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Original Research

ILAE Treatment Guidelines: Evidence-based Analysis of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes

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Summary: *Purpose:* To assess which antiepileptic medications (AEDs) have the best evidence for long-term efficacy or effectiveness as initial monotherapy for patients with newly diagnosed or untreated epilepsy.

Methods: A 10-member subcommission of the Commission on Therapeutic Strategies of The International League Against Epilepsy (ILAE), including adult and pediatric epileptologists, clinical pharmacologists, clinical trialists, and a statistician evaluated available evidence found through a structured literature review including MEDLINE, *Current Contents* and the *Cochrane Library* for all applicable articles from 1940 until July 2005. Articles dealing with different seizure types (for different age groups) and two epilepsy syndromes were assessed for quality of evidence (four classes) based on predefined criteria. Criteria for class I classification were a double-blind randomized controlled trial (RCT) design, ≥48-week treatment duration without forced exit criteria, information on ≥24-week seizure freedom data (efficacy) or ≥48-week retention data (effectiveness), demonstration of superiority or 80% power to detect a ≤20% relative difference in efficacy/effectiveness versus an adequate comparator, and appropriate statistical analysis. Class II studies met all class I criteria except for having either treatment duration of 24 to 47 weeks or, for noninferiority analysis, a power to only exclude a 21–30% relative difference. Class III studies included other randomized double-blind and open-label trials, and class IV included other forms of evidence (e.g., expert opinion, case reports). Quality of clinical trial evidence was used to determine the strength of the level of recommendation.

Results: A total of 50 RCTs and seven meta-analyses contributed to the analysis. Only four RCTs had class I evidence, whereas two had class II evidence; the remainder were evaluated as class III evidence. Three seizure types had AEDs with level A or level B efficacy and effectiveness evidence as initial monotherapy: adults with partial-onset seizures (level A, carbamazepine and phenytoin; level B, valproic acid), children with partial-onset seizures (level A, oxcarbazepine; level B, None), and elderly adults with partial-onset seizures (level A, gabapentin and lamotrigine; level B, None). One adult seizure type [adults with generalized-onset tonic–clonic (GTC) seizures], two pediatric seizure types (GTC seizures and absence seizures), and two epilepsy syndromes (benign epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy) had no AEDs with level A or level B efficacy and effectiveness evidence as initial monotherapy.

Conclusions: This evidence-based guideline focused on AED efficacy or effectiveness as initial monotherapy for patients with newly diagnosed or untreated epilepsy. The absence of rigorous comprehensive adverse effects data makes it impossible to develop an evidence-based guideline aimed at identifying the overall optimal recommended initial-monotherapy AED. There is an especially alarming lack of well-designed, properly conducted RCTs for patients with generalized seizures/epilepsies and for children in general. The majority of relevant existing RCTs have significant methodologic problems that limit their applicability to this guideline's clinically relevant main question. Multicenter, multinational efforts are needed to design, conduct and analyze future clinically relevant RCTs that can answer the many outstanding questions identified in this guideline. The ultimate choice of an AED for any individual patient with newly diagnosed or untreated epilepsy should include

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consideration of the strength of the efficacy and effectiveness evidence for each AED along with other variables such as the AED safety and tolerability profile, pharmacokinetic properties, formulations, and expense. When selecting a patient's AED, physicians and patients should consider all relevant variables and not just efficacy and effectiveness. **Key Words:** Efficacy—Effectiveness—Antiepileptic drugs—Guidelines—Epilepsy treatment.

BACKGROUND

Antiepileptic drugs (AEDs) are the initial treatment modality for the vast majority of patients with epilepsy. Since the advent of bromide therapy 150 years ago, clinicians have selected initial AED therapy for patients with newly diagnosed epilepsy in large part based on the patient's seizure/epilepsy type, as determined according to the classification scheme of the time. Unfortunately, during the majority of these 150 years, minimal formal scientific assessment of the efficacy, safety, and tolerability of AEDs has been done. For example, a number of older commonly used present-day AEDs [e.g., phenobarbital (PB), phenytoin (PHT)] were registered and marketed in countries around the world without any randomized clinical trial (RCT) evidence of efficacy or tolerability in patients with epilepsy. The clinical development programs of carbamazepine (CBZ) and valproic acid (VPA) in the 1960s and 1970s marked the beginning of more formalized AED efficacy and tolerability assessment. The recent influx of new AEDs during the past 15 years has provided clinicians with many more therapeutic options along with significant amounts of RCT data regarding efficacy and tolerability.

In 1998, The International League Against Epilepsy (ILAE) began to develop evidence-based guidelines to assist clinicians worldwide with the treatment of epilepsy. To avoid duplication of effort, the subcommission's first step was to survey 62 ILAE chapters and request copies of any available national guidelines focused on the treatment of epilepsy. The subcommission reviewed guidelines received by December 1999 and issued a second request for additional national guidelines. By the beginning of May 2000, 30 ILAE chapters had responded, but only 11 national guidelines existed. Because so few countries had existing guidelines, the subcommission decided to develop a guideline addressing the medical treatment of epilepsy by using the Institute of Medicine's definition of a guideline: "Practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (1).

PURPOSE OF THIS GUIDELINE AND DEFINITION OF TERMS

The issue of initial monotherapy affects everyone medically treated for epilepsy. Initially, the subcommission thought that the goal of this guideline should be to provide an evidence-based answer to the following question: For patients with newly diagnosed or untreated epilepsy, which AEDs have the best evidence for use as initial monotherapy? The first step in this analysis was to identify the multiple variables that affect a specific AED's suitability for patients with newly diagnosed or untreated epilepsy (Table 1).

Only one variable in Table 1 (seizure- or epilepsy syndrome–specific efficacy/effectiveness) can be analyzed in an evidence-based manner. It is not possible to provide comprehensive balanced evidence-based analysis of AED adverse effects (dose dependence, idiosyncratic reactions, chronic toxicities, teratogenicity, and carcinogenicity) because only a few AEDs have detailed well-controlled data for adverse effects. It is inappropriate to assume that the absence of evidence regarding an AED's adverse effects is equivalent to evidence of absence of these potentially important adverse effects. Similarly, it is not possible to provide an evidence-based approach for the impact of other AED variables such as differential pharmacokinetics.

Given the inability to address rigorously all variables that affect initial AED selection, the subcommission concluded that the main goal of this guideline should be to provide 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?

Definitions are needed for multiple terms in this question. "Patients" included adults, children, and elderly. Studies were classified as either pediatric, adult, elderly, or mixed trials based on the study's intent primarily to enroll patients younger than 16 years, 16 years or older, 60 years or older, or any age between 2 and 85 years, respectively. "Newly diagnosed or untreated" was included because patients may have had seizures for many years and either were misdiagnosed, did not recognize the seizures, refused therapy, or were not able to afford therapy. Because "epilepsy" is not a homogeneous disorder, the guideline's main question was addressed for (a) different seizure subtypes and (b) different epilepsies/epilepsy syndromes based on the ILAE 1981 seizure classification (2) and the 1989 revised classification of epilepsies and epilepsy syndromes (3). "Long-term" refers to $\geq$48 weeks of therapy. "Efficacy" is the ability of that medication to produce seizure freedom; "tolerability" involves the "incidence, severity, and impact" of AED-related adverse effects (4,5), and the term "effectiveness" encompasses both AED efficacy and tolerability, as reflected in retention on treatment (4). "Initial" represented only the first AED used for a patient, whereas "monotherapy" was the use of a single AED.

TABLE 1. *Variables that affect a specific AED's suitability for patients with newly diagnosed or untreated epilepsy*

AED-specific variables	Patient-specific variables	Nation-specific variables
Seizure or epilepsy syndrome specific efficacy/effectiveness	Genetic background	AED availability
Dose-dependent adverse effects	Gender	AED cost
Idiosyncratic reactions	Age	
Chronic toxicities	Comedications	
Teratogenicity	Comorbidities	
Carcinogenicity	Insurance coverage	
Pharmacokinetics	Relative wealth	
Interaction potential	Ability to swallow pills/tablets	
Formulations		

Data were collected from published peer-reviewed original studies, systematic reviews, published book chapters, AED package inserts, and regulatory information obtainable by the public and pharmaceutical companies.

The guideline's recommendations aim to help clinicians worldwide understand the relevant existing evidence for initial AED selection for patients with epilepsy and to assist the clinician in applying it to clinical practice. The guideline is intended for use by individual clinicians, hospitals, health authorities and providers, and individual chapters of the ILAE. We recognize that this guideline will require local scrutiny and adjustment to make it relevant to social and economic environments in which it will be used. This process should lead to a sense of ownership of any adjusted guideline that will be essential for effective implementation and lead to improvement in health care outcomes for people with epilepsy.

SCOPE OF THIS GUIDELINE

This guideline will address the evidence underlying AED efficacy and effectiveness for patients with newly diagnosed or untreated epilepsy. In reviewing the studies, it became apparent that a number of trials of "initial treatment" included also a proportion of patients who had received prior treatment for variable periods; these studies were not excluded from the analysis.

The following issues are not examined in this guideline: when to start AED therapy, when to stop AED therapy, how to titrate or adjust AED dosages, urgent treatment of seizures and status epilepticus, AED efficacy when used as polytherapy, the role of different diagnostic tests [e.g., EEG, computed tomography (CT) scan or magnetic resonance imaging (MRI)], the role of epilepsy surgery, neurostimulation, or ketogenic diet in the management or treatment of patients with epilepsy, or the initial treatment of neonatal seizures or West syndrome. The intercountry variability in AED costs makes it difficult for this guideline to address or incorporate issues of cost-effectiveness and related economic analyses. However, it is recognized that cost and availability are parameters used as criteria for the selection of initial AED therapy, particularly in nonaffluent societies.

This guideline should not be construed as including every proper method of care or as excluding other acceptable methods. The ultimate judgment for therapy must be made in light of all the clinical data presented by the patient and by the treatment options that are locally available for the patient and his or her clinician.

DESCRIPTION OF ANALYTIC PROCESS

Overview

The methods used to construct the evidence-based portion of this guideline combined elements of guideline development used by the Agency for Healthcare Research and Quality, Rockville, MD (http://www.ahcpr.gov/), The Scottish Intercollegiate Guideline Network (http://www.sign.ac.uk/), the American College of Cardiology and the American Heart Association (http://circ.ahajournals.org/manual/), the Cochrane Database of Systematic Reviews (www.cochranelibrary.com or www.cochrane.org), the American Academy of Neurology (http://www.aan.com), and the National Health and Medical Research Council (http://www.health.gov.au/nhmrc/publications/pdf/cp65.pdf).

Description of literature review

Identification of potentially relevant studies began with a series of literature searches by using MEDLINE and *Current Contents*. Studies were considered potentially relevant if they were published any time before July 4, 2005, coded in a computerized database as an RCT, meta-analyses, or systematic reviews, included the words *epilepsy* and *monotherapy* along with at least one of the following 36 terms: acetazolamide (ACZ), adrenocorticotropic hormone (ACTH), barbexaclone, beclamide, carbamazepine (CBZ), clobazam (CLB), clonazepam (CZP), clorazepate (CLP), diazepam (DZP), ethosuximide (ESM), ethotoin (ETH), felbamate (FBM), gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), lorazepam (LZP), mephenytoin (MPH), mephobarbital (MPB), methsuximide (MSM), nitrazepam

(NTZ), oxcarbazepine (OXC), phenacemide (PAC), pheneturide (PTR), phenobarbital (PB), phensuximide (PSM), phenytoin (PHT), pregabalin (PGB), primidone (PRM), progabide (PRO), sulthiame (STM), tiagabine (TGB), topiramate (TPM), valproic acid (VPA), vigabatrin (VGB), zonisamide (ZNS), or 4-amino-3-hydroxybutyric acid. For a particular seizure type or epilepsy syndrome, if no acceptable RCTs, meta-analyses, or systematic reviews were found, then a second search was performed to include non-RCTs, case studies, and opinion documents. All languages were included. No gender and age limits were imposed, but searches were limited to human subjects.

Four additional steps were taken to identify potentially relevant studies. A hand search of major medical and neurology journals for potentially relevant studies was updated to July 2005. The *Cochrane Library* of randomized controlled trials in epilepsy was searched each year during guideline development (last time in July 2005); any relevant meta-analyses or cited reference(s) in the analysis were included for review. The reference lists of all included studies were reviewed to identify any additional relevant studies not identified by these searches. Package inserts of individual AEDs were checked for information about any additional RCTs.

