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Review

# Antiepileptic drug treatment of generalized tonic–clonic seizures: An evaluation of regulatory data and five criteria for drug selection

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ABSTRACT

*Background:* A generalized tonic–clonic seizure (GTCS) is the most severe form of common epileptic seizure and carries the greatest risk of harm. The aim of this review is to provide an evidence-based guide for the selection of antiepileptic drugs (AEDs) for patients with GTCSs. Eight AEDs are approved in Europe and the USA for the treatment of both primarily GTCSs (PGTCSs) and secondarily GTCSs (SGTCSs) and are considered in this paper.
*Methods:* Each AED is evaluated using five criteria: (1) efficacy, by seizure type (a: PGTCSs and b: SGTCSs); (2) adverse effects; (3) interactions; (4) adherence and dosing; and (5) mechanism of action (MOA). To ensure the inclusions of robust data, only efficacy data accepted by regulatory authorities were considered, and data related to adverse effects, interactions, adherence, and MOA were all extracted from UK Summaries of Product Characteristics (SPCs).
*Results:* (1a) There is class 1 evidence of the efficacy of only four AEDs in controlling PGTCSs (lamotrigine, levetiracetam, perampanel, and topiramate). (1b) There is no class 1 evidence of the efficacy of any AED in SGTCSs although some evidence from pooled/subgroup analyses or meta-analyses supports the use of the four AEDs (levetiracetam, perampanel, topiramate, and with less robust data for lamotrigine). (2) AEDs are associated with different, but to some extent overlapping, common adverse effect profiles but have differing idiosyncratic adverse effects. (3) Pharmacokinetic interactions are seen with most, but not all, AEDs and are most common with carbamazepine and phenytoin. (4) Good adherence is important for seizure control and is influenced by frequency of dosing, among other factors. (5) Mechanism of action is also a consideration in rationalising AED selection when switching or combining AEDs.
*Conclusion:* Ultimately, the choice of AED depends on all these factors but particularly on efficacy and adverse effects. Different patients will weigh the various factors differently, and the role of the treating physician is to provide accurate information to allow patients to make informed choices.



## 1. Introduction

It is somewhat paradoxical that although there is universal agreement that generalized tonic–clonic seizures (GTCSs) are the most severe form of common epileptic seizure, treatment of GTCSs has been the subject of relatively few robust clinical studies.

A specific focus on GTCSs is certainly justified. The detrimental effect of these seizures on many aspects of life for patients with epilepsy has been demonstrated in studies worldwide [1–4]. For example, GTCSs carry a much greater risk of accidental death (e.g., from drowning, burns, or falls), sudden unexpected death in epilepsy (SUDEP) [5–8], and accidental injury than focal seizures [9,10]. GTCSs have been associated with cerebral damage and cognitive decline, including risks to memory [11–13]. If prolonged, they are the most dangerous form of status epilepticus and – because of their dramatic and shocking nature – can cause much psychological distress and have negative consequences for education, work, relationships, social interactions, and self-confidence.

Selection of appropriate antiepileptic drugs (AEDs) for initial treatment, and for switching and combining therapies if seizures persist, is of crucial importance for patients with GTCSs. In this review, we evaluate the best available evidence to aid clinicians in selecting AEDs for the treatment of both primarily generalized tonic–clonic seizures (PGTCSs),

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which occur in the context of idiopathic generalized epilepsy (IGE), and secondarily generalized tonic–clonic seizures (SGTCSs), which occur in the context of focal epilepsies.

We evaluated available data using five criteria which are, in our view, the most relevant considerations when making an AED choice: (1) efficacy in treating the specific seizure type; (2) adverse effects — including the common side effects, the uncommon but serious idiosyncratic effects, and the potential teratogenic effects; (3) drug interactions; (4) adherence, which should be optimized to give any treatment the best chance to work; and (5) mechanism of action (MOA), which can help to inform appropriate AED selection when switching or combining drugs.

To avoid bias and provide the best evidence-based evaluation of robust data, we have considered efficacy data only from the randomized, doubly blinded studies submitted to the regulatory authorities and other data only from the drug's official Summary of Product Characteristics (SPCs), which are documents with data approved by a regulatory authority. (We have used the UK SPCs approved by the European Medicines Agency (EMA).) This is a key feature of this review, and we are not aware of other papers that have adopted this methodology.

## 2. Methods

As this study involved a retrospective review of regulatory documents and clinical trial evidence, institutional review board or ethics committee approval was not required. The definitions of levels of evidence we used are consistent with those from the Centre for Evidence-Based Medicine [14].

