

Pharmacologic Management of Epilepsy

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Introduction

Epilepsy is a chronic neurological disorder resulting in recurrent, unprovoked seizures, with or without convulsions.^{1, 2} Almost 3 million people in the United States suffer from epilepsy, inclusive of more than 300,000 school children through age 15 and more than 300,000 persons over the age of 65.³ The exact cause of epilepsy in nearly 80% of patients is unknown (idiopathic or cryptogenic etiology), but some identifiable causes include stroke, trauma, brain tumors, infections, and degenerative disorders.⁴ Epilepsy is readily treatable; however to date, it remains a challenge. Patients are often unaware of their seizures and may significantly underestimate the number of seizures that occur, especially those that occur during sleep or that disrupt consciousness.⁵

Pathophysiology

A seizure results when there is an abnormal firing of a group of neurons in the cerebral cortex or from a sudden imbalance between the excitatory and inhibitory forces within the network of cortical neurons in favor of a sudden-onset net excitation.

Classification of Seizures

The International League Against Epilepsy (ILAE) developed an international classification system to identify epileptic seizures according to site of origin within the brain (see Table 1).^{1, 7} Seizures are initially divided into two major classes, partial seizures and generalized seizures, based on their clinical and electroencephalogram (EEG) presentations. Partial seizures begin in a focal or localized area of the cerebral cortex (one hemisphere), whereas generalized seizures involve both cerebral hemispheres. Not all seizure types can be classified as partial or generalized. The subtypes of partial seizures were revised in 2010 and because of the difficulty in scientifically defining these subtypes, the authors of the classification system recommend only using these as descriptive terms if needed for treatment or research purposes and emphasize that the subtypes are not natural classes of seizures.⁶

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Table 1: ILAE International Classification of Epileptic Seizures with General Descriptions of Seizures ^{1, 7}

Seizure Type	General Description
Partial seizures	Involve one hemisphere of the brain at onset, focal
Simple	Consciousness not impaired, clinical manifestation related to area involved
Complex	Consciousness impaired
Secondarily generalized	Simple or complex partial seizures evolving into generalized tonic-clonic seizures or simple seizures evolving into complex partial seizures, then to generalized tonic-clonic seizures
Generalized seizures	Involve both hemispheres of the brain at onset
Absence	Brief loss of consciousness; consist of staring spells, unresponsiveness, eyelid fluttering, lip smacking, twitching of hands, or mouth
Myoclonic	Brief shock-like muscular contractions of the face, trunk
Tonic	Results in mainly muscle stiffness and rigidity
Clonic	Rhythmic jerking movements of the arms and legs
Tonic-clonic	Sudden loss of consciousness; violent muscle contractions, post-ictal exhaustion, sleep disorientation, incontinence
Atonic	Sudden loss of postural muscle tone
Unclassified seizures	Cannot be classified as partial or generalized

Pharmacotherapy

Management of patients with epilepsy focuses on three main goals: controlling seizures, avoiding treatment side effects, and maintaining or restoring quality of life. In selecting an antiepileptic drug (AED) that is most appropriate for the individual patient, it is important to consider: seizure type, side effects, patient profile (e.g., sex, age, and childbearing potential), ease of medication use, and cost.⁸ A balance between efficacy, tolerability, and safety must be obtained. Overall, up to 80 percent of patients can become seizure free on AED treatment.^{9, 10} Epilepsy may be a lifetime diagnosis for some patients (e.g., mentally challenged, inoperable brain tumors, etc), but antiepileptic therapy is not necessarily lifelong.

AED therapy is as likely to fail from adverse effects of medication as from lack of efficacy.¹¹ To effectively evaluate therapeutic outcomes, patients should be monitored for seizure control, side effects, social adjustment, drug interactions, adherence, quality of life, and toxicity. Monotherapy with AEDs is preferred and combination AED therapy should be considered only after a patient has failed at least 2 AEDs in monotherapy. A 2005 survey by experts in the field of epilepsy attempted to determine which treatment options might be best in a number of clinical situations (idiopathic generalized epilepsy and symptomatic localization-related epilepsy). Figure 1a demonstrates findings related to an overall treatment strategy for idiopathic generalized epilepsy and Figure 1b demonstrates findings related to an overall treatment strategy for symptomatic localization-related epilepsy.¹²

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Figure 1a: Overall Strategy for Idiopathic Generalized Epilepsy¹²

