Therapeutic index estimation of antiepileptic drugs: a systematic literature review approach

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Abstract

Objectives—To determine whether data obtained from the medical literature can be used to estimate the therapeutic index of 5 antiepileptic drugs (AEDs): carbamazepine, lamotrigine, phenobarbital, phenytoin, and valproate.

Methods—We performed a literature search using PubMed and Embase to collect published safety, efficacy, and therapeutic monitoring data for 5 AEDs, and extracted all relevant information into a drug- and study-specific drug database. For each AED, we summarized: 1) type, severity, and incidence of toxicity-related adverse events and toxicity-associated range of drug doses or concentrations; 2) effective versus toxic concentration and dose (therapeutic range); and 3) therapeutic drug monitoring practices. We defined therapeutic index as the ratio of the minimum toxic concentration to the minimum effective concentration.

Results—We reviewed a total of 810 full-text articles and extracted data from 163. The literature suggests that the therapeutic index of phenytoin is 2. The therapeutic indices of phenobarbital and valproate exceed 2. There was insufficient data to precisely quantify the therapeutic indices of carbamazepine and lamotrigine.

Conclusions—For some drugs, this approach offers a low-cost method of therapeutic index estimation. Our results can serve as preliminary data for future trials, and as guidance for FDA decision-making regarding narrow therapeutic index classification.

Keywords

Antiepileptic drugs; narrow therapeutic index; carbamazepine; lamotrigine; phenobarbital; phenytoin; valproate; valproic acid

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Conflicts of Interest
For the remaining authors none were declared.

INTRODUCTION

Over 150 generic antiepileptic drug (AED) formulations have been approved by the US Food and Drug Administration (FDA).[1] In order to market a generic version of any drug, the sponsor must provide evidence of pharmaceutical equivalence and bioequivalence between the brand-name and the generic drug. In 2010, the FDA proposed that certain drugs classified as having a narrow therapeutic index (NTI) should achieve more stringent regulatory standards for approval.[2] NTI drugs generally have the following characteristics: (a) there is little separation between therapeutic and toxic doses (or the associated blood/plasma concentrations); (b) sub-therapeutic concentrations may lead to serious therapeutic failure; (c) they are subject to therapeutic monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures; (d) they possess low-to-moderate (i.e., no more than 30%), within-subject variability; and (e) doses are often adjusted in very small increments (less than 20%) in clinical practice. For generic drugs classified as NTI, the proposed bioequivalence criteria require the use of reference-scaled testing and variability comparison, which makes these criteria tighter than the traditional average bioequivalence criteria.[2–4]

For these new standards to be implemented, it is critical to define which drugs can be classified as NTI. Conversion from brand-name to generic formulations of AEDs has been associated with increased frequency of seizures and adverse effects, which has led to a lack of confidence by some providers and patients in generic products.[5–8] If certain AEDs could be identified as NTI drugs, application of the new criteria to the development of generic formulations could improve patient safety, enhance physician confidence in generic products, and result in overall cost savings due to increased generic drug prescribing. NTI classification requires therapeutic index estimation, which is not well-established for many generic AEDs. The purpose of our study was to determine whether data obtained from an exhaustive search of the medical literature could be used to estimate the therapeutic index of 5 off-patent AEDs.

MATERIALS AND METHODS

Through collaboration with the FDA, review of international regulatory agency websites (including Health Canada,[9] the European Medicines Agency,[10] and the National Institute of Health Sciences-Japan[11]), and consultation with neurology therapeutic experts, we identified the 5 AEDs as potential NTI drugs requiring closer evaluation to determine if they may benefit from tighter bioequivalence standards for generic drug development. carbamazepine, lamotrigine, phenobarbital, phenytoin, and valproate.