Pharmaceutical companies were asked to supplement data from any publicly known RCTs if data were missing (e.g., RCTs mentioned in package inserts) and for any unpublished potentially relevant clinical trials. Any studies in press known to the subcommission were also included.

Literature categorization and abstraction

Studies were divided into groups based on the study population's seizure type or epilepsy syndrome (using the ILAE classification) and then further subdivided (if possible) by age. In general, children refers to patients younger than 16 years, adults to patients 16 years or older, and elderly to patients 60 years or older. The categories included the following: (a) patients (adults, children, or elderly) with partial-onset seizures; (b) patients (adults or children) with generalized-onset seizures; (c) idiopathic localization-related epilepsies (e.g., benign childhood epilepsy with centrotemporal spikes); and (d) idiopathic generalized epilepsies (e.g., juvenile myoclonic epilepsy).

Each potentially relevant study found through this search method was abstracted for specific data, which were placed in evidence tables including but not limited to study title, author, journal citation, description of study patient's prior epilepsy therapy (e.g., untreated, undertreated, previously treated but off AEDs), presence or absence of blinding/masking [open label (OL), double blind (DB)], patient flow (parallel-group or crossover design), description of power analysis/sample-size calculation, randomization procedure, planned and actual age range of patients enrolled, seizure type(s) or epilepsy syndrome under study, number of patients enrolled (subdivided by seizure type, AED, and age if possible), AED dosages used (initial dosage, target dosage, mean/median dosages if available), duration of titration/maintenance/follow-up, and outcomes examined (efficacy and effectiveness/retention).

Key criteria for literature analysis

Consensus was reached that all identified RCT studies be evaluated by five major criteria (Table 2):

1. The first criterion relates to the requirement that information on adequate effectiveness and/or efficacy parameters be provided. It was agreed that effectiveness data (retention) should be available for a treatment period of $\geq$48 weeks. This relates to the considerations given later on the minimal duration of treatment. For efficacy outcomes, the minimum duration of seizure freedom was set at 24 weeks for all seizure types. Consensus was reached that seizure freedom assessed over shorter periods could not be considered clinically relevant in view of the need to document a sustained response and, in many trials, the inclusion of patients with infrequent seizures (e.g., two seizures over the preceding 6 months).
   The subcommission acknowledged that these study-duration requirements penalize studies that used time-to-exit outcome measures, particularly trials including a low-dose active control in which patients are required to exit after only one or two seizures. The latter studies, however, are also the least useful in addressing the objective of the present guideline, because the nature of comparator and the criteria for treatment failure have little or no relevance to the mode of drug use in therapeutic practice.
2. The second criterion relates to minimal duration of treatment, which must be appropriate for assessing the primary outcome variable(s) for the seizure type or epilepsy syndrome under consideration. This was set at $\geq$48 weeks to allow time for dose titration and dose adjustments and for assessment of sustained response in a disorder that, for most seizure types, requires treatment for many years.
3. The third criterion relates to the need to minimize bias in enrollment and assessment. The presence/absence of blinding and the description of treatment groups' baseline characteristics were used to determine whether bias was minimized (6). Ideally, details on the randomization procedure for each study would have been incorporated into this bias assessment because poor concealment of randomization can have considerable impact on the estimates of treatment effects (7); unfortunately

TABLE 2. *Classification criteria for study evaluation*

Criteria	Required	Comment/Example
Primary outcome variable	Clearly defined Either effectiveness (patient retention) or efficacy (seizure freedom)	Ideal: Assessment of retention after a minimum of 48-wk treatment for all seizure types Ideal: Assessment of efficacy based on a minimum of 24-wk 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 in this guideline is 48 wk
Potential for bias	Enrollment or treatment bias minimized by randomization, double blinding and description of treatment groups baseline characteristics	Ideal: Randomized double-blind clinical trial design
Detectable noninferiority boundary based upon actual sample size	A positive superiority trial is acceptable For all other trials or superiority trials failing to identify a difference, actual sample size (for age/seizure-type subgroups) must be large enough to show noninferiority with a $\leq$20% relative difference between treatment arms based on 80% power in a noninferiority analysis vs. an acceptable comparator	For noninferiority outcomes, an acceptable comparator: (1) must have been shown to be superior to another treatment in at least one trial satisfying all other criteria listed in this table OR (2) if no drug meets condition 1, must have been shown to be superior to another treatment in at least one trial satisfying all other criteria listed in this table except for minimum duration of treatment/retention/seizure freedom
Statistical analysis	Appropriate statistical analysis presented or data presented allowing statistical analysis	

randomization information was not available for most studies that stated that allocation to treatments was randomized. Requirements for bias minimization were considered unmet when a study was not double-blind (DB) or failed to provide information on the baseline clinical characteristics of the treatment groups. The subcommission acknowledged that these criteria heavily penalize non-DB studies, but there was consensus that seizure reporting and retention are not objective outcomes (such as death) and that blind outcome assessment was preferred (8). However, the subcommission also recognized that unblinded studies, by being simpler to perform, may recruit larger numbers of patients than do DB studies. This may have a balancing effect against any loss of precision due to lack of blinding and may also increase the external validity (applicability) of the study.

4. The fourth criterion relates to the ability of the study to detect a difference in outcome. For initial monotherapy trials, a 1998 guideline produced by the ILAE Commission on Antiepileptic Drugs (4) estimated at 20% (not stated whether absolute or relative difference) the minimum outcome difference that should be regarded as clinically important. After extensive discussion, it was agreed that any relative difference $>$20% in primary outcome (effectiveness or efficacy) versus the comparator's arm (as defined in the study protocol) should be regarded as clinically significant. For example, if seizure-freedom rate in the comparator's group was 50%, an outcome with seizure-freedom rate $<$40% or $>$60% (50% $\pm$ 0.2 $\times$ 50%) in other groups(s) would be regarded as clinically important.

For a trial to qualify as being able to detect a difference, one of the following two conditions had to be met: (a) the trial demonstrated a statistically significant difference in effectiveness or efficacy between treatment arms; or (b) actual sample size (for age/seizure-type subgroups) was large enough to assess a $\leq$20% relative difference between treatment arms, based on 80% power, type I error set at $\leq$0.05, a noninferiority analysis, and use of an acceptable comparator (defined later). This condition would apply only to superiority trials failing to identify a difference and for noninferiority or equivalence trials.

An acceptable comparator for a specific seizure/epilepsy/age category was defined as any drug shown to be superior to another drug, another dose of the same drug or another treatment modality or placebo in at least one trial satisfying all other criteria listed in Table 2. In case no drug qualified by the latter criterion, an acceptable comparator would be any drug shown to be superior to another drug, another dose of the same drug, or another treatment modality or placebo in at least one trial satisfying all other criteria listed in Table 2 except for minimal duration of treatment/retention/seizure freedom. The concept of acceptable comparator was introduced to minimize the possibility that a comparator

might be used for which no adequate evidence of effectiveness/efficacy exists, thereby leading to the interpretation that both the comparator and the noninferior treatment may be ineffective or inefficacious. The subcommission acknowledged that satisfying noninferiority criteria versus an acceptable comparator did not exclude the possibility of the two compared treatments being equally ineffective or inefficacious. Nevertheless, there was consensus that a noninferiority outcome in a trial meeting all criteria listed in Table 2 is acceptable evidence of effectiveness or efficacy.

The detectable noninferiority boundary (DNIB) was calculated for all RCTs that failed to identify a difference for the appropriate end point(s). These trials were analyzed assuming a noninferiority study design rather than a superiority study design. The adequate comparator's arm (e.g., CBZ) was assumed to have a response rate of 50%. The null hypothesis was that the compared treatment had a lower response rate, and the alternative, to be detected with 80% power, while controlling for one-sided type I error of 0.05, was that the compared treatment was not inferior, in terms of response rate, to the comparator.

The DNIB was established by using the actual sample sizes of evaluated patients in the study, relative to a response rate of 50%. For example, a 1999 study comparing 226 newly diagnosed adults with partial-onset seizures with CBZ with 220 newly diagnosed adults with partial-onset seizures receiving VGB would have been large enough to establish the noninferiority of VGB as compared with CBZ with a noninferiority relative boundary of 24% (9). In other words, assuming that the true response rate on CBZ was 50%, the study was large enough to establish that the response rate on VGB would be no worse than 38% [$0.5 \times (1 - 0.24)$] with >80% power. Assuming a 50% response rate as the reference, in addition to approximating true response rates for most epilepsy types, gives the largest noninferiority boundary (i.e., the "worst-case scenario"). Sensitivity analysis shows that for any response rate on CBZ ranging from 40 to 60%, on this study, the noninferiority boundary would have changed to $\leq$23%. For studies with a smaller sample size, the sensitivity analysis shows virtually no difference in the detectable noninferiority boundary based on establishing the response rate at 40–60%.

The sample sizes were calculated based on the formulas developed by Chan (10), implemented in StatXact Version 6.0 (Cytel, Inc., Cambridge, MA, U.S.A.) (11) and assumed that the test statistic to be used was the score test.

For studies in which more than two treatments were compared, all pairwise power calculations were performed. The reported detectable level is the smallest noninferiority level that the study could accomplish from all comparisons assessed.

For studies in which a sample size was provided combining adults and children, the largest-power possible scenario was evaluated for each group (i.e., that all but one patient was from the group currently assessed for power). Thus each study was assessed as to the smallest possible DNIB that it could detect, taking into account all the features in the study (sample size, number of treatments compared, different populations compared).

5. The fifth criterion relates to the requirement that appropriate statistical analysis is presented in the article or, alternatively, that data be presented or made available for appropriate statistical analysis by the subcommission. Age-specific seizure types or epilepsy syndrome categories were analyzed independently. When studies included mixed populations in terms of seizure/syndrome/age categories, data were extracted and analyzed separately for each category, and any analysis done on mixed categories was regarded as inadequate in meeting the criterion for appropriate statistical analysis. Meta-analyses were also evaluated based on the same criteria applied to individual RCTs.

Rating of potentially relevant studies

All potentially relevant studies were evaluated for their Class of Evidence based on criteria adapted from the United States Agency for Health Care and Policy Research (12) and the American Academy of Neurology (13) scoring systems (Table 3).

This method focuses on certain study characteristics at the potential expense of other design characteristics. A schematic diagram of how this scoring system works for efficacy and effectiveness studies is shown in Fig. 1.

Level-of-evidence classification

The level-of-evidence classification approach using each category's conclusions was a modification of the United States Agency for Health Care and Policy Research (12) and the American Academy of Neurology (13) scoring systems. The six levels are labeled A–F; the relation between level of evidence and clinical trial rating is shown in Table 4. Levels A through D are defined by specific combinations of clinical trials ratings (based on the criteria in Table 2). 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 that no published RCTs exist of the AED's use as initial monotherapy for a specific seizure type/epilepsy syndrome. Level F indicates documented

TABLE 3. *Rating scale of evidence for potentially relevant studies*

Class	Criteria
I	A RCT, or meta-analysis of RCTs, in a representative population that meets all six criteria: 1. Primary outcome variable: efficacy or effectiveness 2. Treatment duration: ≥48 wk and information on ≥24 wk seizure freedom data (efficacy) or ≥48 wk retention data (effectiveness) 3. Study design: Double blind 4. Superiority demonstrated, or if no superiority demonstrated, the study's actual sample size was sufficient to show noninferiority of no worse than a 20% relative difference in effectiveness/efficacy (see text for detailed explanation of this detectable noninferiority boundary) 5. Study exit: Not forced by a predetermined number of treatment-emergent seizures 6. Appropriate statistical analysis
II	A RCT or meta-analysis meeting all the class I criteria except that 1. No superiority was demonstrated and the study's actual sample size was sufficient only to show noninferiority at a 21–30% relative difference in effectiveness/efficacy OR 2. Treatment duration: ≥24 wk but <48 wk
III	A RCT or meta-analysis not meeting the criteria for any class I or class II category (e.g., an open-label study or a double-blind study with either a detectable noninferiority boundary of >30% or forced exit criteria)
IV	Evidence from nonrandomized, prospective, controlled or uncontrolled studies, case series, or expert reports

evidence of the AED's lack of efficacy and effectiveness or AED-associated seizure aggravation.

Recommendations for use as initial monotherapy

Evidence-based AED efficacy and effectiveness recommendations for a specific seizure/epilepsy type are divided into five categories (Table 4). If no AED for a specific seizure/epilepsy type met criteria for either of the top two levels of evidence, then the entry in this category would be "No first-line monotherapy candidates exist at this time."