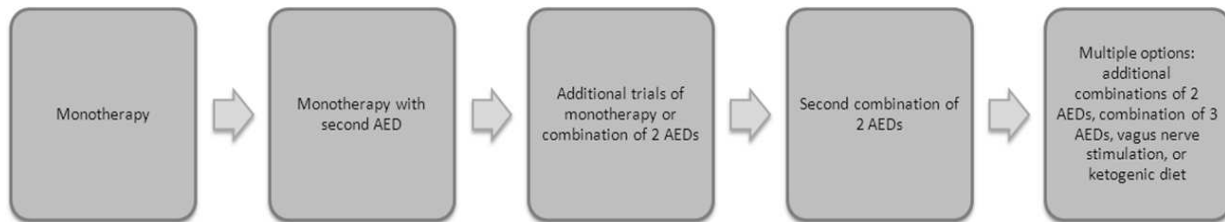
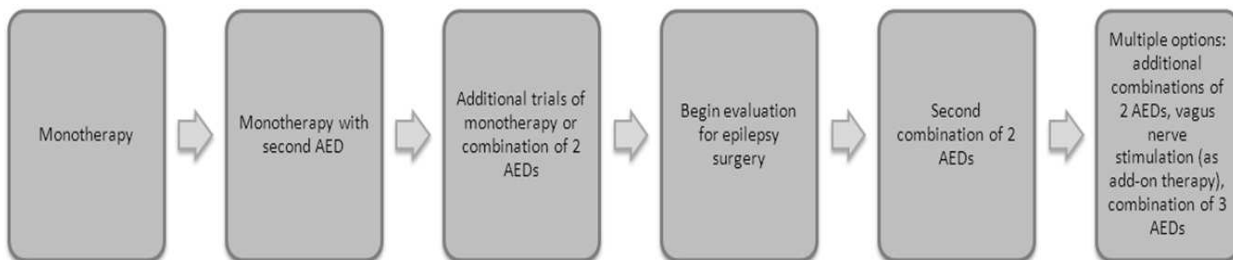


Figure 1b: Overall Strategy for Symptomatic Localization-Related Epilepsy¹²



The mechanism of action of many AEDs is not well understood and several AEDs act via multiple mechanisms. However, antiepileptic drugs can be divided into 9 groups based upon their proposed mechanisms of action: ^{7,13}

1. Blockers of repetitive activation of sodium channel - phenytoin, carbamazepine, oxcarbazepine, lamotrigine, topiramate
2. Enhancer of slow inactivation of sodium channel - lacosamide
3. GABA-A receptor enhancers - phenobarbital, benzodiazepines
4. Glutamate modulators - topiramate, lamotrigine, felbamate
5. Calcium channel blockers:
 - T-calcium channel blockers - ethosuximide, valproate
 - N- and L-calcium channel blockers - lamotrigine, topiramate, zonisamide, valproate
6. H-current modulators - gabapentin, lamotrigine
7. Blockers of unique binding sites - gabapentin, levetiracetam
8. Inhibition of GABA-T - vigabatrin
9. Carbonic anhydrase inhibitors - topiramate, zonisamide

Detailed information on labeled indications, dosing, and selected adverse effects for each AED is provided in Tables 2a and 2b. Table 3 summarizes selected pharmacokinetic parameters (half-life and target serum concentration) for individual AEDs.

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Table 2a: Antiepileptic Drugs with Generics Available¹³

Medication	Labeled Indication (seizure type)	Adult Dosage Range: Usual Initial mg/d (Max mg/d)	Selected Adverse Effects & Boxed Warnings
Carbamazepine (CBZ) (Carbatrol®, Tegretol®)	Tonic-clonic, complex partial, mixed	400 (1600 divided BID-QID)	Diplopia, drowsiness, nausea, sedation, hyponatremia (Boxed Warnings: blood dyscrasias, dermatologic reactions)
Ethosuximide (Zarontin®)	Absence	500 (1500 in divided doses)	Ataxia, aggressiveness, sedation, rash, headache, abdominal pain
Gabapentin (Neurontin®)	Adjunctive therapy partial with and without secondary generalization	900 (2400 divided TID) ^a	Drowsiness, sedation, dizziness , ataxia, fatigue
Lamotrigine (Lamictal®)	Partial, tonic-clonic, adjunctive	25 (225-375 divided BID) ^{a,b,c}	Ataxia, dizziness, diplopia, headache, nausea, vomiting (Boxed Warnings: Life-threatening skin rash)
Levetiracetam (Keppra®)	Adjunctive therapy with tonic-clonic, myclonic, partial	1000 (3000 divided BID) ^a	Somnolence, dizziness, headache, behavior symptoms
Oxcarbazepine (Trileptal®)	Partial	600 (1200 divided BID)	Diplopia, somnolence, dizziness, headache, tremor, nausea, vomiting
Phenobarbital (C-IV)	Tonic-clonic, partial	1-3 mg/kg/d (50-100 mg BID-TID)	Sedation, cognitive impairment, ataxia, headache, hyperactivity, attention deficit behavior, mood changes, sleep problems, rash
Phenytoin (Dilantin®, Phenytek®)	Complex partial, generalized tonic-clonic , prevention of seizures following head trauma/neurosurgery	5-6 mg/kg/d (divided TID)	Nystagmus, ataxia, cognitive impairment, lethargy, sedation, fatigue, headache, dizziness, behavior changes, visual blurring, gingival hyperplasia, hirsutism, coarsening of facial features, acne, folate deficiency, rash (Boxed Warnings IV: hypotension)
Primidone (Mysoline®)	Generalized tonic-clonic, partial	100-125 (2000 divided TID or QID)	Anemia, granulocytopenia, agranulocytosis
Topiramate (Topamax®)	Monotherapy or adjunctive therapy partial, or generalized tonic-clonic	25-50 (200 BID) ^a	Sedation, confusion, mental slowing, word-finding difficulty, anorexia, serum bicarbonate decreased
Valproic Acid (Depakene®, Stavzor®-delayed capsules) Divalproex sodium (Depakote®)	Complex partial, absence	10-15 mg/kg/d (60 mg/kg/d)	GI upset, headache, lethargy, tremor, thrombocytopenia, sedation, alopecia (Boxed Warnings: hepatic failure, pancreatitis, pregnancy)
Zonisamide (Zonegran®)	Adjunctive therapy partial	100-200 (400 QD)	Somnolence, ataxia, fatigue, anorexia, dizziness, headache