Literature search

For each of the 5 AEDs, we performed an exhaustive literature search of all available indexed articles using Pubmed and Embase. We did not limit our search to a particular time period. The search was conducted with the aid of professional librarians from Duke University Medical Library (Figure 1). We reviewed abstracts for all articles identified by the search to determine whether they might contain relevant data focused on: 1) efficacy and/or safety data from prospective randomized controlled trials in the labeled indication for

the drug; 2) therapeutic drug range and/or monitoring; or 3) adult PK data. Full text articles were reviewed for all abstracts of potential interest, and data was extracted into a drug- and study-specific drug database. Specific variables extracted included: study demographics, drug dosing and formulation, PK parameters (e.g., maximum concentration (Cmax), area under the curve (AUC), clearance, half-life ($t_{1/2}$)), and efficacy data (study phase, primary outcome, and study result). Among safety data, we collected black box warnings and precautions indicated on the drug label, and all adverse events (AEs) with a placebo-adjusted frequency >10%. When it was uncertain whether data should be included, the manuscript was reviewed by a second study team member to reach consensus. As a quality assurance measure, 5% of the extracted data underwent an independent full review by 1 reviewer.

Therapeutic index estimation

For each AED, we summarized by patient population: 1) type, severity, and incidence of toxicity-related AEs and toxicity-associated range of drug doses and concentrations; and 2) effective versus toxic concentration and dose (therapeutic range). To determine the therapeutic index of each drug, we aimed to determine the concentration of drug associated with selected AEs in approximately 50% of the population (TC50) and the concentration associated with efficacy in approximately 50% of the population (EC50). We defined the therapeutic index as TC50 divided by EC50. However, in the absence of available data in the literature to calculate TC50 and EC50, we defined therapeutic index as the ratio of the minimum toxic concentration to the minimum effective concentration.[12,13] Even though the FDA does not specify a threshold value to determine whether a therapeutic index is narrow, in this study we considered a therapeutic index 2 as one criterion to support classification as an NTI drug.[12,13]

RESULTS

Carbamazepine

Safety—AEs associated with carbamazepine use in patients with epilepsy include somnolence, dizziness, gastrointestinal disturbance, and hematologic abnormalities (Table 1).[14–22] There were conflicting results regarding the relationship between systemic exposure and toxicity. Several studies demonstrated that the prevalence of carbamazepine AEs was concentration-related, with toxicity occurring at concentrations >8. 7–11. 8 μg/mL.[23–28] Conversely, other studies found no significant difference in mean carbamazepine serum concentrations between patients with and without AEs.[18,19]

Efficacy—Carbamazepine efficacy with mono- and combination therapy was assessed in studies using 3 different measures: 1) percentage of patients with a 50% reduction in seizures; 2) reduction in total seizures during the study period; and 3) percentage of patients who were seizure-free in specific time periods (Table 2).[14, 17, 18, 20, 21] Only one study reported a positive correlation between carbamazepine concentration and seizure control.[22]

Therapeutic range and drug monitoring—The conventionally accepted therapeutic range of plasma concentrations of carbamazepine in adults is 4–12 μg/mL.[29] The dose range associated with efficacy and toxicity partially overlaps. Serum concentrations associated

with efficacy range between 1.9 and 11.7 μg/mL, though concentrations less than 4 μg/mL result in less optimal seizure control in the overall epilepsy population.[22,30,31] AEs have been reported in carbamazepine concentrations ranging from 4–19. 6 μg/mL, and higher concentrations are generally associated with more AEs.[24,28,32–34]

In clinical practice, therapeutic drug monitoring (TDM) is often not routinely performed for carbamazepine, though there is variability among clinicians. Drug levels may be checked when patients experience adverse effects or experience break-through seizures, and to monitor compliance with therapy. Patients taking interacting medications or patients converting from one drug formulation to another may require TDM.

Therapeutic index estimation—Information from the medical literature generally supports the accepted carbamazepine therapeutic range of 4–12 μg/mL. However, the response to carbamazepine therapy is reportedly variable, and patients may require lower or higher serum concentrations to achieve adequate seizure control. The available information suggests an approximate carbamazepine therapeutic index of 3. However, TDM may be required for patient safety in certain settings, such as when a patient experiences an adverse effect or break-through seizures. Further data, other than literature reviews, are needed to determine whether carbamazepine may require stricter bioequivalence criteria in these instances.