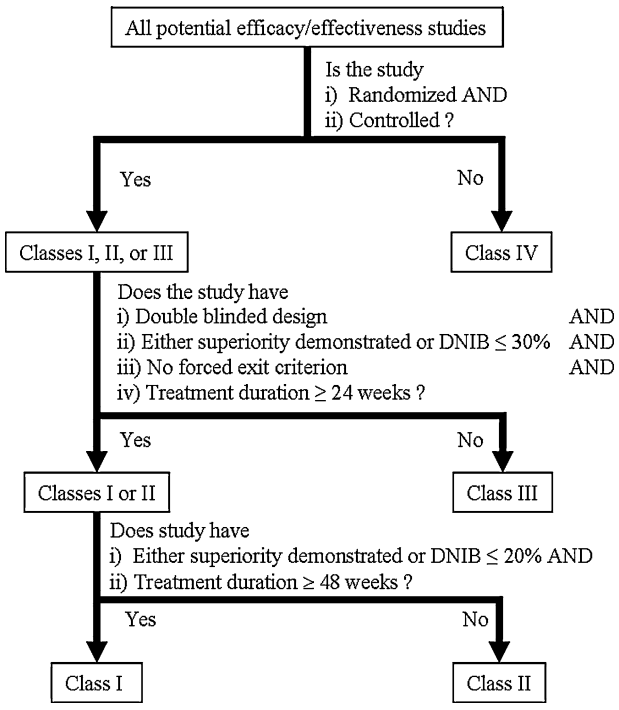

FIG. 1. Application of evidence-rating criteria for efficacy/effectiveness studies. (DNIB = detectable noninferiority boundary)

Because multiple AED-specific factors affect the selection of initial monotherapy, for each first-line and alternative first-line candidate AED identified by this method, consideration must be given to the other AED-, patient-, and nation-specific variables from Table 1 that can affect final AED selection (e.g., adverse effects, pharmacokinetics).

Potential limitations of proposed method

1. Guideline method may undervalue important data by emphasizing DB, long-duration trials with no forced-exit criteria: This guideline's proposed method emphasizes (a) DB over OL RCTs, (b) longer-duration trials over shorter-duration trials, and (c) trials not using forced-exit criteria over those that do. This approach may underemphasize important data from certain trials not meeting this guideline's rating criteria for a class I or II trial. The subcommission thought that this differential approach would focus the guideline on those trials that most contribute to the main question: For patients with newly diagnosed or with untreated epilepsy, which AEDs have the best evidence for long-term efficacy or effectiveness as initial monotherapy?
2. Guideline method may undervalue important data from RCTs that were designed primarily for regulatory or marketing purposes. In general, regulatory and marketing-driven trials may have limited utility for the development of treatment guidelines because they tend to incorporate methodologic features (e.g., inclusion criteria, choice of dosages, dosing intervals, titration rates, formulation, end points) that bias the results in favor of the sponsor's product. Additionally, starting and maintenance dosages, titration rates, and outcome variables (e.g., time to first seizure) in these studies

TABLE 4. *Relation between clinical trial ratings, level of evidence, and conclusions*

Combination(s) of clinical trial ratings	Level of evidence	Conclusions	Recommendation (based on efficacy and effectiveness data only)
≥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	AED should be considered for initial monotherapy—first-line monotherapy candidate
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	AED may be considered for initial monotherapy—alternative first-line monotherapy candidate
1 class III double-blind or open-label study	D	AED potentially efficacious or effective as initial monotherapy	Weak efficacy or effectiveness data available to support the use of the AED for initial monotherapy
≥1 class IV clinical studies OR expert committee reports, OR opinions from experienced clinicians OR absence of directly applicable clinical evidence upon which to base a recommendation	E	No RCT data available to assess if AED is effective as initial monotherapy	Either no data or inadequate efficacy or effectiveness data available to decide if AED could be considered for 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 considered as ineffective or significant risk of seizure aggravation	AED should not be used for initial monotherapy

often do not reflect routine clinical care, meaning that results may not be fully generalizable to routine practice.

3. This guideline relied predominantly on published aggregate data. Ideally individual data would be preferred for time-to-event outcome analysis, but these data were not available.
4. This guideline did not use effect estimates with confidence intervals because this analysis was not used for most of the published studies.
5. This guideline treats all "negative" trials as noninferiority trials even if the initial intent of the trial was to demonstrate superiority. Calculations are based on the number of patients with data, but sometimes this information was not available and intent-to-treat numbers were used. These numbers may have overestimated the power of a given study, since loss to follow-up was not accounted for.
6. Clinical trials may enroll all types of epilepsy across many age ranges but not publish subgroup data or analysis. This differential availability of subgroup data and analysis could result in a possible publication and selection bias.
7. There are few or no RCTs for certain seizure types or epilepsy syndromes. Insufficient RCTs exist, especially in adults with idiopathic generalized epilepsies and in children with many types of epilepsy. For these categories, it is impossible to identify any AEDs with sufficient evidence to qualify as first-line initial monotherapy candidates.

RESULTS

Article and meta-analysis identification

The initial step in identifying potentially relevant studies and systematic reviews was to search MEDLINE by using the following four search strategies:

1. Search Epilepsy AND monotherapy AND (acetazolamide OR adrenocorticotropic hormone OR barbexaclone OR beclamide OR carbamazepine OR clobazam OR clonazepam OR clorazepate OR diazepam OR ethosuximide OR ethotoin OR felbamate OR gabapentin OR lamotrigine OR levetiracetam OR lorazepam OR mephenytoin OR mephobarbital OR methsuximide OR nitrazepam OR oxcarbazepine OR phenacemide OR pheneturide OR phenobarbital OR phensuximide OR phenytoin OR pregabalin OR primidone OR progabide OR sulthiame OR tiagabine OR topiramate OR valproic acid OR vigabatrin OR zonisamide OR 4-amino-3-hydroxybutyric acid). Field: All Fields. Limits: Randomized Controlled Trial, Human. This search yielded 3,770 studies.
2. Search "Epilepsy/drug therapy" (MeSH) monotherapy. Limits: Randomized Controlled Trial, Human. This search yielded 126 studies.
3. Search Drug therapy (MeSH) AND Epilepsy. Limits: Randomized Controlled Trial, Human. This search yielded 614 studies.
4. Search (epilepsy therapy) AND systematic (sb). This search yielded 499 studies.

These computerized searches were last performed on July 4, 2005. The resulting studies were reviewed for relevancy and placed into one of the eight seizure-type or epilepsy syndrome categories listed earlier. The reference lists of all included studies were reviewed to identify any additional relevant studies not identified by these searches. In total, 50 relevant RCTs were identified, some of which were included in multiple categories.

A search of the *Cochrane Library* yielded six additional completed and relevant published meta-analyses. Pharmaceutical companies provided requested additional information on one meta-analysis and six RCTs. Seventeen systematic reviews and guidelines were identified that were thought to be relevant to these guidelines, covering topics such as management of newly diagnosed epilepsy (14–18), tonic–clonic (TC) seizures (19), absence seizures (20), treatment of women with epilepsy (21,22), adults with epilepsy and intellectual disability (23), childhood epilepsies (24), AED clinical trials (25), AEDs and cognitive function (26,27), quality of life (28), and AED economic issues (29,30). In total, 50 RCTs, seven meta-analyses, and 17 systematic reviews were included as sources in the development of these guidelines.

Presentation of evidence, conclusions, and recommendations

The guideline is divided by seizure type (n = 6) and epilepsy syndrome (n = 2). Each section has an overview of the available RCT evidence followed by a summary of effectiveness and efficacy data. For each AED with class I, II, or DB class III RCT data, effectiveness evidence is presented before efficacy evidence. Meta-analysis evidence (if available) is then discussed. Each section closes with conclusions and recommendations.

Partial-onset seizures (adults, children, elderly)

The goals of treatment for adults and children with partial-onset seizures, as for patients with other seizure types, are the best quality of life with no seizures and the fewest adverse effects from treatment. The guideline for the treatment of adults, children, and elderly with partial-onset seizures was developed to identify AEDs with the strongest evidence for efficacy or effectiveness as first-line monotherapy. Emphasis was on trials involving adults, children, or elderly with new-onset or newly treated partial seizures rather than adults, children, or elderly with treatment-resistant partial seizures. The guideline for the initial treatment of partial-onset seizures was subdivided into three separate populations: adult, children, and elderly.

The ultimate choice of an AED for any individual patient with newly diagnosed or untreated partial-onset epilepsy should include consideration of the strength of each AED's efficacy and effectiveness evidence along with the other variables in Table 1 (e.g., the AED's safety profile, pharmacokinetic properties, formulations, and expense). When selecting a patient's AED, physicians and patients must consider all relevant variables and not just an AED's efficacy and effectiveness.

Adults with partial-onset seizures

Overview of evidence

A total of 37 RCTs (9,31–66) and five meta-analyses (66–71) examined initial monotherapy of adults with partial-onset seizures. Among the 37 RCTs, two RCTs (9,31) were considered class I studies, one RCT was rated as class II (34), and 30 RCTs met criteria for class III studies (32,33,35–61,66). Four RCTs did not report effectiveness or efficacy as a primary outcome variable and are not included further in the analysis (62–65).

One RCT was considered class II because it met all class I criteria except that no superiority was demonstrated between treatments, and the study had a DNIB of 23% (34). The majority of RCTs were classified as class III. Fifteen DB RCTs were classified as class III because of a forced-exit criterion alone (n = 4) (40,42,44,66), forced-exit criterion plus either too short a duration of treatment (n = 1) or DNIB ≥31% (n = 1) (45,56), or DNIBs ≥31% with or without too short a duration of treatment (n = 9) (33,37–39,41,43,47–49). The remaining 15 RCTs were classified as class III because they were OL trials (32,35,36,46,50–55,57–61).

Among the 33 RCTs considered for evaluation, CBZ was the most frequently studied (n = 19) followed by PHT (n = 11) and VPA (n = 11). The majority of RCTs involving these AEDs were OL class III studies. The number of studies for each AED and their distribution by RCT class of evidence are shown in Table 5.

Effectiveness-outcome evidence

Six AEDs (CBZ, PHT, PB, PRM, VPA, and VGB) had either class I or class II evidence regarding effectiveness in adults with partial-onset seizures. Five AEDs (CZP, GBP,

TABLE 5. *Adults with partial-onset seizures: number of relevant studies categorized by class of study and AED involved*

Class	CBZ	PHT	VPA	LTG	PB	OXC	TPM	VGB	GBP	CZP	PRM
I	2	1	0	0	1	0	0	1	0	0	1
II	1	0	1	0	0	0	0	0	0	0	0
III-DB	6	4	2	3	0	4	3	0	2	1	0
III-OL	10	6	8	2	4	0	0	2	0	0	0
Total	19	11	11	5	5	4	3	3	2	1	1

LTG, OXC, TPM) had class III DB RCT evidence regarding effectiveness in adults with partial-onset seizures.

CBZ, PHT, PB, PRM, VGB (class I, n = 2): In a 1985 trial of 622 adults with epilepsy, retention in the study at 36 months in adults with partial-onset seizures was greater for CBZ and PHT compared with PB or PRM ($p < 0.02$) (31). In this same study, for patients with partial secondarily generalized tonic–clonic (GTC) seizures, CBZ, PHT, and PB had significantly greater patient retention at 36 months than did PRM ($p < 0.01$) (31). In a comparative trial of 459 patients with epilepsy, VGB and CBZ demonstrated similar time to withdrawal for lack of efficacy or adverse effects (hazard ratio, 0.83; 95% CI, 0.57–1.20) (9).

CBZ, VPA (class II, n = 1): A class II CBZ–VPA comparison study involving 480 adults with partial-onset epilepsy contained two distinct substudies; one substudy enrolled 206 patients with complex partial seizures, and the other substudy included 274 patients with partial secondarily GTC seizures. Patients entering the trial were assigned to a substudy based on their predominant seizure type. The substudies had identical designs and procedures. The results of each substudy were analyzed separately and together. CBZ and VPA had similar treatment success rates (defined by length of time taking study drug without being discontinued) for the combined group and for either seizure group separately. For the combined groups and the complex-partial subgroup, patients receiving CBZ had a significantly better composite score (incorporating efficacy and tolerability aspects) than did VPA at 12 months but not at 24 months. At both 12 and 24 months, CBZ and VPA had similar composite scores in patients with secondarily GTC seizures (34).

CZP, GBP, LTG, OXC, TPM (class III DB, n = 12): Seven comparative RCTs (LTG-CBZ, LTG-PHT, LTG-GBP, OXC-CBZ, OXC-PHT, OXC-VPA, and TPM-CBZ-VPA) enrolled both patients with partial-onset seizures and patients with generalized-onset seizures (33,37–39,41,43,49). For each trial, the DNIB for the partial-onset seizure subgroup was >31%, resulting in a class III designation.

