et al., 2004) and one meta-analysis (Posner et al., 2003) for this seizure type. Since the last report, one class I study (Glauser et al., 2010) and one class III study (Fattore et al., 2011) has been published, one meta-analysis has been updated (Posner et al., 2005), and there is a new systematic review (Posner, 2008). The one RCT was considered a class III study because of too short a treatment duration and a forced exit criteria. Combined with the previous six RCTs from the last report, VPA was the most frequently studied AED (n = 5), ethosuximide (ESM) was examined in four studies, LTG in three studies, whereas GBP and LEV in one study each. The number of studies for each AED and their distribution by RCT class of evidence is shown in Table S5.

*Summary of new evidence*

In this update, three AEDs (VPA, ESM, and LTG) had new class I or class II evidence regarding efficacy or effectiveness in children with absence seizures. One AED (LEV) had additional class III evidence regarding efficacy or effectiveness in children with absence seizures.

*VPA, ESM, LTG (Class I, n = 1).* A 2010 double-blind superiority trial compared VPA, ESM, and LTG in 446 children with absence seizures (Glauser et al., 2010). The initial report focused on the short-term (16–20 week) freedom from failure rate, an effectiveness outcome measure defined as seizure freedom without intolerable side effects; the rate was 58% for VPA and 53% for ESM (no significant difference between VPA and ESM), both of which were higher than the rate for LTG (29%; $p < 0.001$ for both comparisons). These findings persisted over the first 12 months of double-blind therapy, allowing this study to qualify as a successful class I study as per this review's criterion (T. Glauser, personal communication). At the 16–20 week visit mark, the mean (±standard deviation [SD]) daily doses were the following: VPA 34.9 ± 15.8 mg/kg/day, ESM 33.5 ± 15.3 mg/kg/day, and LTG 9.7 ± 6.3 mg/kg/day. The study protocol allowed dosage adjustments based on clinical response.

*LEV (Class III, n = 1).* A short-duration double-blind RCT compared LEV and placebo in 59 children with newly diagnosed childhood or juvenile absence epilepsy. Response to LEV was not significantly better to that of placebo.

*Conclusions*

**1** There are two adequate comparators for this category: ESM and VPA.

**2** ESM and VPA are established (level A) and LTG is possibly (level C) efficacious/effective as initial monotherapy for children with newly diagnosed or untreated absence seizures.

**3** GBP is established as inefficacious/ineffective for children with absence seizures (level F). Based solely on scattered reports (class IV), the following AEDs may precipitate or aggravate absence seizures: CBZ, OXC, PB, PHT, TGB, and VGB (Guerrini et al., 1998; Genton, 2000; Somerville, 2009).

**4** No conclusion can be made about LEV's efficacy/effectiveness for absence seizures since the failed class III placebo-controlled trial was uninformative.

### Children with benign childhood epilepsy with centrotemporal spikes (BECTS)

*Overview of evidence*

Since the last review, only one RCT (Coppola et al., 2007) examined initial monotherapy of children with BECTS. The RCT was considered a class III study because of an open-label design. The previous two class III RCTs from the last report were separate placebo-controlled studies of GBP and sulthiame (STM) (Bourgeois et al., 1998; Rating et al., 2000), whereas the new RCT is a comparison of LEV and OXC.

*Summary of new evidence*

*LEV and OXC (Class III OL, n = 1).* A 2007 open-label RCT compared LEV and OXC monotherapy in patients with newly diagnosed BECTS. The seizure-free rate for the 21 LEV children was similar to that for the 18 OXC children (Coppola et al., 2007).

*Conclusions*

**1** There are no adequate comparators for this category.

**2** CBZ and VPA are possibly (level C) and GBP, LEV, OXC, and STM are potentially (level D) efficacious/effective as initial monotherapy for children with BECTS.

### Juvenile myoclonic epilepsy

*Overview of evidence*

Since the last report, one RCT (Levisohn & Holland, 2007) examined initial monotherapy of children with juvenile myoclonic epilepsy (JME). The RCT was considered a class III study because of too short a treatment

duration. There had been no previous RCTs for this category.

*Summary of new evidence*

*TPM and VPA (Class III DB, n = 1).* A 2007 double-blind RCT compared TPM and VPA monotherapy in both newly diagnosed and previously treated JME patients (Levisohn & Holland, 2007). There were only 16 newly diagnosed previously untreated patients among the 28 children in the study. These 16 children were randomized between TPM (n = 12) and VPA (n = 4). The low number of previously untreated patients prevents drawing conclusions from this study.

*Conclusions*

**1** There are no adequate comparators for this category.
**2** TPM and VPA are potentially (level D) efficacious/effective for patients with newly diagnosed JME.
**3** Class IV studies indicate that CBZ, GBP, OXC, PHT, TGB, and VGB may precipitate or aggravate absence seizures, myoclonic seizures, and in some cases generalized tonic–clonic seizures. There has been a report that LTG may exacerbate seizures in JME (level F) (Guerrini et al., 1998; Genton, 2000; Somerville, 2009).