Lamotrigine

Safety—AEs associated with lamotrigine use in patients with refractory seizure occur in dose ranges of 100–500 mg/day (Table 1).[35–40] The prevalence of AEs with lamotrigine use has been shown to be dose-related and generally independent of concomitantly administered medications.[41] However, co-administration of valproate with lamotrigine has been associated with skin rash.[42] Moreover, the fraction of subjects necessitating dose modification or discontinuation increased by 25% when plasma levels exceeded 20 μg/mL.[41]

Efficacy—Lamotrigine efficacy with mono- and combination therapy was assessed in studies using 3 different measures: 1) percentage of patients who had a >50% reduction in seizures; 2) reduction in total seizures during the study period; and 3) percentage of patients with seizure freedom in a specific time period (Table 2).[18,19,37,43,44]

Therapeutic range and drug monitoring—The dose range associated with efficacy and toxicity partially overlaps. In a large-scale observational study (N=811), overall toxicity of lamotrigine increased gradually with increasing serum concentrations, whereas efficacy of lamotrigine did not correlate with serum levels when the concentration of lamotrigine was below 15 μg/mL.[41] In this study, about 50% of the population was seizure-free at 6 months at levels ranging from 1–15 μg/mL. The therapeutic index calculated based on the available data for lamotrigine was in the range of 1.3–20. In clinical practice, TDM is not routinely performed for lamotrigine. However, the American Academy of Neurology recommends that TDM of lamotrigine should be considered in pregnant women with epilepsy because pregnancy causes an increase in the clearance and a decrease in the level of lamotrigine.[45,46] Due to the widely varying doses of lamotrigine, there is no well-defined one-size-fits-all

target range in these patients. Individualized dosing or target concentrations are determined by attending physicians based on a range of other parameters including response, severity of symptoms, other drugs, and side effects.[47]

Therapeutic index estimation—Based on literature data, the therapeutic range of lamotrigine is not well established, nor is there a clear dose-to-response curve for safety or efficacy. The therapeutic index determined from the medical literature extends from a value on the border of supporting classification of the therapeutic index as narrow to a ten-fold higher value that would not be consistent with the therapeutic index being narrow (Table 3). Due to this uncertainty, our method of estimating the therapeutic index was unable to distinguish whether the therapeutic index of lamotrigine should be determined as narrow.

Phenobarbital

Safety—AEs associated with phenobarbital use occur at a wide range of doses (Table 1).[48–51] In a single study evaluating the relationship between dose or plasma concentration and development of an AE, most AEs occurred in subjects with total serum phenobarbital levels at or below the standard accepted therapeutic range of 15–40 μg mL.[51] The investigators did not find a relationship between phenobarbital levels and occurrence of AEs; however, there was a significant relationship between the number of concomitant antiepileptic agents (i.e., phenytoin, carbamazepine, and benzodiazepines) and occurrence of AEs.

Efficacy—Phenobarbital efficacy with mono- and combination therapy was assessed in studies using 3 different measures: 1) reduction in seizure frequency; 2) achievement of seizure remission for a predefined period of time; and 3) percentage of patients with treatment failure (Table 2).

Therapeutic range and drug monitoring—The conventional therapeutic range for phenobarbital is 15–40 μg/mL.[52] In the vast majority of available studies, phenobarbital functioned as an active control or an adjunct drug in the study of other antiepileptic agents and was noted to be efficacious when serum concentrations were within the stated therapeutic range.[31,53–57] In addition, it has been reported that some subjects have remained seizure-free at phenobarbital levels well below 10 μg/mL,[52] while clearly other subjects can have seizures refractory to phenobarbital therapy despite levels in the therapeutic range.[58]

In clinical practice, TDM is routinely performed for phenobarbital.[52] However, some clinicians choose to rely more on clinical response rather than targeting a range of concentrations. It has been reported that the majority of patients can achieve satisfactory results by adjusting dose based on clinical signs and symptoms.[59]

Therapeutic index estimation—The therapeutic range of phenobarbital has been well established and accepted. However, there are subjects who are successfully treated with phenobarbital levels below this range. Furthermore, there are numerous subjects who experience AEs despite having serum drug levels within this range, and there does not appear to be a significant relationship between drug level and frequency of AEs. Thus, we were unable to quantify the therapeutic index of phenobarbital. Studies evaluating the

efficacy and safety of phenobarbital are frequently confounded by concomitant treatment with other antiepileptic medications. Despite these limitations, treatment strategies adjusting dose based on clinical signs and symptoms have been shown to be as successful as strategies relying on TDM.