### 2.1. Antiepileptic drugs

For this review, we considered evidence related to the eight AEDs that are licensed for the treatment of both PGTCSs and SGTCSs in Europe and the USA: carbamazepine [15,16], clobazam [17], lamotrigine [18], levetiracetam [19], perampanel [20], phenytoin [21], topiramate [22], and valproate [23] (Table 1), according to European SPCs and US prescribing information (USPI).

Lamotrigine, levetiracetam, perampanel, and topiramate are licensed on the basis of randomized control trial (RCT) evidence of efficacy (level 1 evidence). However, the licenses of carbamazepine, clobazam, phenytoin, and valproate are simply based on “grandfather clauses” (i.e., that the drugs were in use before current licensing

**Table 1**
Approved indications of the eight antiepileptic drugs licensed for use in primarily and secondarily generalized tonic–clonic seizures.

| Antiepileptic drug | Europe | | USA | |
|---|---|---|---|---|
| | Seizure types | Adjunctive/monotherapy | Seizure types | Adjunctive/monotherapy |
| Carbamazepine | Generalized tonic–clonic seizures, partial seizures | Not specified | Partial seizures, generalized tonic–clonic seizures (grand mal), and mixed seizure patterns | Not specified |
| Clobazam | Epilepsy | Adj | Seizures associated with LGS in patients ≥2 years of age | Adj |
| Lamotrigine | In adults and adolescents aged ≥13 years:<br>• Partial seizures and generalized seizures,[a] including tonic–clonic seizures<br>• Seizures associated with LGS<br>In children and adolescents aged 2–12 years:<br>• Partial seizures, generalized seizures,[a] and seizures associated with LGS<br>• Typical absence seizures | <br>Adj and Mono<br><br>Adj[b]<br>Adj<br><br>Mono | In patients aged ≥2 years:<br>• Partial seizures, PGTCS, generalized seizures of LGS<br>In adults aged 16 years and receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED:<br>• Partial seizures | Adj<br>Conversion to Mono |
| Levetiracetam | In adults and adolescents aged ≥16 years with newly diagnosed epilepsy with partial-onset seizures[c]<br>In patients aged ≥1 month:<br>• Partial-onset seizures[c]<br>Adults and adolescents ≥12 years:<br>• Myoclonic seizures in JME<br>• PGTCS in IGE | Mono<br>Adj<br>Adj<br>Adj | In patients aged ≥6 years:<br>• PGTCSs in IGE<br>In patients aged ≥1 month:<br>• Partial-onset seizures<br>In patients aged ≥12 years:<br>• Myoclonic seizures in JME | Adj<br>Adj<br>Adj |
| Perampanel | In adults and adolescents aged ≥12 years:<br>• Partial-onset seizures[c]<br>• PGTCSs in IGE | Adj<br>Adj | In adults and adolescents aged ≥12 years:<br>• Partial-onset seizures[c]<br>• PGTCSs | Adj and Mono<br>Adj |
| Phenytoin | Tonic–clonic seizures, partial seizures, or a combination of these<br>Prevention and treatment of seizures following neurosurgery and/or severe head injury | Not specified | Tonic–clonic seizures and psychomotor (temporal lobe) seizures<br>Prevention and treatment of seizures occurring during or following neurosurgery | Not specified |
| Topiramate | In patients aged >6 years<br>• Partial seizures[c] and PGTCSs<br>In patients aged ≥2 years:<br>• Partial-onset seizures[c] and PGTCSs<br>• Seizures associated with LGS | Mono<br>Adj<br>Adj | In patients aged ≥2 years:<br>• Partial-onset seizures and PGTCSs<br>• Seizures associated with LGS | Adj and Mono<br>Adj |
| Valproate | Generalized, partial, or other epilepsy | Not specified | Complex partial seizures<br>Simple and complex absence seizures<br>Patients with multiple seizure types that include absence seizures | Adj and Mono<br>Adj and Mono<br>Adj |

AED, antiepileptic drug; Adj, adjunctive; IGE, idiopathic generalized epilepsy; JME, juvenile myoclonic epilepsy; LGS, Lennox–Gastaut syndrome; Mono, monotherapy; PGTCSs, primarily generalized tonic–clonic seizures.

[a] Including tonic–clonic seizures.

[b] Lamotrigine is given as adjunctive therapy but may be the initial AED in LGS.

[c] With or without secondary generalization.