## Discussion

This update evidence review spans six age-related seizure types and two epilepsy syndromes. Conclusions were based on 64 RCTs (completed over the last 72 years) and 11 meta-analyses. A systematic rigorous method of assessment was applied equally to all seizure types and epilepsy syndromes. A summary of the studies and level of evidence for each seizure type and epilepsy syndrome is listed in Table 4.

There continues to be an alarming lack of well-designed epilepsy RCTs, especially for generalized seizures/epilepsies and in children. Three of the seven class I trials in the entire updated evidence review have been conducted during the last decade. This lack of class I and class II trials is not due to an overly strict rating scale but rather a lack of adequate trials. Correcting this problem has been and will continue to be challenging.

The previous report discussed two forms of superiority studies (placebo controlled and high dose-low dose) that

**Table 4. Summary of studies and level of evidence for each seizure type and epilepsy syndrome**

| Seizure type or epilepsy syndrome | Class I studies | Class II studies | Class III studies | Level of efficacy and effectiveness evidence (in alphabetical order) |
|---|---|---|---|---|
| Adults with partial-onset seizures | 4 | 1 | 34 | Level A: CBZ, LEV, PHT, ZNS<br>Level B: VPA<br>Level C: GBP, LTG, OXC, PB, TPM, VGB<br>Level D: CZP, PRM |
| Children with partial-onset seizures | 1 | 0 | 19 | Level A: OXC<br>Level B: None<br>Level C: CBZ, PB, PHT, TPM, VPA, VGB<br>Level D: CLB, CZP, LTG, ZNS |
| Elderly adults with partial-onset seizures | 1 | 1 | 3 | Level A: GBP, LTG<br>Level B: None<br>Level C: CBZ<br>Level D: TPM, VPA |
| Adults with generalized onset tonic–clonic seizures | 0 | 0 | 27 | Level A: None<br>Level B: None<br>Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA<br>Level D: GBP, LEV, VGB |
| Children with generalized-onset tonic–clonic seizures | 0 | 0 | 14 | Level A: None<br>Level B: None<br>Level C: CBZ, PB, PHT, TPM, VPA<br>Level D: OXC |
| Children with absence seizures | 1 | 0 | 7 | Level A: ESM, VPA<br>Level B: None<br>Level C: LTG<br>Level D: None |
| Benign epilepsy with centrotemporal spikes (BECTS) | 0 | 0 | 3 | Level A: None<br>Level B: None<br>Level C: CBZ, VPA<br>Level D: GBP, LEV, OXC, STM |
| Juvenile myoclonic epilepsy (JME) | 0 | 0 | 1 | Level A: None<br>Level B: None<br>Level C: None<br>Level D: TPM, VPA |

could potentially fill the gap. However, the only class I trials in adults since the last report have been noninferiority trials. Noninferiority trials possess many advantages including fewer ethical issues than placebo-controlled or high-dose low-dose trials and are easier to recruit into. This evidence review has clarified how to assess both superiority and noninferiority trials in a consistent fashion.

This updated evidence review reiterates the problem that many RCTs and especially those involving new AEDs are methodologically flawed and cannot answer important clinical questions. We hope that the clarified methodology in this updated evidence review can assist investigators, government agencies, and pharmaceutical companies in evaluating whether proposed studies (1) will answer important clinical questions; (2) pose major methodologic flaws; or (3) will be able to answer the questions posed. We realize that multiple trial designs can be used to evaluate the efficacy/effectiveness of AEDs and that one trial design will not satisfy the needs of all the above constituencies.

Lastly, in this updated evidence review, we reiterate the importance of using RCTs to make recommendations. Some of the available AEDs may be useful in specific seizure types according to experience, consensus, or small case reports, but these cannot be dealt with here. However, it must ultimately remain for the individual physician to use his or her judgment and expertise when deciding on the most appropriate AED for a specific patient. This document is not intended to be used for regulatory purposes; we trust that regulatory bodies will understand that this document is only the first attempt to create a working framework rather than a rulebook about the treatment of new-onset epilepsy. Multicenter, multinational efforts are needed to design, conduct, and analyze clinically relevant RCTs that answer the many outstanding questions identified in this evidence review.

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## Supporting Information

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

**Table S1.** Adults with partial-onset seizures: number of relevant studies categorized by class of article and AED involved.

**Table S2.** Children with partial-onset seizures: number of studies by class of article and AED involved.

**Table S3.** Elderly adults with partial-onset seizures: number of relevant studies categorized by class of article and AED involved.

**Table S4.** Adults with generalized-onset tonic–clonic seizures: number of relevant studies categorized by class of article and AED involved.

**Table S5.** Children with absence seizures: number of relevant studies categorized by class of article and AED involved.