Phenytoin

Safety—AEs associated with phenytoin use usually occur in dose ranges of 200–450 mg (Table 1).[60–63] The prevalence of AEs with phenytoin use has been shown to be dose-related and independent of concomitantly administered medications.[64] In one study, 86% of patients with toxicity had phenytoin-free levels >2 μg/mL.[64]

Efficacy—Phenytoin efficacy with mono- and combination therapy was assessed in studies using 3 different measures: 1) percentage of patients who had a >50% reduction; 2) reduction in total seizures during the study period; and 3) percentage of patients with seizure freedom in a specific time period (Table 2).[62,65–68]

Therapeutic range and drug monitoring—The conventionally accepted therapeutic range of phenytoin is 10–20 μg/mL. This therapeutic range was primarily established from small, often retrospective studies performed in the 1960s and 1970s combined with clinical experience and expert opinion.[69] The dose range associated with efficacy and toxicity partially overlaps. The available studies evaluating serum phenytoin concentrations and seizure control suggest that seizure frequency is dose-related and seizure control is generally poor at concentrations <10 μg/mL.[70–74] Serum concentrations between 15 and 20 are associated with improved seizure control. Although target total phenytoin concentrations of 10–20 μg/mL have been used in clinical trials, several studies have shown that total phenytoin values >20 μg/mL in certain patients may be optimal.[70,75]

In clinical practice, TDM is often not routinely performed for phenytoin. Levels may be checked when patients experience adverse effects or experience break-through seizures. There is a large inter-individual variability in the PK of phenytoin. For patients with ongoing physiological changes such as pregnancy, decreased renal clearance, decreased hepatic function, or microalbuminemia, TDM may be needed.[64,71]

Therapeutic index estimation—There is considerable overlap in the toxic and therapeutic ranges for phenytoin, and TDM is recommended in certain populations. Based on available literature, the therapeutic index for phenytoin is approximately 2. The relatively low therapeutic index is one criterion that supports NTI classification for phenytoin (Table 3).

Valproate

Safety—Valproate is generally well-tolerated at doses that produce concentrations that effectively reduce seizures (Table 1).[76,77] One study evaluating the safety of rapidly infused valproate noted that adverse events often occurred around the time of maximal drug concentrations.[77]

Efficacy—Valproate efficacy was typically studied as a >50% reduction in seizure frequency or complete remission within a given time period (Table 2).[30,76,78–80] Seizure control has been reported across a wide concentration range of 60–800 µmoles/L (8.7–115.4 ug/mL).[30]

Therapeutic range and drug monitoring—The therapeutic range of total valproate reported on the FDA label for epilepsy is 50–100 µg/mL (4–15 µg/mL unbound), which is consistent with published studies that have evaluated valproate efficacy and safety.[81] Many clinicians perform TDM when adding drugs with potential interactions, when patients experience breakthrough seizures or toxicities, or to monitor compliance with therapy. However, clinicians do not consistently perform TDM.

Therapeutic index estimation—Valproate concentrations associated with adequate reductions in seizure frequency have been shown to vary widely, and there is little overlap between the toxic and therapeutic range. Thus, we were not able to estimate the therapeutic index. Clinicians do not consistently perform TDM.

DISCUSSION

There is considerable concern among physicians and patients regarding the safety and efficacy of generic AEDs.[5] The American Academy of Neurology has issued a position statement opposing generic substitution of AEDs without attending physician's approval, citing concerns for toxicity and break-through seizures.[6] While much of the evidence for these concerns is anecdotal, there has been at least one survey study documenting cases in which patients who switched to generic AED formulations experienced lower drug levels and breakthrough seizures.[82] In addition, a large Canadian claims database study compared the frequency of switchback rates for AEDs and other drugs in patients who had been compulsorily switched to generic formulations.[83] In this study, the switchback rates to brand-name formulations were higher for both lamotrigine (13%) and valproate (20%) compared to non-AED drugs (1.5–2.9%).