Abbreviations: BID-twice daily; QD-once daily; QID-four times daily; TID-three times daily; VPA-valproic acid; C-IV-Schedule IV controlled substance

^aDosage adjustment needed in renal impairment

^bDosage adjustment needed in hepatic impairment

^cDosage adjustment needed if taken in conjunction with other AEDs.

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Table 2b: Antiepileptic Drugs-Generics Not Available¹³

Medication	Labeled Indication (seizure type)	Adult Dosage Range: Usual Initial mg/d (Max mg/d)	Selected Adverse Effects & Boxed Warnings
Felbamate (Felbatol®)	Partial, with or without generalization	1200 (3600 divided TID or QID)	Anxiety, insomnia, nausea, anorexia, headache, dizziness, somnolence (Boxed Warnings: aplastic anemia, hepatotoxicity)
Lacosamide(Vimpat®) (C-V)	Partial (adjunct)	100 (400 divided BID) ^{a,b}	Ataxia, dizziness, diplopia, headache, nausea, PR interval prolongation
Pregabalin (Lyrica®) (C-V)	Partial (adjunct)	150 (600 divided BID or TID) ^a	Ataxia, blurred vision, dizziness, nausea, headache, somnolence, peripheral edema, weight gain
Tiagabine (Gabitril®)	Partial (adjunct)	4 (56 divided BID to QID)	Dizziness, somnolence, irritability, slowed thinking, exacerbation of generalized seizures
Vigabatrin (Sabril®) ^c	Refractory complex partial	1000 (3000 divided BID) ^a	Seizure, dizziness, headache, insomnia, tremor, pharyngitis, somnolence, weight gain (Boxed Warning: permanent vision loss)

Abbreviations: BID-twice daily; QID-four times daily; TID-three times daily; C-V-Schedule V controlled substance

^aDosage adjustment needed in renal impairment

^bDosage adjustment needed in hepatic impairment

^cMust be obtained via SHARE program - a special restricted distribution program. More information available at www.lundbeckshare.com.

Table 3: Pharmacokinetics of AEDs in Adults¹³

Medication	Half-life (hrs)	Target Serum Concentration (mg/L)
Carbamazepine	25-65 initially then 12-17 after repeated doses ^a	4-12
Ethosuximide	50-60	40-100
Felbamate	20-23	Not established
Gabapentin	5-7	Not established
Lacosamide	13	Not established
Lamotrigine	25-33	Not established
Levetiracetam	6-8	Not established
Oxcarbazepine	~2 (parent drug) 9 (metabolite)	Not established
Phenobarbital	53-140	20-40
Phenytoin	~22 (7-42)	10-20 (total) 1-2.5 (free)
Pregabalin	6.3	Not established
Primidone	5-15	5-12 (must monitor phenobarbital if on both)
Tiagabine	2-5 (with enzyme inducers) 7-9 (without enzyme inducers)	Not established
Topiramate	21	Not established
Valproic acid	9-16	50-100
Vigabatrin	7.5 12-13 (elderly)	Not established
Zonisamide	~63	Not established

^a Half-life is variable because of autoinduction which is usually complete 3-5 weeks after initiation of a fixed carbamazepine regimen