No effectiveness data for the partial-onset seizure subgroup were presented in either the LTG-CBZ or LTG-PHT study, but GBP and LTG had similar time to exit by seizure type in a separate class III RCT (37,41,49). Treatment retention (defined by the rate of premature discontinuation for any reason) was similar between treatment arms for the subset of patients with partial-onset seizures in an OXC-PHT comparative trial and in a separate OXC-VPA comparative trial (38,39). No effectiveness outcome data were reported for an OXC-CBZ comparative trial (33). In the forced-exit TPM-CBZ-VPA trial, the investigators report that the times-to-exit results (based on the clinical responses in the CBZ branch, the VPA branch, and the two TPM branches) for the partial-onset seizure subgroup were similar to those for the intent-to-treat population, but the study did not report p values or confidence intervals (43).

No effectiveness outcome data were reported for one forced exit, brief-duration placebo-controlled class III OXC RCT (45) or for two high-dose low-dose forced-exit TPM RCTs (42,72). A four-arm forced-exit GBP-CBZ trial involving 292 adults with newly diagnosed partial-onset seizures used three different dosages of blinded GBP and one dosage of OL CBZ. The completion rate between GBP, 900 mg/day and 1,800 mg/day, was similar to that for CBZ, 600 mg/day. GBP, 900 mg/day, was shown not to be inferior to CBZ, 600 mg/day, when both exit rate and adverse-event withdrawal rate were considered (40). In a small comparative RCT, CBZ and CZP had similar withdrawal rates from the study (47).

Efficacy-outcome variable

Six AEDs (CBZ, PHT, PB, PRM, VPA, and VGB) had either class I or class II evidence regarding efficacy in adults with partial-onset seizures. Five AEDs (CZP, GBP, LTG, OXC, TPM) had class III DB RCT evidence regarding efficacy in adults with partial-onset seizures.

CBZ, PHT, PB, PRM, VGB (class I, n = 2): In the class I 1985 four-arm RCT comparison of CBZ, PHT, PB, and PRM, more patients with partial-onset seizures receiving CBZ were seizure-free after 18 months compared with those taking either PB or PRM ($p < 0.03$) (31). All four arms of the trial had equal seizure freedom at 18 months for patients with secondarily GTC seizures (ranging from 43% to 48%) (31). In a class I RCT of CBZ and VGB, seizure freedom at 1 year was statistically significantly higher for CBZ patients compared with VGB patients (58% vs. 38%) as was time to first seizure after the first 6 weeks from randomization ($p < 0.0001$). The time to achieve 6 months' remission from seizures was similar between the two AEDs (9).

CBZ, VPA (class II, n = 1): In a class II RCT, CBZ and VPA had similar seizure-freedom rates for both subgroups and the combined group at 12 and 24 months of follow-up. Time to first seizure was significantly shorter for VPA patients in the combined group and the complex partial subgroup compared with the CBZ patients. Although multiple efficacy variables favored CBZ over VPA for the complex partial-seizure subgroup, this difference was not seen in the secondarily GTC seizure subgroup (34).

CZP, GBP, LTG, OXC, TPM (class III DB, n = 13): In separate OXC-PHT and OXC-VPA trials, for those patients with partial-onset seizures, seizure-free rates during the 48-week maintenance phase were not statistically significantly different between the AEDs (38,39). In a OXC-CBZ comparative trial, no statistically significant differences in seizure-free rates occurred during the 48-week maintenance phase in the subset of patients with partial-onset seizures (33). In one class III forced exit, brief-duration placebo-controlled OXC trial, OXC

monotherapy was superior to placebo monotherapy in time to first seizure ($p = 0.0457$) and also superior in the number of seizures per 28 days ($p = 0.033$) (45).

In two separate trials, the proportion of partial-onset seizure patients seizure-free during the last 40 weeks or 24 weeks of treatment and the time to first seizure after 6 weeks of treatment were similar for LTG and CBZ in one trial and LTG and PHT in the other (37,41). In another class III comparative study, GBP and LTG had similar time to first seizure and proportion of seizure-free patients during the last 12 weeks of a 30-week maintenance phase (49).

Comparisons between TPM, CBZ, and VPA in the subset of patients with newly diagnosed partial-onset seizures showed that a similar proportion of patients were seizure free during the last 6 months of treatment for CBZ, VPA, and two different dosages of TPM (43). In a forced exit TPM trial involving 252 patients with partial-onset seizures, TPM, 500 mg/day, was superior to TPM, 50 mg/day, in time to exit for the whole group if time to first seizure was used as a covariant ($p = 0.01$). Seizure-free rates for TPM, 500 mg/day, were higher than those for TPM, 50 mg/day (54% vs. 39%; $p = 0.02$) (42). In a second forced exit TPM dose–response trial, TPM, 400 mg/day, had a longer time to first seizure than TPM, 50 mg/day, and a higher seizure-free rate at both 6 months and 1 year for the entire cohort. However, for the subset of patients with only partial-onset seizures, no statistical difference was found between the high-dose and low-dose seizure-free rates at 12 months (66 vs. 56%; $p = 0.11$) (44).

A GBP dose–response trial demonstrated that GBP, 900 mg/day, and GBP, 1,800 mg/day, had a longer time to exit event (one GTC, three simple or complex-partial seizures, or status epilepticus) than GBP, 300 mg/day ($p = 0.0395$ and $p = 0.0175$, respectively) (40). A class III comparative trial of CBZ and the investigational AED remacemide found CBZ to have superior efficacy on every efficacy outcome variable including time to first seizure after dose titration, time to second seizure after randomization, time to third seizure after randomization, time to fourth seizure after randomization, and seizure freedom at 12 months (66). In a small comparative RCT, CBZ and CZP had similar seizure-free rates during 6 months (47).

Meta-analyses

Five meta-analyses have examined AED efficacy and effectiveness for adults with partial-onset seizures. These meta-analyses have compared CBZ with VPA (67), PHT with VPA (69), CBZ with PHT (68), PHT with PB (70), and CBZ with PB (71), with a focus on three end points: time to withdrawal, number of patients achieving 12-month seizure freedom, and time to first seizure. The vast majority of data used in these meta-analyses were from class III studies. The meta-analyses found "no reliable evidence to distinguish CBZ and VPA for partial onset seizures and generalized-onset seizures" (67) and that CBZ is better tolerated than PB, but no efficacy difference between the two could be demonstrated (71). No differences were found for PHT versus VPA, or CBZ versus PHT (68,69). For the PHT versus PB comparison, PHT was superior to PB for time to withdrawal of treatment, but no difference was noted between the two AEDs for time to 12-month remission and a nonsignificant trend toward a preference for PB over PHT for time to first seizure (70).

Summary and conclusions

1. Major general conclusions: A paucity of class I and class II RCTs for adults with partial-onset seizures was found. Based on this guideline's definition, the adequate comparators for this category are CBZ and PHT.
2. Based on available efficacy and effectiveness evidence alone, CBZ and PHT are established as efficacious or effective as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures (level A).
   a. In a class I trial, CBZ and PHT demonstrated superior effectiveness (compared with PB and PRM), and CBZ demonstrated superior efficacy (compared with PB and PRM). In a separate class I trial, CBZ had superior efficacy and similar effectiveness to VGB.
3. Based on available efficacy and effectiveness evidence alone, VPA is probably efficacious or effective as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures (level B).
   a. In one class II trial, for the combined group of 480 patients, CBZ and VPA had similar treatment-success rates, similar seizure-freedom rates at 12 and 24 months of follow-up and similar composite scores at 24 months. However, CBZ patients had a significantly better composite score than VPA at 12 months and a longer time to first seizure.
4. Based on available efficacy and effectiveness evidence alone, for adults with newly diagnosed or untreated partial-onset seizures, CBZ (level A), PHT (level A), and VPA (level B) should be considered as candidates for initial monotherapy. Among these first-line AED candidates, no clear first-choice AED is evident for initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures based solely on efficacy or effectiveness. Selection of the initial AED therapy for an adult with newly diagnosed or untreated partial-onset seizures requires integration of patient-specific, AED-specific, and nation-specific variables that can affect overall response to therapy (Table 1).

5. Based on available efficacy and effectiveness evidence alone, GBP, LTG, OXC, PB, TPM, and VGB are possibly efficacious or effective as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures (level C).
   a. GBP had similar efficacy/effectiveness as LTG (one class III DB trial) and demonstrated efficacy/effectiveness in a dose–response class III DB trial.
   b. LTG had similar efficacy/effectiveness to CBZ, PHT, and GBP in three separate class III DB trials, and CBZ in two class III OL trials.
   c. OXC had similar efficacy/effectiveness to CBZ, PHT, and VPA in three separate class III DB trials and superior efficacy/effectiveness compared with placebo in one class III DB trial.
   d. PB had inferior efficacy/effectiveness to CBZ (one class I trial) but similar efficacy/effectiveness to CBZ, PHT, and VPA in three separate class III OL trials and unclear results in a 1941 class III OL study.
   e. TPM had similar efficacy/effectiveness to CBZ and VPA (one class III DB trial) and demonstrated efficacy/effectiveness in two separate dose–response class III DB trials.
   f. VGB had inferior efficacy/effectiveness to CBZ (one class II trial) but similar efficacy/effectiveness to CBZ in two separate class III OL trials.
   g. GBP, LTG, OXC, PB, TPM, and VGB either have significantly less efficacy/effectiveness evidence than the previous candidates for initial monotherapy or they have evidence of inferior efficacy/effectiveness compared with the earlier candidates for initial monotherapy. These AEDs may be considered as initial monotherapy in selected situations.
6. Based on available efficacy and effectiveness evidence alone, CZP and PRM are potentially efficacious or effective as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures (level D).
   a. CZP had similar efficacy/effectiveness to CBZ in one small class III DB trial.
   b. PRM had inferior efficacy/effectiveness to CBZ in a class I trial.
7. Either no data or inadequate efficacy or effectiveness data are available to decide whether ACZ, ACTH, barbexaclone, beclamide, CLB, CLP, DZP, ESM, ETH, FBM, LEV, LZP, MPH, MPB, MSM, NTZ, PAC, PTR, PSM, PGB, PRO, STM, TGB, ZNS, or 4-amino-3-hydroxybutyric acid could be considered for initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures (level E).

Children with partial-onset seizures

Overview of evidence

A total of 25 RCTs (42,46,47,50,52,54,57–60,73–87) and one meta-analysis examined initial monotherapy of children with partial-onset seizures. Among the 25 RCTs, only one RCT (75) was considered as class I study, none were rated as class II, and 17 RCTs met criteria for class III studies (42,46,47,50,52,54,57–60,73,74,76–79,87). One RCT was only reported briefly with preliminary reports and not enough details about study design for a full evaluation; the study is not included further in the analysis (80). Six RCTs did not report effectiveness or efficacy as a primary outcome variable and are not included further in the analysis (81–86). Evidence focused exclusively on benign epilepsy with centrotemporal spikes is discussed later in the guideline.

Seventeen RCTs were classified as class III; five of them were DB RCTs classified as class III because of a forced-exit criterion alone (n = 2) (42,87) or DNIBs $\geq$31% with or without too short a duration of treatment (n = 3) (47,76,78). The remaining 12 RCTs were classified as class III because they were OL trials (46,50,52,54,57–60,73,74,77,79).

Among the 25 RCTs considered for evaluation, CBZ was the most frequently studied (n = 11) followed by VPA (n = 7), PHT (n = 6), PB (n = 5), and TPM (n = 3). CZP, CLB, LTG, OXC, and VGB were involved in single studies. The number of studies for each AED and their distribution by RCT class of evidence are shown in Table 6.

Effectiveness-outcome evidence

Two AEDs (PHT and OXC) had class I evidence regarding effectiveness in children with partial-onset seizures. Five AEDs (CBZ, CLB, CZP, TPM, and VPA) had class III DB RCT evidence regarding effectiveness in children with partial-onset seizures.

OXC, PHT (class I, n = 1): Only one study in this category demonstrated differential effectiveness between two treatment arms. In a comparative trial in children 5–17 years of age, treatment retention (defined as the rate of premature discontinuation due to adverse events or unsatisfactory therapeutic response) was significantly better for patients receiving OXC than for patients receiving PHT in the subset of patients with partial-onset seizures (75).