If the FDA were to enact tighter bioequivalence standards for generic formulations of certain drugs, clinicians and patients could more confidently choose less expensive products, leading to health care cost savings. Tighter bioequivalence standards, however, are not necessary for drugs that have a wide therapeutic index, because larger variations in patient exposure can be well-tolerated. Identification of NTI drugs is therefore key to the implementation of new bioequivalence standards.

In our study, we completed a comprehensive literature search to estimate the therapeutic index of 5 AEDs, a crucial step towards determining whether these drugs could be classified as NTI. We found that the therapeutic index we estimated from the available literature supported NTI classification for 1 of the 5 AEDs studied (phenytoin), while 2 other AEDs (carbamazepine, lamotrigine) require the evaluation of multiple other factors to determine whether they may be classified as NTI. A recent study of generic-to-generic switches in epilepsy patients taking different forms of lamotrigine showed bioequivalence of disparate lamotrigine products, with no apparent difference in clinical effects.[84] For the 2 drugs for

which NTI status could not be adequately determined (carbamazepine and lamotrigine), TDM is advisable for at least some clinical situations, and there is some concentration-dependent efficacy and toxicity. Approval of generic formulations of these drugs without stringent testing of PK and pharmacodynamics properties could result in unacceptable risk of adverse effects or breakthrough seizures. In 2014 and 2015, the FDA updated the bioequivalence guidance for phenytoin and carbamazepine to request tighter bioequivalence standards for NTI drugs.[85]

The strengths of our study include a thorough review of all available toxicity and efficacy data for 5 AEDs. Based on the compiled information, we calculated therapeutic indices for use in classification of most of our drugs of interest. This study represents a proof-of-concept method that can be replicated to other drug classes to estimate therapeutic indices. During the period of brand-name drug exclusivity (5–7 years) when post-marketing data is generated, a data review can be performed to estimate the therapeutic index, and to potentially support its NTI classification.

Our study is limited by the heterogeneity of the data available in the existing literature; our results are based on a wide variety of trials that included different populations, study designs, indications, and drug dosages and regimens. In addition, for some drugs, very limited data were available from which we were able to draw conclusions. Our search methods, while comprehensive, may have led to incomplete retrieval of data. We also did not capture clinical practice data, which is an important component required for NTI classification. Finally, our estimation of therapeutic index was based on the population therapeutic range, which may be wider than that of an individual. Therefore, we may have overestimated the therapeutic index that can be applied to an individual. We have also included AE data from both titration and maintenance phases, and the therapeutic index may differ in different clinical situations. Given these limitations, combining the results of our review with other methods of NTI classification, including expert opinion and PK/PD modeling, may help determine which drugs should be subjected to more stringent bioequivalence criteria. The ideal source of data regarding safety and efficacy of generic formulations would be trials in which patients are randomized to continuing on brand-name formulations vs. switching to generics, with drug levels collected in patients experiencing toxicity. However, the cost of such trials to evaluate all possible NTI drugs is prohibitive. Our approach offers a low-cost method of therapeutic index determination. Our results can serve as preliminary data for future trials and as guidance for FDA decision-making regarding NTI drugs.
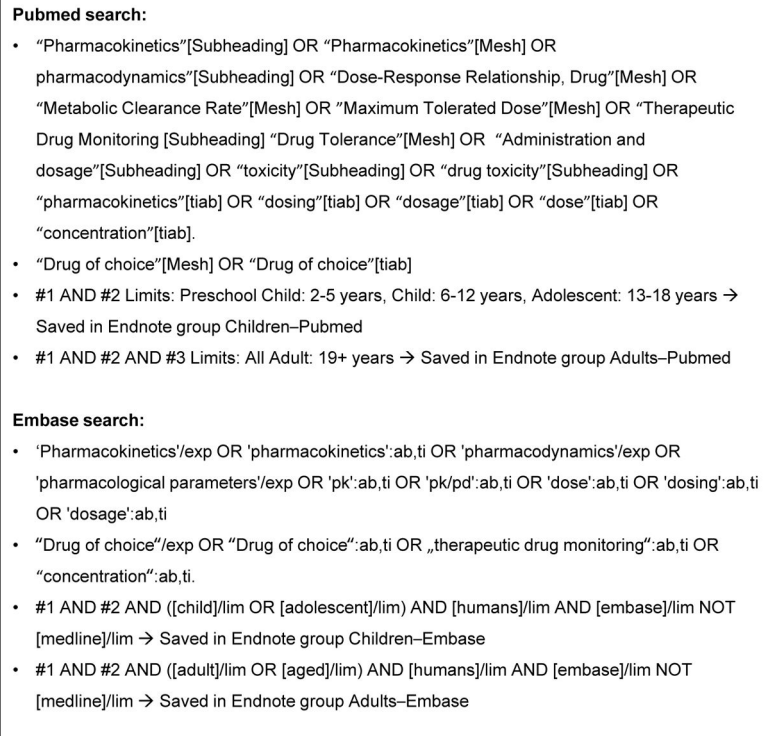
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Pubmed search:

- "Pharmacokinetics"[Subheading] OR "Pharmacokinetics"[Mesh] OR pharmacodynamics"[Subheading] OR "Dose-Response Relationship, Drug"[Mesh] OR "Metabolic Clearance Rate"[Mesh] OR "Maximum Tolerated Dose"[Mesh] OR "Therapeutic Drug Monitoring [Subheading] "Drug Tolerance"[Mesh] OR "Administration and dosage"[Subheading] OR "toxicity"[Subheading] OR "drug toxicity"[Subheading] OR "pharmacokinetics"[tiab] OR "dosing"[tiab] OR "dosage"[tiab] OR "dose"[tiab] OR "concentration"[tiab].
- "Drug of choice"[Mesh] OR "Drug of choice"[tiab]
- #1 AND #2 Limits: Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years → Saved in Endnote group Children–Pubmed
- #1 AND #2 AND #3 Limits: All Adult: 19+ years → Saved in Endnote group Adults–Pubmed

Embase search:

- 'Pharmacokinetics'/exp OR 'pharmacokinetics':ab,ti OR 'pharmacodynamics'/exp OR 'pharmacological parameters'/exp OR 'pk':ab,ti OR 'pk/pd':ab,ti OR 'dose':ab,ti OR 'dosing':ab,ti OR 'dosage':ab,ti
- "Drug of choice"/exp OR "Drug of choice":ab,ti OR „therapeutic drug monitoring":ab,ti OR "concentration":ab,ti.
- #1 AND #2 AND ([child]/lim OR [adolescent]/lim) AND [humans]/lim AND [embase]/lim NOT [medline]/lim → Saved in Endnote group Children–Embase
- #1 AND #2 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [embase]/lim NOT [medline]/lim → Saved in Endnote group Adults–Embase

Figure 1.
Search strategies

Table 1

Representative drug-related adverse events (AEs) and associated dose ranges

Number of subjects	AE Type	AE Severity	Incidence	Range of AED doses
Carbamazepine				
91–301[1–3,5,6]	Somnolence Decreased appetite	Mild/moderate	8–36% 2%	400–1200 mg/day
91–378[15, 16, 18–21]	Gastrointestinal	Mild/moderate	4–29%	400–2000 mg/day
91–378[15–20]	Rash	Mild/serious	8–32%	200–2000 mg/day
20–230[17, 21, 22]	Decreased white blood cells	Mild	Not reported	200–1400 (5–24 mg/kg/day)
Lamotrigine				
8 – 334[35, 39, 40]	Rash	Moderate/serious	1%, 3%, 8%	100–500 mg (serious), 100 mg (moderate)
156 – 334[37, 40]	Stevens-Johnson syndrome	Serious	0. 1%, 1%	300–400 mg, 300 mg/day, and 250 mg bid
141[36]	Grand mal seizures	Serious	1%	300–400 mg/day
126[38]	Diplopia	Serious	1%	250 mg
334[40]	Dizziness	Serious	0. 6%	100–500 mg
334[40]	Blurry vision	Serious	0. 6%	100–500 mg
334[40]	Ataxia	Serious	0. 3%	100–500 mg
334[40]	Nausea	Serious	0. 3%	100–500 mg
Phenobarbital				
114[48]	Elevated GGT	Mild	58%	NR
18–124[e-ref 82, e- ref 83]	Hypotension	NR	11–49%	10–30 mg/kg
18[54]	Intubation	Severe	33%	10–30 mg/kg
10–143 [e-ref 71, e- ref 78]	Somnolence	Mild	30%	8. 3–133. 3 mg/day
143[50]	Fatigue	Mild	21%	8. 3–133. 3 mg/day
Phenytoin				
127–151[59, 60]	Rash	Moderate/serious	19% (mild), 8% (moderate), 2% (serious)	300 mg (serious)
114[e-ref 61]	Stevens-Johnson syndrome	Serious	1%	300 mg
141[59]	Suicide attempt	Serious	1%	300 mg
67[e-ref 62]	Myalgia	Moderate	2%	200–450 mg
Valproate				
112[e-ref 76]	Somnolence	Mild	10–15%	1. 5–3. 0 mg/kg/min
112[e-ref 76]	Dizziness	Mild	8–10%	1. 5–3. 0 mg/kg/min
112[e-ref 76]	Nausea	Mild/moderate	8–10%	1. 5–3. 0 mg/kg/min
112[e-ref 76]	Paresthesia	Mild	8%	1. 5–3. 0 mg/kg/min