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Special Topics

Generic Substitution of AEDs

Generic substitution is allowed if medications are bioequivalent (A-rated) as determined by the FDA. This determination always involves comparing the generic to the reference listed drug (RLD), which is usually the brand-name drug. To be considered A-rated, the 90% confidence interval for maximum concentration (C_{max}) and area under the curve (AUC) must be within 80 to 125% of the values listed for the RLD. Therefore, two generic versions of the same drug could have as much as a 45% difference in AUC and C_{max} and still be considered bioequivalent.¹⁴

A small number of case reports and national surveys of patients with epilepsy and physicians treating epilepsy, like those reported by Berg, et al. in 2008, suggest that generic substitution of antiepileptic drugs is a potential problem.^{15, 16} As reported by Berg et al., results of a survey of physicians who treat patients with epilepsy (n=606) and adult patients with self-reported epilepsy (n=550) indicated that 75% of physicians and 65% of patients reported concern over the efficacy of generic medications, 88% of physicians reported a specific concern that generic interchange in controlled patients could result in a breakthrough seizure, and 65% of physicians reported they had cared for a patient who had experienced a breakthrough seizure that could be associated with a switch from a branded to a generic agent.¹⁶ In a second study, Berg et al. reported results of a chart audit survey completed by neurologists of 50 cases where loss of seizure control was attributed to generic AED interchange. In 21 or 26 cases where data were available for comparison, AED levels were on average 33% lower at the time of the seizure (on generic AED) as compared to the AED level at baseline (on brand AED).¹⁵

Further evidence that generic interchange is a potential problem is seen in three large case-control studies that found A-rated antiepileptic drug substitution was a risk factor for emergency or hospital-level treatment of epilepsy (OR: 1.78 to 1.81).¹⁷⁻¹⁹ Studies using medical and pharmacy claims databases have found that generic interchange of AEDs is associated with higher epilepsy-related medical utilization rates, such as hospitalizations.²⁰⁻²²

In contrast, a meta-analysis of 7 randomized controlled trials (n=204) found no difference in the chance of a patient on generic AEDs experiencing loss of seizure control compared to patients taking brand-name medications (aggregate odds ratio: 1.1, 95% CI 0.9, 1.2). The drugs in these trials included brand-name and generic versions of carbamazepine (5 studies), phenytoin (3 studies) and valproic acid (1 study). Although these studies were primarily short in duration and in small patient populations, they suggest that for most patients, generic substitution is not associated with increased risk of seizures.²³

Generic substitution is often not avoidable, since generic medications are usually less expensive and sometimes required by insurance providers. For many patients, use of generic medications presents no problems. However, variations in pharmacokinetics between brand-name drugs and their generic equivalents, and within generics, as allowed by the FDA can result in breakthrough seizures or toxicity for a subset of patients.²⁴⁻²⁷ Patients at higher risk include elderly patients, patients with liver or kidney disease, comorbid conditions, and patients taking medications that may interact with AEDs, leading to altered AED pharmacokinetics.²⁶ The Epilepsy Foundation issued a position statement in 2009 recommending that both the physician and patient be informed if interchange occurs.²⁸

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Pharmacists can be a key resource for patients and physicians by providing information on generic availability of AEDs and by recognizing changes in generic manufacturers. Providing this information allows patients and physicians to monitor for possible changes in efficacy or side effects which may be attributable to AED substitution.

Suicidality and AEDs

An increased risk of suicidal behavior and ideation has been linked to several AEDs in randomized placebo-controlled studies of patients with epilepsy according to a January 2008 FDA report.²⁹ The FDA's actions are based on the agency's review of 199 clinical trials of 11 AEDs.³⁰ The elevated risk (0.43 versus 0.24 %) was observed as early as one week after starting medication and continued through the 24 weeks of study observation.³¹ The effect was consistent in the 11 AEDs studied (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide), and the FDA considers this risk likely to be shared by all AEDs. A literature review that was not affiliated with the FDA estimated that the overall standardized mortality ratio for suicide was 3.3. This increased risk appeared to be present among most subgroups of individuals with epilepsy.³² The FDA has required updated labeling for these AEDs and medication guides describing the increased risk are required to be provided to patients at the time of dispensing. Updated medication guides are currently available for AEDs through the FDA website.³³

Conclusion

- Individual patient characteristics (eg, age, sex, type of seizures, health insurance coverage, etc) must be considered when choosing an AED.
- Potential side effects and drug interactions should also be carefully considered.
- Monotherapy with an appropriate AED is the preferred treatment when possible.
- Pharmacists can play an important role by providing physicians, patients, and other healthcare professionals with information about potential side effects and available AEDs, especially as new agents and new generics become available.

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