CBZ, CLB, CZP, TPM, and VPA (class III DB, n = 5): In a class III DB RCT comparing TPM with standard therapy (either CBZ, 600mg/day or VPA, 1250mg/day), the times to exit based on clinical response in the pediatric partial-onset seizure subset for TPM, 100 mg, or TPM, 200 mg, was similar to the time to exit for the CBZ or VPA arms (78). No effectiveness outcome data were reported for the pediatric partial-seizure subset of two high-dose low-dose forced-exit TPM RCTs (42,87).

TABLE 6. *Children with partial-onset seizures: number of studies by class of study and AED involved*

Class	CBZ	VPA	PHT	PB	TPM	LTG	OXC	VGB	CZP	CLB
I	0	0	1	0	0	0	1	0	0	0
II	0	0	0	0	0	0	0	0	0	0
III-DB	3	1	0	0	3	0	0	0	1	1
III-OL	8	6	5	5	0	1	0	1	0	0
Total	11	7	6	5	3	1	1	1	1	1

A class III DB RCT comparing CLB with standard therapy (either CBZ or PHT) showed CLB retention in the study for the first 12 months of therapy to be equal to that of standard therapy. This specific analysis was for the entire study cohort that included untreated and previously treated children and children with either partial-onset seizures or primary generalized seizures. In those previously untreated children, retention for the first 12 months after initiation of therapy showed no difference between CLB and CBZ; however, the data for the partial-onset seizure subgroup were not presented (76).

In a class III DB comparative trial of CBZ and CZP, too few pediatric patients (n = 6 CBZ, n = 8 CZP) were included to provide meaningful effectiveness data (47).

Efficacy-outcome evidence

Two AEDs (PHT and OXC) had class I evidence regarding efficacy in children with partial-onset seizures. Five AEDs (CBZ, CLB, CZP, TPM, and VPA) had class III DB RCT evidence regarding efficacy in children with partial-onset seizures.

OXC, PHT (class I, n = 1): The class I RCT comparing OXC and PHT in children showed no difference in seizure-free rates in patients with partial-onset seizures (75).

CBZ, CLB, CZP, TPM and VPA (class III DB, n = 5): In a class III DB study comparing TPM with standard therapy (either CBZ or VPA), the time to first seizure in the subset of pediatric partial-onset seizure patients receiving TPM, 100 mg, or TPM, 200 mg, was similar to the time to first seizure for patients in the CBZ or VPA arms. The proportions of seizure-free partial-onset seizure patients during the last 6 months of treatment were similar between the TPM, 100 mg/day, TPM, 200 mg/day, VPA, and CBZ arms (78). In a class III DB dose–response RCT, no statistical difference was found in seizure-free rates at 12 months between TPM, 400 mg/day, and TPM, 50 mg/day (81 vs. 60%; p = 0.08) (87). In a separate high-dose low-dose forced-exit TPM RCT, no efficacy data were reported for the pediatric partial-seizure subset (42). A class III DB RCT comparing CLB with standard therapy (either CBZ or PHT) did not present seizure-free data for the partial-onset seizure subgroup (76).

In a class III comparative trial of CBZ and CZP, too few pediatric patients were used (CBZ, n = 6; CZP, n = 8) to provide meaningful efficacy data (47).

Meta-analysis

One meta-analysis examined the efficacy of OXC as monotherapy in children with partial-onset seizures. Individual patient data from eight OXC DB RCTs (both published and unpublished) were pooled. Five of those eight studies were called adequate and well controlled (AWC). In the five AWC studies, 24 patients taking 600–2,400 mg/day OXC, called treated, were compared with 23 patients taking 300 mg/day OXC or placebo, called control. The other three DB studies contributed an additional 113 treated patients. Two outcome variables were examined: time to reach a protocol-specific end point (AWC studies only) and change in seizure frequency (both sets of studies). The first variable exhibited a trend toward better efficacy for OXC, with p = 0.08. The second variable showed superior efficacy for OXC with p = 0.02 and p = 0.002 for the five AWC studies and all eight DB studies, respectively. As a result, the meta-analysis concluded that OXC was efficacious as monotherapy in children with partial-onset seizures (45).

Summary and conclusions

1. Major general conclusions: A paucity of class I and class II RCTs exists for children with partial-onset seizures. Based on this guideline's definition, the adequate comparator for this category is OXC.
2. Based on available efficacy and effectiveness evidence alone, OXC is established as efficacious or effective as initial monotherapy for children with newly diagnosed or untreated partial-onset seizures (level A). In the lone class I trial in this category, OXC demonstrated superior effectiveness (compared with PHT) and equal efficacy.
3. Based on available efficacy and effectiveness evidence alone, for children with newly diagnosed or untreated partial onset seizures, OXC (level A) should be considered a candidate for initial monotherapy.
4. Based on available efficacy and effectiveness evidence alone, CBZ, PB, PHT, TPM, and VPA are possibly efficacious or effective as initial monotherapy for children with newly diagnosed or untreated partial-onset seizures (level C).
   a. Although 3 class III DB studies involved CBZ, only one was informative; in that trial CBZ had efficacy/effectiveness similar to that of TPM.

For this guideline analysis, the CLB-CBZ and CBZ-CZP class III DB trials were uninformative because data were presented only for the whole group (not specifically for the pediatric partial onset seizure subgroup) and too few pediatric patients were included (n = 6 CBZ, n = 8, CZP), respectively, to provide meaningful data. CBZ's efficacy/effectiveness in children with partial-onset seizures was similar to that of PB, PHT, LTG, and VPA in eight class III OL trials.

b. PB's efficacy/effectiveness in children with partial-onset seizures was similar to that of CBZ, PHT, and VPA in five class III OL trials.
c. PHT had inferior effectiveness to OXC in a class I trial but similar efficacy/effectiveness to CBZ, PB, and VPA in five separate class III OL trials.
d. TPM was involved in three class III DB trials, but only two were informative. TPM has similar efficacy/effectiveness to that of CBZ and VPA and a trend to a dose–response effect in a separate trial.
e. In a class III DB trial, VPA had similar efficacy/effectiveness to TPM. VPA's efficacy/effectiveness in children with partial-onset seizures was similar to CBZ, PB, and PHT in six class III OL trials.

5. Selection of the initial AED therapy for a child with newly diagnosed or untreated partial-onset seizures requires integration of patient-specific, AED-specific, and nation-specific variables that can affect overall response to therapy (Table 1).
6. Based on available efficacy and effectiveness evidence alone, LTG and VGB are potentially efficacious or effective as initial monotherapy for children with newly diagnosed or untreated partial–onset seizures (level D).
   a. LTG and VGB had similar efficacy/effectiveness to CBZ in separate class III OL trials.
7. Either no data or inadequate efficacy or effectiveness data are available to decide whether ACZ, ACTH, barbexaclone, beclamide, CLB, CZP, CLP, DZP, ESM, ETH, FBM, GBP, LEV, LZP, MPH, MPB, MSM, NTZ, PAC, PTR, PSM, PGB, PRM, PRO, STM, TGB, ZNS, or 4-amino-3-hydroxybutyric acid could be considered for initial monotherapy for children with newly diagnosed or untreated partial-onset seizures (level E).

Elderly adults with partial-onset seizures

Overview of evidence

In total, 30 initial monotherapy RCTs (9,31–34,37–53,55,56,58,61,66,88–90) included elderly adults with partial–onset seizures. Among the 30 RCTs, only one RCT (88) was considered a class I study, one RCT was rated as a class II study (89), and two RCTs met criteria for class III studies (43,46). Twenty-five RCTs included elderly adults but did not report their results independent of the entire adult cohort and are not included further in the analysis (9,31–34,37–42,44,45,47–53,55,56,58,61,66). One RCT did not report effectiveness or efficacy as a primary outcome variable and is not included further in the analysis (90).

TABLE 7. *Elderly adults with partial-onset seizures: number of relevant studies categorized by class of study and AED involved*

Class	CBZ	LTG	GBP	TPM	VPA
I	1	1	1	0	0
II	1	1	0	0	0
III-DB	1	0	0	1	1
III-OL	1	1	0	0	0
Total	4	3	1	1	1

One RCT was considered class II because it met all class I criteria except that the duration of treatment and assessment was only 24 weeks (89). Two RCTs were classified as class III because of a DNIB $\geq$31% (n = 1) (43) or because of an OL trial design (46).

Among the four RCTs considered for evaluation, CBZ was the most frequently studied (n = 4) followed by LTG (n = 3), 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 7.

Effectiveness-outcome evidence

Three AEDs (CBZ, GBP, LTG) had class I or class II evidence regarding effectiveness in elderly adults with partial-onset seizures. Two AEDs (TPM and VPA) had class III RCT evidence regarding effectiveness in adults with partial-onset seizures.

CBZ, GBP, LTG (class I, n = 1): A 2005 trial of 593 elderly adults with newly diagnosed epilepsy (ages 60 years and older) compared CBZ, GBP, and LTG as initial monotherapy. Unlike pediatric and adult trials, this study's entry criteria did not clearly require a specific number of lifetime seizures before randomization but did state that the subjects needed to have a diagnosis of epilepsy requiring therapy and a minimum of one seizure during the 3 months preceding enrollment. The investigators supplied additional data that showed that >60% of the enrolled subjects had two or more seizures during the 3 months preceding enrollment; overall, the investigators considered the patient population to be representative of patients with new-onset geriatric epilepsy. Given the elderly age at epilepsy onset and the authors' comment that "of the 25.3% with GTCs alone, none had evidence of primary generalized epilepsy; for example, generalized spike–wave discharges in the EEG" (88), all patients in

the study were considered to have partial-onset seizures. This is in contrast to other analyses in this guideline in which generalized-onset TC seizures are analyzed separately from partial-onset seizures because they may represent true primary generalized epilepsy, a condition rarely seen de novo in the elderly.

Early terminations in the study at 12 months were greater for CBZ compared with either LTG or GBP (44.2% LTG vs. 64.5% CBZ; $p < 0.0001$; and 51% GBP vs. 64.5% CBZ; $p = 0.008$) (88). No difference was found between the treatment groups for study exits due to inadequate seizure control; instead, differential retention rates were related to terminations resulting from adverse reactions. The LTG group had significantly fewer terminations related to adverse reactions than did either the CBZ group ($p < 0.0001$) or the GBP group ($p = 0.015$) (88).

CBZ, LTG (class II, n = 1): In a study involving 150 elderly adults with epilepsy, 71% of the LTG patients completed the study compared with 42% of the CBZ patients. The hazard ratio based on withdrawal rates was 2.4 (95% CI, 1.4–4.0) favoring greater retention for LTG ($p < 0.001$).

CBZ, LTG, TPM, VPA (class III, n = 2): In the TPM-CBZ-VPA class III DB trial, the investigators reported that the times to exit results in the CBZ, VPA, and two TPM branches for the elderly partial-onset seizure subgroup were similar to those for the intent-to-treat population but the study did not report p values or confidence intervals (43). In an OL comparative trial of CBZ and LTG, a trend was found for a larger percentage of the subgroup of elderly patients receiving LTG to complete the study compared with those elderly patients receiving CBZ (66% LTG vs. 36% CBZ) (46). The authors suggested that the difference in retention is due to tolerability because a higher percentage of CBZ patients withdrew because of adverse reactions compared with the LTG group (LTG 20% vs. CBZ 50%; $p < 0.05$) (46).

Efficacy-outcome evidence

Three AEDs (CBZ, GBP, and LTG) had either class I or class II evidence regarding efficacy in elderly adults with partial-onset seizures. None of the four AEDs (CBZ, LTG, TPM, and VPA) studied in class III RCTs of elderly adults with partial-onset seizures had efficacy data reported.

CBZ, GBP, LTG (class I, n = 1): In the class I 2005 three-arm RCT comparison of CBZ, GBP, and LTG, no difference was found between the treatments in (a) seizure freedom at 12 months, (b) time to first, second, fifth, or tenth seizure during the first year, or (c) seizure-free retention at 12 months (88).

CBZ, LTG (class II, n = 1): In a class II RCT, a larger percentage of LTG patients were seizure free during the last 16 weeks of treatment compared with CBZ patients (39% vs. 21%; $p = 0.027$). No difference was noted between CBZ and LTG in time to first seizure (88).

CBZ, LTG, TPM, and VPA (class III, n = 2): No seizure-freedom comparisons were reported in the subset of elderly adults with newly diagnosed partial-onset seizures during the last 6 months of treatment for CBZ, VPA, and two different dosages of TPM (43). In the OL comparative trial of CBZ and LTG, the authors reported that the efficacy of LTG and CBZ "appeared to be similar" but did not present any specific results (46).