GGT: gamma-glutamyl transpeptidase

Table 2

Representative range of antiepileptic drug (AED) doses in studies with successful monotherapy.

Number of subjects	Outcome measure	Efficacy results	Dose range
Carbamazepine			
300[14]	Seizure-free at 26 weeks	75%	400–1200 mg
230[17]	Withdrawn from treatment at <52 weeks	42%	200–1400 mg
129[18]	Seizure-free at 48 weeks	38%	300–1400 mg
236[20]	Seizure-free at 48–96 weeks	34%	Mean: 722 mg
101[21]	Withdrawn from treatment at <36 months	45%	600 mg
Lamotrigine			
249[42]	Seizure-free at 12 months	61%	25–600 mg
226[19]	Seizure-free at 7 weeks	60%	100–200 mg
156[37]	Remaining on monotherapy	56%	100–500 mg
222[43]	Seizure-free at 1 year	89%	50–150 mg
131[18]	Seizure-free at 40 weeks	26%	100–300 mg
Phenobarbital			
124[53]	Resolution of all clinical and electrical evidence of seizure activity within 20 minutes of start of infusion	58%	15 mg/kg
18[54]	Resolution of status epilepticus	61%	5–23 mg/kg
8[56]	Fewer seizures than clorazepate comparator	50%	148 ± 21. 8 mg/day
Phenytoin			
114[e-ref 61]	>50% seizure reduction	57%	200–300 mg
50[e-ref 64]	Seizure-free at 6 months	53%	3–5 mg/kg
26[e-ref 65]	Seizure-free at 12–41 months	76%	200–300 mg
37[e-ref 66]	>50% reduction in seizure frequency at 14–24 months	82%	300 mg
95[e-ref 67]	Seizure-free at 10 months	24%	300 mg (mode)
Valproate			
238[e-ref 75]	Time to treatment failure	Valproate significantly better than topiramate, but no significant difference between valproate and lamotrigine	200–3000 mg
16[e-ref 77]	Seizure-free at 12 months	25%	1000–2000 mg
64[30]	>50% reduction in seizure frequency at >3 months	80%	600 mg (adults); 5–10 mg/kg (children)
13[e-ref 78]	Reduction in seizure frequency	A statistically significant difference was observed between VPA levels and seizure frequency. The relationship was curvilinear.	300–4000 mg
10[e-ref 79]	>50% reduction in seizure frequency at 12 weeks	50%	900 mg

Table 3

Narrow therapeutic index (NTI) classification. AED: antiepileptic drug.

AED	Articles meeting search criteria (Pubmed / Embase)	Full text articles reviewed	Articles from which data extracted	Therapeutic index	NTI classification supported by literature?
Carbamazepine	1022 / 344	364	34	3	Possibly
Lamotrigine	384 / 187	132	49	1. 3–20	Possibly
Phenobarbital	384 / 283	150	35	**	No
Phenytoin	1007 / 284	111	34	2	Yes
Valproate	608 / 317	53	11	**	No

** Therapeutic index could not be estimated due to poor correlation of toxicity symptoms with drug concentration.