Summary and conclusions

1. Major general conclusions: A paucity of class I and class II RCTs exist for elderly adults with partial-onset seizures. Based on this guideline's definition, the adequate comparators for this category are LTG and GBP.
2. Based on available efficacy and effectiveness evidence alone, LTG and GBP are established as efficacious or effective as initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures (level A).
   a. In the lone class I trial in this category, LTG and GBP demonstrated superior effectiveness compared with CBZ. In the single class II elderly adult trial, LTG had superior efficacy/effectiveness compared with CBZ. In an elderly adult class III OL study, LTG had better tolerability than CBZ and a trend toward better effectiveness.
3. Based on available efficacy and effectiveness evidence alone, for elderly adults with newly diagnosed partial-onset seizures, LTG (level A) and GBP (level A) should be considered as candidates for initial monotherapy. Among these first-line AED candidates, LTG had the greater body of RCT evidence for efficacy/effectiveness, but no clear first-choice AED was found for initial monotherapy for elderly adults with newly diagnosed partial-onset seizures based solely on efficacy or effectiveness. Selection of the initial AED therapy for an elderly adult with newly diagnosed or untreated partial-onset seizures requires integration of patient-specific, AED-specific, and nation-specific variables that can affect overall response to therapy (Table 1).
4. Based on available efficacy and effectiveness evidence alone, CBZ is possibly efficacious/effective as initial monotherapy for elderly adults with newly diagnosed partial-onset seizures (level C).
   a. In the lone class I trial in this category, CBZ demonstrated inferior effectiveness but similar efficacy compared with LTG and GBP. In the single class II elderly adult trial, CBZ had inferior efficacy/effectiveness compared with LTG.

In an elderly adult class III OL study, CBZ had worse tolerability than LTG and a trend toward worse effectiveness. In an elderly adult class III DB trial, CBZ, VPA, and TPM were reported to have had similar effectiveness, but specific data were not presented.

b. CBZ has evidence of inferior efficacy/effectiveness compared with the other candidates for initial monotherapy. CBZ may be considered as initial monotherapy for elderly adults with newly diagnosed partial-onset seizures in selected situations.

5. Based on available efficacy and effectiveness evidence alone, TPM and VPA are potentially efficacious or effective as initial monotherapy for elderly adults with newly diagnosed partial-onset seizures (level D).
   a. In an elderly adult class III DB trial, CBZ, VPA, and TPM were reported to have had similar effectiveness, but specific data were not presented (level D).
6. Either no data or inadequate efficacy or effectiveness data are available to decide whether ACZ, ACTH, barbexaclone, beclamide, CLB, CZP, CLP, DZP, ESM, ETH, FBM, LEV, LZP, MPH, MPB, MSM, NTZ, OXC, PAC, PTR, PB, PSM, PHT, PGB, PRM, PRO, STM, TGB, VGB, ZNS, or 4-amino-3-hydroxybutyric acid could be considered for initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures (level E).

Generalized-onset seizures (adults and children)

This section examines initial monotherapy for three types of generalized-onset seizures: adults with generalized onset tonic–clonic (GTC) seizures, children with GTC, and children with absence seizures. The goals of treatment for adults and children with GTC seizures are the best quality of life with no seizures and the fewest adverse effects from treatment. The final recommendations for the individual patient should be based on the systematic review of efficacy/effectiveness evidence combined with data concerning safety, pharmacokinetic properties, formulations, and expense. Physicians and patients must weigh each of these characteristics in the context of the individual patient.

Adults with generalized-onset tonic–clonic seizures

Overview of evidence

A total of 26 RCTs (32,33,35–39,41,43,44,48–51,53–60,63–65,91) and five meta-analyses (67–71) examined initial monotherapy of adults with GTC seizures. Three RCTs did not report effectiveness or efficacy as a primary outcome variable and are not included further in the analysis (63–65).

Twenty-three RCTs were classified as class III. Ten were DB RCTs classified as class III because of a forced-exit criterion alone (n = 1) (44), forced-exit criteria plus too short a duration of treatment, and DNIB ≥31% (n = 1) (56), or DNIBs ≥31% with or without too short a duration of treatment (n = 8) (33,37–39,41,43,48,49). The remaining 13 RCTs were classified as class III because they were OL trials (32,35,36,50,51,53–55,57–60,91).

Among the 23 RCTs, PHT, CBZ, and VPA were the most commonly studied AEDs (n = 11, 11, and 10, respectively). The majority of RCTs involving these AEDs were OL class III studies. PB and LTG were both examined in four studies, OXC in three studies, and TPM in two studies. In contrast, the majority of studies involving LTG, OXC, and TPM were DB RCTs. GBP, VGB, and PTR were involved in single studies. The number of studies for each AED and the distribution by RCT class of evidence is shown in Table 8.

Effectiveness-outcome evidence

No AEDs had class I or class II evidence regarding effectiveness in adults with GTC seizures. Seven AEDs (CBZ, GBP, OXC, PHT, LTG, TPM, and VPA) had class III DB RCT evidence regarding effectiveness in adults with GTC seizures.

CBZ, GBP, OXC, PHT, LTG, TPM, VPA (class III DB, n = 9): No effectiveness data for the generalized-onset TC seizure subgroup was presented in either the LTG-CBZ or LTG-PHT study (37, 41) but in a separate class III DB RCT, GBP and LTG had similar time to exit by seizure type (49). However, in the latter study, 5 of 31 GBP-treated patients with GTC seizures exited prematurely, compared with 0 of 27 LTG-treated patients. Treatment retention (defined by the rate of premature discontinuation for any reason) was similar between treatment arms for the subset of patients with GTC seizures in an OXC-PHT comparative trial and in a separate OXC-VPA comparative trial (38,39). No effectiveness-outcome data were reported for an OXC-CBZ comparative trial (33). In the forced-exit TPM-CBZ-VPA trial, the investigators reported that the times-to-exit results (based on the clinical responses in the CBZ branch, the VPA branch, and the two TPM branches) for the GTC seizure subgroup were similar to those for the intent-to-treat population, but the study did not report p values or confidence intervals (43). No effectiveness-outcome data were reported for a high-dose, low-dose forced-exit TPM RCT (44) or a CBZ-PHT comparative study (48).

Efficacy-outcome evidence

No AEDs had class I or class II evidence regarding efficacy in adults with GTC seizures. Six AEDs (CBZ, OXC, PHT, LTG, TPM, and VPA) had class III DB RCT evidence regarding effectiveness in adults with GTC seizures.

CBZ, OXC, PHT, LTG, TPM, VPA (class III DB, n = 9): In three separate class III DB OXC comparison studies, OXC had similar proportion of seizure-free

TABLE 8. *Adults with generalized-onset tonic–clonic seizures: number of relevant studies categorized by class of study and AED involved*

Class	PHT	CBZ	VPA	PB	LTG	OXC	TPM	GBP	PTR	VGB
I	0	0	0	0	0	0	0	0	0	0
II	0	0	0	0	0	0	0	0	0	0
III-DB	4	4	2	0	3	3	2	1	1	0
III-OL	7	7	8	4	1	0	0	0	0	1
Total	11	11	10	4	4	3	2	1	1	1

patients to CBZ, PHT, and VPA for the subset of patients with GTC seizures (33,38,39). In separate class III DB studies, LTG had the same percentage of patients remaining on treatment and seizure-free in the last 24 or 40 weeks and also the same time to first seizure after the first 6 weeks of treatment as CBZ and PHT in the GTC seizure subgroup (37,41); GBP and LTG had similar time to first seizure and proportion of seizure-free patients during the last 12 weeks of a 30-week maintenance phase in a class III DB comparative study (49). A class III DB comparative trial of CBZ and PHT was uninformative because of the low number of patients with GTC seizures in the study (48).

Comparisons between TPM, CBZ, and VPA in the subset of patients with newly diagnosed GTC seizures showed that a similar proportion of patients were seizure-free during the last 6 months of treatment for CBZ, VPA, and two different dosages of TPM (43). In a TPM forced-exit dose–response trial, TPM, 400 mg/day, had a longer time to first seizure than TPM, 50 mg/day, and a higher seizure-free rate at both 6 months and 1 year for the entire cohort. However, for the subset of adult patients with only GTC seizures, no statistical difference was found between the high-dose and low-dose seizure-free rates at 12 months (78% vs. 60%; $p = 0.06$) (44).

Meta-analyses

Five meta-analyses have examined AED efficacy and effectiveness for adults with partial-onset and GTC seizures. These meta-analyses compared CBZ versus VPA (67), PHT versus VPA (69), CBZ versus PHT (68), PHT versus PB (70), and CBZ versus PB (71), with a focus on three end points: time to withdrawal, number of patients achieving 12-month seizure freedom, and time to first seizure. The vast majority of data used in these meta-analyses were from class III studies. The meta-analyses found "no reliable evidence to distinguish CBZ and VPA for partial-onset seizures and generalized-onset seizures" (67). No significant differences were found for PHT versus VPA, CBZ versus PHT, or CBZ versus PB for the outcomes examined for GTC seizures (68,69,71). For the PHT-versus-PB comparison, PHT was superior to PB for time to withdrawal of treatment, but no difference was noted between the two AEDs for time to 12-month remission, and a nonsignificant trend toward a preference for PB over PHT for time to first seizure (70).

Summary and Conclusions

1. Major general conclusions: The absence of class I and class II RCTs for adults with GTC seizures implies a marked deficiency in adequately powered, seizure type–specific, published studies. No AEDs reach the highest levels of evidence (levels A and B) for efficacy/effectiveness for adults with GTC seizures. Based on this guideline's definition, no adequate comparator exists for this category.
2. Based on RCT efficacy and effectiveness evidence, CBZ, LTG, OXC, PB, PHT, TPM, and VPA are possibly efficacious/effective as initial monotherapy for adults with GTC seizures and may be considered for initial therapy in selected situations (level C).
   a. Three class III DB trials involved CBZ, were informative, and reported similar efficacy/effectiveness to TPM, LTG, and OXC in adults with GTC seizures. Seven separate class III OL trials involved CBZ and showed similar efficacy/effectiveness to PB, PHT, LTG, and VPA.
   b. LTG had similar efficacy/effectiveness to CBZ, PHT, and GBP in three separate class III DB trials, and CBZ, in one class III OL trial.
   c. OXC had similar efficacy/effectiveness to CBZ, PHT, and VPA in three separate class III DB trials.
   d. The efficacy/effectiveness of PB was similar to CBZ, PHT, and VPA in three class III OL trials.
   e. TPM was involved in two class III DB trials with similar efficacy/effectiveness as CBZ and VPA and a trend to a dose–response effect in a separate trial.
   f. PHT had two informative class III DB trials (showing similar efficacy/effectiveness to OXC and LTG), two uninformative class III DB trials, and seven class III OL trials demonstrating similar efficacy/effectiveness to CBZ, PB, and VPA.
   g. VPA had similar efficacy/effectiveness to TPM and OXC in two separate class III DB trials

and to CBZ, PB, and PHT in eight class III OL trials.

3. Based on available efficacy and effectiveness evidence alone, for adults with newly diagnosed or untreated GTC seizures, CBZ, LTG, OXC, PB, PHT, TPM, and VPA may be considered as candidates for initial monotherapy (level C). Among these first-line AED candidates, no clear first-choice AED exists for initial monotherapy for adults with newly diagnosed or untreated GTC seizures based solely on efficacy or effectiveness. Selection of the initial AED therapy for an adult with newly diagnosed or untreated generalized-onset TC seizures requires integration of patient-specific, AED-specific, and nation-specific variables that can affect overall response to therapy (Table 1).
4. Class IV evidence suggests that CBZ, OXC, and PHT may precipitate or aggravate GTC seizures and, more commonly, other generalized seizure types in patients with GTC seizures and therefore these drugs should be used with caution in these patients (92–95).
5. Based on RCT efficacy and effectiveness evidence, GBP and VGB are potentially efficacious/effective as initial monotherapy for adults with generalized-onset TC seizures (level D).
   a. GBP had similar efficacy/effectiveness to LTG in one class III DB trial. VGB had similar efficacy/effectiveness to CBZ in one class III OL trial.
6. Either no data or inadequate efficacy or effectiveness data are available to decide whether ACZ, ACTH, barbexaclone, beclamide, CLB, CZP, CLP, DZP, ESM, ETH, FBM, LEV, LZP, MPH, MPB, MSM, NTZ, PAC, PTR, PSM, PGB, PRM, PRO, STM, TGB, ZNS, or 4-amino-3-hydroxybutyric acid could be considered for initial monotherapy for adults with newly diagnosed or untreated GTC seizures (level E).
7. For this guideline analysis, both the CBZ-PHT and PHT-PTR class III DB trials were uninformative, because it was not possible to determine the outcome or analysis for the very small subgroup of patients with GTC seizures.

Children with generalized-onset tonic–clonic seizures

Overview of evidence

A total of 20 RCTs and no meta-analyses examined initial monotherapy of children with GTC seizures (44,50,54,57–60,73–78,80,81,83–87,96). No studies were classified as class I or class II. Fourteen RCTs met criteria for a class III study (50,54,57–60,73–78,87,96). One RCT was only a preliminary report and did not have enough details about study design for a full evaluation; the study is not included further in the analysis (80). Five RCTs did not report effectiveness or efficacy as a primary outcome variable and are not included further in the analysis (81,83–86).

TABLE 9. *Children with generalized-onset tonic–clonic seizures: number of relevant studies categorized by class of study and AED involved*

Class	PHT	CBZ	VPA	PB	TPM	OXC	CLB
I	0	0	0	0	0	0	0
II	0	0	0	0	0	0	0
III-DB	2	2	2	1	2	1	1
III-OL	5	5	5	5	0	0	0
Total	7	7	7	6	2	1	1

Fourteen RCTs were classified as class III; one DB study had a forced-exit criterion (n = 1) (87), four DB studies had DNIBs ≥31% (n = 4) (75,76,78,96), whereas the remaining nine studies were classified as class III because they were OL trials (50,54,57–60,73,74,77).

Among the 14 class III RCTs, PHT, CBZ, and VPA were the most commonly studied AEDs (n = 7, 7, and 7, respectively). PB was examined in six studies, TPM in two studies, and OXC and CLB in one study each (Table 9).

Effectiveness-outcome evidence

CBZ, CLB, PB, PHT, OXC, TPM, and VPA (class III DB, n = 5): In a class III DB RCT comparing TPM with standard therapy (either CBZ or VPA), the time to exit in the pediatric GTC seizure subset for TPM, 100 mg, or TPM, 200 mg, was similar to the time to exit for the CBZ or VPA arms (78). No effectiveness-outcome data was reported for the pediatric GTC seizure subset of a high-dose, low-dose forced-exit TPM RCT (87). In a class III pediatric DB study, OXC and PHT had similar treatment retention in the subset of patients with GTC seizures (75). A class III pediatric DB RCT of PB, PHT, and VPA did not report effectiveness data (96). A class III DB RCT comparing CLB with standard therapy (either CBZ or PHT) did not present effectiveness data for the previously untreated GTC seizure subgroup (76).

Efficacy-outcome evidence

CBZ, CLB, PB, PHT, OXC, TPM, and VPA (class III DB, n = 5): Only one study in this category demonstrated differential efficacy between two treatment arms. In the pediatric GTC seizure subgroup in a class III DB dose–response trial of TPM, 400 mg/day, versus TPM, 50 mg/day, the higher TPM-dose subgroup had a significantly higher seizure-free rate at 12 months than the lower TPM-dose subgroup (88% vs. 63%; p = 0.02) (87). For the GTC seizures subgroup, both the time to first seizure and the proportion of patients seizure free during the last 6 months of treatment were similar in the class III DB TPM-CBZ and TPM-VPA comparison study (78).

In a class III DB RCT focused solely on newly diagnosed children ages 4 to 12 years with GTC seizures, no difference was found in the recurrence of seizures between PB, PHT, and VPA (96). No difference was found between OXC and PHT in the proportion of patients with GTC seizures remaining seizure free over a 48-week maintenance period (75). A class III DB RCT comparing CLB with standard therapy (either CBZ or PHT) did not present seizure-free data for the GTC seizure subgroup (76).

Summary and conclusions

1. Major general conclusions: The absence of class I and class II RCTs for children with GTC seizures implies a marked deficiency in adequately powered, seizure type–specific, published studies for this category. No AEDs reached the highest levels of evidence (level A or B) for efficacy/effectiveness for children with GTC seizures. No adequate comparator exists for this category. TPM would have been an adequate comparator for this category if the superiority dose–response trial had not been a forced-exit class III trial (87).
2. Based on RCT efficacy and effectiveness evidence, CBZ, PB, PHT, TPM, and VPA are possibly efficacious/effective for children with GTC seizures (level C).
   a. Two class III DB trials involved CBZ, but only one was informative; in five class III OL trials, CBZ had similar efficacy/effectiveness to PB, PHT, and VPA. For this guideline analysis, the CLB-CBZ class III DB trial was uninformative because data were presented only for the whole group and not specifically for the pediatric GTC seizure subgroup.
   b. PB had similar efficacy/effectiveness to PHT and VPA in one class III DB trial and CBZ, PHT, and VPA in five separate class III OL trials.
   c. PHT had similar efficacy/effectiveness to PB and VPA in one class III DB trial and CBZ, PB, and VPA in five separate class III OL trials.
   d. TPM had similar efficacy/effectiveness to CBZ and VPA in one class III DB trial, and demonstrated a dose–response effect in another class III DB trial.
   e. VPA had similar efficacy/effectiveness to TPM (one class III DB trial), to PB and PHT (one class III DB trial), and to CBZ, PB, and PHT (five separate class III OL trials).
3. Based on available efficacy and effectiveness evidence alone, for children with newly diagnosed or untreated GTC seizures, CBZ, PB, PHT, TPM, and VPA may be considered as candidates for initial monotherapy. Among these AED candidates, no clear first-choice AED exists for initial monotherapy for children with newly diagnosed or untreated GTC seizures based solely on efficacy or effectiveness. Selection of the initial AED therapy for a child with newly diagnosed or untreated GTC seizures requires integration of patient-specific, AED-specific, and nation-specific variables that can affect overall response to therapy (Table 1).
4. Class IV evidence suggests that CBZ, OXC, and PHT may precipitate or aggravate GTC seizures and, more commonly, other generalized seizure types in patients with GTC seizures and therefore these drugs should be used with caution in these patients (92–95).
5. Based on RCT efficacy and effectiveness evidence, OXC is potentially efficacious/effective for children with GTC seizures (level D).
   a. OXC had similar efficacy/effectiveness to PHT in one class III DB trial.
6. Either no data or inadequate efficacy or effectiveness data are available to decide whether ACZ, ACTH, barbexaclone, beclamide, CLB, CZP, CLP, DZP, ESM, ETH, FBM, GBP, LTG, LEV, LZP, MPH, MPB, MSM, NTZ, PAC, PTR, PSM, PGB, PRM, PRO, STM, TGB, VGB, ZNS, or 4-amino-3-hydroxybutyric acid could be considered for initial monotherapy for children with newly diagnosed or untreated GTC seizures (level E).

TABLE 10. *Children with absence seizures: number of relevant studies categorized by class of study and AED involved*

Class	VPA	ESM	LTG	GBP
I	0	0	0	0
II	0	0	0	0
III-DB	1	1	1	1
III-OL	3	2	1	0
Total	4	3	2	1

Children with absence seizures

Overview of evidence

A total of six RCTs and one meta-analysis examined initial monotherapy of children with either typical absence seizures or childhood absence epilepsy (97–103). None of these RCTs met the criteria for a class I or II study. All six studies were classified as class III and included for analysis; three had a DB design with an inadequate treatment duration (2–12 weeks) (97,98,100), and three were OL studies (99,101,102). Among the six class III RCTs, VPA was the most frequently studied AED (n = 4). ESM was examined in three studies, LTG in two studies, and GBP in one study (Table 10).

Effectiveness-outcome evidence

None of the class III DB trials presented long-term effectiveness data.

Efficacy-outcome evidence

ESM, GBP, LTG, VPA (class III DB and OL, n = 6): In a class III DB trial, VPA and ESM were equally effective in reducing generalized spike–wave discharges in 16 previously untreated patients with absence seizures in a DB response conditional crossover study (100). A class III DB trial with a 2-week DB phase found no difference between GBP monotherapy (n = 15) and placebo monotherapy (n = 18) in 33 patients with previously untreated childhood absence epilepsy. Seizure frequency was determined by using 24-h ambulatory EEGs (97).

Another class III DB trial was not a pure initial monotherapy trial but rather a conditional, randomized conversion to placebo DB trial. In the study, 45 patients entered into an OL dose-escalation phase of LTG lasting 5–25 weeks followed by a 4-week DB placebo-controlled phase in which patients with well-controlled absence seizures were randomized either to continue LTG at their current dose or to be weaned to placebo (98). Overall, 28 patients were randomized to LTG (n = 14) or placebo (n = 14). The proportion of patients remaining seizure-free during the DB treatment phase was greater for LTG compared with placebo ($p = 0.03$) (98).

Two class III OL RCTs compared VPA and ESM in the initial monotherapy treatment of children with absence seizures. These small studies (involving 28 and 20 patients, respectively) were OL RCTs that reported equal efficacy for VPA and ESM in achieving complete remission of absence seizures (99,101,104). In a class III OL RCT, 38 patients were randomized to either VPA (n = 19) or LTG (n = 19) and followed for 1 year. At the end of 12 months, no statistical difference in seizure-free rates was found between the two groups (102) although VPA acted faster in achieving seizure freedom.

Meta-analyses

One meta-analysis examined AED efficacy and effectiveness for children with absence seizures (103). This meta-analysis compared ESM, VPA, and LTG with a focus on four end points: proportion of children seizure-free at 1, 6, and 18 months after randomization, children with a ≥50% reduction in seizure frequency, normalization of the EEG, and adverse effects. The majority of data used in this meta-analysis were from class III studies. The meta-analysis found "insufficient evidence to inform clinical practice" (103).

Summary and conclusions

1. Major general conclusions: The absence of class I and class II RCTs for children with absence seizures implies a marked deficiency in adequately powered, seizure type–specific, published studies for this category. No AEDs reach the highest levels of evidence (level A or B) for efficacy/effectiveness for children with absence seizures. No adequate comparator exists for this category.
2. Based on RCT efficacy and effectiveness evidence, ESM, LTG, and VPA are possibly efficacious/effective for children with absence seizures (level C).
   a. ESM had similar efficacy/effectiveness to VPA (one class III DB trial and two class III OL trials).
   b. LTG had superior efficacy to placebo (one short-term class III DB trial) and slower onset of efficacy compared to VPA (one class III OL trial).
   c. VPA had similar efficacy/effectiveness to ESM (one class III DB trial and two class III OL trials) and faster onset of efficacy compared to LTG (one class III OL trial).
3. Based on available efficacy and effectiveness evidence alone, for children with newly diagnosed or untreated absence seizures, ESM, LTG, and VPA may be considered as candidates for initial monotherapy. Among these three AED candidates, no clear first-choice AED exists for initial monotherapy for children with newly diagnosed or untreated absence seizures based solely on efficacy or effectiveness. Selection of the initial AED therapy for a child with newly diagnosed or untreated absence seizures requires integration of patient-specific, AED-specific, and nation-specific variables that can affect overall response to therapy (Table 1).
4. Either no data or inadequate efficacy or effectiveness data are available to decide whether ACZ, ACTH, barbexaclone, beclamide, CBZ, CLB, CZP, CLP, DZP, ETH, FBM, GBP, LEV, LZP, MPH, MPB, MSM, NTZ, OXC, PAC, PTR, PB, PSM, PHT, PGB, PRM, PRO, STM, TGB, TPM, VGB, ZNS, or 4-amino-3-hydroxybutyric acid could be considered for initial monotherapy for children with newly diagnosed or untreated absence seizures (level E).
5. Based on RCT efficacy and effectiveness evidence, GBP may be considered as inefficacious/ineffective for children with absence seizures (level F).
   a. GBP had similar efficacy to placebo in one short-term class III DB trial.
6. Based solely on scattered reports (class IV), the following AEDs may precipitate or aggravate absence seizures: CBZ, OXC, PB, PHT, TGB, and VGB (92–95).

Idiopathic localization-related epilepsy syndromes

The goals of treatment for patients with idiopathic localization related epilepsy syndromes are the best quality of life with no seizures and the fewest adverse effects from treatment. The ultimate choice of an AED for any individual patient with a newly diagnosed idiopathic

localization-related epilepsy syndrome should include consideration of the strength of each AED's efficacy and effectiveness evidence along with the other variables in Table 1 (e.g., the AED safety profile, pharmacokinetic properties, formulations and expense). When selecting a patient's AED, physicians and patients should consider all relevant variables and not just AED efficacy and effectiveness. This section examines initial monotherapy for children with benign epilepsy with centrotemporal spikes (BECTS), also called benign rolandic epilepsy.

Children with benign epilepsy with centrotemporal spikes (BECTS)

Overview of evidence

Because this specific epilepsy syndrome is characterized by partial-onset seizures, evidence used to make recommendations will be taken from (a) RCTs that focused specifically on children with newly diagnosed or untreated BECTS, and (b) RCTs focused on children with newly diagnosed or untreated partial-onset seizures.

BECTS RCTs: In total, three RCTs and no meta-analyses specifically examined the initial monotherapy of children with BECTS (105–107). None of these RCTs met the criteria for a class I or II study. Two RCTs were considered class III studies (105,107); the other RCT did not report efficacy or effectiveness as a primary outcome variable and is not further considered in the analysis (106). Both RCTs were placebo-controlled, forced-exit class III DB trials that were 24 and 36 weeks in duration; the medication studied in these trials were STM and GBP, respectively.

Partial-onset seizure clinical trials: The identification and analysis of RCTs focused on children with newly diagnosed or untreated partial-onset seizures is presented earlier in this manuscript and is not repeated. The subcommission decided that a specific AED's evidence from the partial-onset seizure analysis could be considered in this BECTS analysis as long as (a) at least one study of the specific AED in BECTS was found (including studies with class IV evidence); *and* (b) the specific AED had a C or better level of evidence in the partial-onset seizure analysis. For each AED evaluated by class IV evidence, only a single representative study is referenced.

Effectiveness-outcome evidence

Two AEDs (STM and GBP) have class III DB RCT evidence regarding effectiveness in children with BECTS.

STM and GBP (class III DB, n = 2): A forced-exit class III placebo-controlled DB trial of 66 children with BECTS randomized patients to either STM (n = 31) or placebo (n = 35). STM showed superior effectiveness compared with placebo (p = 0.00002) in patients completing 6 months without a treatment-failure event (105). A separate forced-exit class III placebo-controlled DB trial of 225 children with BECTS randomized patients to either GBP (n = 113) or placebo (n = 112). Depending on the statistical analysis, GBP showed superior effectiveness compared with placebo (Wilcoxon test, p = 0.0395) or a trend toward significance (log rank test, p = 0.06) (107).

Efficacy-outcome evidence

Neither class III BECTS study reported specific efficacy-outcome variables (105,107).

Relevant partial-onset seizure trials

Among the six AEDs that received a C or better level of evidence rating in the partial-onset seizure analysis (OXC, CBZ, PB, PHT, TPM, and VPA), only CBZ and VPA have BECTS-related clinical studies (all class IV nonrandomized trials) (108). Other AEDs with BECTS-related nonrandomized clinical studies [such as CLB (109), LTG (110), and LEV (111)] are not further considered because these AEDs had not received a C or better level of evidence rating in the partial-onset seizure analysis.

Summary and conclusions

1. Major general conclusions: The absence of class I and class II RCTs for children with BECTS implies a marked deficiency in adequately powered, epilepsy syndrome–specific, published studies for this category. Based on BECTS-specific studies, no AED reaches the highest levels of evidence (level A or B) for efficacy/effectiveness for children with BECTS. No adequate comparator exists for this category.
2. Based on available efficacy and effectiveness evidence alone, CBZ and VPA are possibly efficacious or effective as initial monotherapy for children with BECTS (level C).
   a. Both CBZ and VPA have a level C evidence of efficacy/effectiveness for children with partial-onset seizures with class IV evidence of efficacy for BECTS.
3. Based on available efficacy and effectiveness evidence alone, for children with newly diagnosed BECTS, CBZ and VPA may be considered as candidates for initial monotherapy. Between these two AED candidates, no clear-choice AED exists for initial monotherapy for children with BECTS based solely on efficacy or effectiveness. Selection of the initial AED therapy for a child with BECTS requires integration of patient-specific, AED-specific, and nation-specific variables that can affect overall response to therapy (Table 1).
4. Based on available efficacy and effectiveness evidence alone, GBP and STM are potentially efficacious or effective as initial monotherapy for children with BECTS (level D).
   a. Both GBP and STM had superior effectiveness compared with placebo in separate forced-exit class III DB trials.

5. Either no data or inadequate efficacy or effectiveness data are available to decide whether ACZ, ACTH, barbexaclone, beclamide, CLB, CZP, CLP, DZP, ESM, ETH, FBM, LTG, LEV, LZP, MPH, MPB, MSM, NTZ, OXC, PAC, PTR, PB, PSM, PHT, PGB, PRM, PRO, TGB, TPM, VGB, ZNS, or 4-amino-3-hydroxybutyric acid could be considered for initial monotherapy for children with BECTS (level E). Although OXC, PHT, PB, and TPM have demonstrated efficacy and effectiveness for partial-onset seizures (level C or above), no published reports have documented their efficacy or effectiveness in BECTS, and therefore they are not considered to have adequate data yet for this epilepsy syndrome.
6. Class IV evidence suggests that, unlike other epilepsy syndromes, some children with BECTS do not need AED therapy.

Idiopathic generalized epilepsy syndromes

The goals of treatment for adults and children with idiopathic generalized epilepsy syndromes are the best quality of life with no seizures and the fewest adverse effects from treatment. The ultimate choice of an AED for any individual patient with a newly diagnosed idiopathic epilepsy syndrome should include consideration of the strength of each AED's efficacy and effectiveness evidence along with the other variables in Table 1 (e.g., the AED's safety profile, pharmacokinetic properties, formulations, and expense). When selecting a patient's AED, physicians and patients should consider all relevant variables and not just AED efficacy and effectiveness. This section examines initial monotherapy for patients with juvenile myoclonic epilepsy.

Juvenile myoclonic epilepsy

Overview of evidence

No RCTs have examined the initial monotherapy for patients with juvenile myoclonic epilepsy (JME). Two RCTs involving JME populations did not report efficacy or effectiveness as a primary outcome variable and are not further considered in the analysis (112–114). Because of the lack of studies with class I, II, or III evidence, studies with class IV evidence (both initial monotherapy and adjunctive therapy) were included for this analysis.

Effectiveness-outcome evidence

No class I, II, III, or IV effectiveness studies exist in this patient population.

Efficacy-outcome evidence

No class I, II, or III efficacy studies exist in this patient population. Class IV studies have indicated CZP, LTG, LEV, TPM, VPA, and ZNS have some evidence of efficacy as monotherapy or adjunctive therapy for patients with JME (115–128).

Summary and conclusions

1. Major general conclusions: The absence of class I, class II, and class III RCTs for patients with JME implies a marked deficiency in adequately powered, epilepsy syndrome type–specific, published studies for this category. No AEDs reach the highest levels of evidence (level A, B, or C) for efficacy/effectiveness for patients with JME. No adequate comparator exists for this category.
2. Class IV studies suggest that CZP, LTG, LEV, TPM, VPA, and ZNS may have some efficacy for patients with newly diagnosed JME.
3. Among these AEDs, no clear first-choice AED exists for initial monotherapy for children with newly diagnosed or untreated JME based solely on efficacy or effectiveness. Selection of the initial AED therapy for a patient with newly diagnosed JME requires integration of patient-specific, AED-specific, and nation-specific variables that can affect overall response to therapy (Table 1).
4. No efficacy or effectiveness data are available to decide whether ACZ, ACTH, barbexaclone, beclamide, CBZ, CLB, CLP, DZP, ESM, ETH, FBM, GBP, LZP, MPH, MPB, MSM, NTZ, OXC, PAC, PTR, PB, PSM, PHT, PGB, PRM, PRO, STM, TGB, VGB, or 4-amino-3-hydroxybutyric acid could be considered for initial monotherapy for patients with newly diagnosed or untreated JME (level E).
5. Class IV studies indicate that CBZ, GBP, OXC, PHT, TGB, and VGB may precipitate or aggravate absence seizures, and myoclonic seizures (92,93,95). A report suggests that LTG may exacerbate seizures in JME (129).

CONCLUSION

This guideline spans six seizure types in different age groups and two epilepsy syndromes. Conclusions were based on 50 RCTs (completed over the past 65 years) and seven meta-analyses. A systematic rigorous method of assessment was applied equally to all seizure types and epilepsy syndromes. A summary of the class of study for each seizure type/syndrome along with the AED(s) that were given a recommendation grade of A, B, or C is listed (Table 11).

It is clear that an alarming lack of well-designed, properly conducted epilepsy RCTs exist, especially for generalized seizures/epilepsies and in children. The four class I trials in the entire guideline were published in 1985, 1997, 1999, and 2005. Only two class II trials are in the guideline. This lack of class I and II trials is not due to an overly strict rating scale but rather to a lack of adequate trials. Correcting this problem is not easy.

TABLE 11. *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 alphabetic order)
Adults with partial-onset seizures	2	1	30	Level A: CBZ, PHT Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB
Children with partial-onset seizures	1	0	17	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA
Elderly adults with partial-onset seizures	1	1	2	Level A: GBP, LTG Level B: None Level C: CBZ
Adults with generalized-onset tonic–clonic seizures	0	0	23	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA
Children with generalized-onset tonic–clonic seizures	0	0	14	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA
Children with absence seizures	0	0	6	Level A: None Level B: None Level C: ESM, LTG, VPA
BECTS	0	0	2	Level A: None Level B: None Level C: CBZ, VPA
JME	0	0	0	Level A: None Level B: None Level C: None

Two more-definitive types of monotherapy studies for new-onset epilepsy exist: a placebo-controlled monotherapy trial or a high-dose versus low-dose study. The purest study is a placebo-controlled monotherapy trial, but many ethical issues are involved. For example, because already effective, registered drugs exist for new-onset seizures, is it ethical to give a placebo to a patient with seizures and wait for another seizure to occur and possibly have a traumatic or life-threatening event? Compounding this problem is the idea that seizures beget seizures. Although not proven, it makes investigators uncomfortable giving a placebo to a patient with new-onset epilepsy.

High-dose versus low-dose comparative studies are another alternative. The low-dose arm can use the same or a different AED than the high-dose arm. Demonstrating a difference between the two arms will provide definitive evidence of efficacy for the high-dose AED. The low-dose arm is designed to protect the patient against a GTC seizure or status epilepticus, while not being potent enough to eliminate a statistical difference in favor of the high-dose AED in the clinical trial. Unfortunately, no proof exists that a low dose of an AED is effective in preventing GTC seizures or status epilepticus, so some investigators believe that this type of study has the same ethical shortcomings as a placebo-controlled one.

The result is that many recent clinical trials are comparative studies between an AED (already licensed as a monotherapy drug) and the new one. Many think this is the most ethical of trials, and recruitment of patients is usually more successful. Most of the trials that we have found are comparative trials between at least two drugs. The advantage of this is that the new drug must show noninferiority (or superiority) in efficacy to an already existing therapy, making this type of trial more clinically relevant to the practicing physician. The multiple disadvantages of these types of trial, as performed to date, include (a) the trials are often not truly designed as noninferiority trials, resulting in their being underpowered; (b) the assessment timeline for the primary outcome variable is not long enough; (c) the titration schedules tend to be fixed and forced; (d) the trials encompass multiple age groups and seizure types, which leads to an inability to make clean conclusions about age or seizure-type results, (e) these trials are often designed, conducted, and analyzed

by pharmaceutical companies and not by independent unbiased sponsors.

Even with the multiple studies for new-onset partial seizures, many problems remain. One concern with the existing partial-onset seizures RCTs and especially those involving new AEDs is that many of the studies are methodologically flawed. We do not really know if the new AEDs might have better efficacy than the older drugs or vice versa, as this requires participation of many more patients in comparative trials. The same is true for tolerability. Although many believe some of the new drugs seem to be better tolerated than the older ones, statistically this has been very hard to show, except in a few studies. Many of these studies were designed to support marketing strategies, and some of the methodologic features of these trials can skew the results in favor of the sponsor's product. For example, choice of inclusion and exclusion criteria, choice of comparative drug and formulation (slow release or not), dosing intervals, titration rates, and end points can influence outcome.

Clinical end points are very important in determining the efficacy of a drug. Often for regulatory purposes the end point of time to first seizure is used. This, however, is clinically irrelevant and can be biased by the study design. A more important end point would be the rate of seizure freedom at 1 year. This end point is clinically important and has been the end point that we have used, discarding the end-point difference of time to first seizure.

Another consistent limitation has been the definition of an "adequately powered" study. The concept of power varies from study to study, and very few studies really do have enough power to be considered adequate to determine whether a meaningful difference between AEDs exists. Interpretation can be even more difficult, because the number of patients that are assessed can influence the power calculations. For example, in some trials, the number of enrolled patients is provided, but the number of patients who are then lost to follow-up is large. At the end, using the enrolled patients instead of those who were actually assessed in the study would overestimate the true power of the observations.

Some may question our strict use of only RCTs to make recommendations in this guideline. Indeed, 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 guideline.

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