

# Optimizing Antiepileptic Treatment

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## Abstract

- **Objective:** To describe the properties of the available antiepileptic drugs (AEDs) and to provide a framework for tailoring antiepileptic therapy to the individual patient.
- **Methods:** Review of the literature.
- **Results:** The decision of when to begin antiepileptic therapy is a challenging one, and the benefits of treatment must be carefully weighed against the risk of adverse effects and costs. The number of therapeutic options is staggering, and a framework is needed to make appropriate drug choices. Decisions must take into account (1) efficacy against specific seizure types and epileptic syndromes, (2) pharmacologic properties, and (3) potential adverse effects and interactions with other medications. In general, drug monotherapy is the ideal strategy for seizure control. Approximately 50% of newly diagnosed patients become seizure-free on the first drug initiated and approximately 70% with switching to a second or third drug.
- **Conclusion:** Approximately 70% of those with epilepsy can achieve successful remission (5 or more years without a seizure) with medical therapy. For refractory cases, there have also been advances. However, epilepsy remains a difficult and in some cases disabling chronic illness.

Epilepsy is a common illness, with a prevalence of 0.5% to 1% in most countries [1]. People living in the United States have an estimated 3% lifetime incidence of epilepsy, with approximately 3 million people suffering from active epilepsy and 200,000 newly diagnosed cases each year. The yearly cost of epilepsy is high with estimated direct and indirect expenses in the United States totaling \$15.5 billion. Medical advances in the last quarter of the 20th century have helped to reduce the burden of epilepsy on patients and its cost to society. Multiple new antiepileptic drugs (AEDs) have been approved since 1993 (known as the “new-generation” AEDs), and in general they have fewer side effects than the older therapies. Currently, approximately 70% of those with epilepsy can achieve successful remission (5 or more years without a seizure) with medical therapy [2]. For refractory cases, there have also

been advances and increased use of other treatments, including epilepsy surgery, vagus nerve stimulation, and the ketogenic diet. However, epilepsy remains a difficult and in some cases a disabling chronic illness.

Perhaps equally important as medical therapy is optimizing quality of life for patients with this chronic illness. Historically, a diagnosis of epilepsy carried certain social and economic hardships. Even by the latter half of the 20th century, many states still had laws against patients with epilepsy marrying or having children, and it was not until 1985 that Delaware became the last state to repeal its involuntary sterilization law for persons with epilepsy. Since then, there has been significant improvement in the stigma associated with the disease, and passage of the Americans with Disabilities Act in 1990 provided equal opportunity in employment, state and local government, public accommodations, commercial facilities, transportation, and telecommunications [3]. However, patients living with epilepsy still face significant hurdles in daily life including coping with the uncertainties of having an unpredictable disease as well as dealing with nonmedical issues such as driving restrictions or difficulties obtaining health or life insurance. This inevitably impacts the patient’s quality of life, and therefore physicians must continually strive to not only provide the best medical therapy to improve seizure control but also to adopt a more holistic approach to treatment.

In this article, we will review data with respect to providing a framework for tailoring antiepileptic therapy to the individual patient and also touch on other factors affecting quality of life in epilepsy and likely impacting treatment outcomes. In a second article to be published in a subsequent issue, we will provide case examples illustrating a patient-centric approach to optimizing antiepileptic therapy.

## Initiation of Antiepileptic Therapy

The decision of when to begin antiepileptic therapy is a challenging one, and the benefits of treatment must be carefully weighed against the risk of adverse effects and costs. Following a first unprovoked seizure, about 50% of patients experience recurrent seizures [4]. The MESS trial [5] showed that immediate treatment following first

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reported seizure versus delayed treatment until a later time when both patient and clinician deemed treatment necessary reduces short-term risk of seizures but does not affect long-term remission rates. Therefore, it is reasonable that decisions regarding starting antiepileptic therapy after a single seizure should follow a prediction of which patients might be at highest risk for recurrent seizures in the short term. The MESS group [6] went on to identify 3 factors possibly helpful in stratifying patients into groups with low, medium, and high risk of seizure recurrence: number of seizures at presentation, abnormal electroencephalogram (EEG), and presence of a neurological disorder. Low-risk patients were those with lifetime history of a single seizure, normal EEG, and no neurological disorder. For patients with this profile only, there was no significant difference in the probability of seizure recurrence between those started on immediate versus deferred antiepileptic therapy. This suggests that patients with more than 1 unprovoked seizure, an abnormal EEG (epileptiform activity not more specific than other abnormalities, including slow-wave disturbance), or a neurological disorder might benefit from early antiepileptic therapy, assuming that other social, psychological, or medical issues do not taint the risk-benefit analysis.

### Choice of Antiepileptic Drug

Prior to 1993, antiepileptic drug therapy options were limited to 6 major drugs: carbamazepine, phenobarbital, phenytoin, primidone, valproate, and ethosuximide. Since then, the market has expanded with development of the new-generation AEDs, and now multiple antiepileptic drugs are available including both primary anticonvulsants and countless medications with secondary antiepileptic properties. The number of therapeutic options is staggering, and a framework is needed to make appropriate drug choices. Decisions must take into account (1) efficacy against specific seizure types and epileptic syndromes, (2) pharmacologic properties, and (3) potential adverse effects and interactions with other medications.

### Efficacy of AEDs Against Specific Seizure Types and Epileptic Syndromes

A generic diagnosis of "seizures" or "epilepsy" is insufficient given that therapeutic decisions depend on the type of seizure or epilepsy syndrome. The International League Against Epilepsy (ILAE) has set forth a classification scheme that uses 2 major divisions [7–9]. First, seizures are separated into either partial (focal) or generalized type. Partial seizures are subdivided into simple partial (consciousness not impaired), complex partial (impairment of consciousness), and partial evolving to secondarily generalized seizures. Generalized seizures are subdivided into absence, atypical absence, myoclonic, clonic, tonic, tonic-clonic, and atonic seizures. Second, epilepsies are separated into idiopathic (primary, likely genetic) or

symptomatic (secondary, from known or suspected disorder of the central nervous system) etiologies. Common idiopathic epilepsy syndromes include childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, West syndrome, and Lennox-Gastaut syndrome.

In general, AEDs are approved for seizure type, although certain AEDs have known efficacy against specific epileptic syndromes as well. We will focus on choice of AEDs by seizure type, given that it is likely many of the patients with specific epilepsy syndromes will be followed by pediatric or epilepsy-specialized neurologists. Agents may be broad-spectrum against many types of seizures or narrow-spectrum against partial seizures, generalized seizures, or certain types of generalized seizures. Also, certain AEDs can exacerbate some types of generalized seizures. There is no known differential efficacy of AEDs against subtypes of partial seizures.

Approved indications for the different AEDs are listed in **Table 1**. In addition, the American Academy of Neurology (AAN) published an evidence-based review on the efficacy and tolerability of the new-generation AEDs in the treatment of new-onset epilepsy that additionally supported the use of gabapentin, lamotrigine, and topiramate as monotherapy in adolescents and adults with either partial or mixed seizure disorders and lamotrigine as monotherapy in children with newly diagnosed absence seizures [10]. The reason for divergence is that the U.S. Food and Drug Administration (FDA) requires proof of superiority and does not accept the finding of equivalency of 2 drugs in controlling seizures as a proof of efficacy, noting the possibility that 2 ineffective drugs could also show this outcome. The AAN, in contrast, accepts equivalence of a new drug with an established drug as proof of efficacy [10]. Nonetheless, trial data have suggested that although multiple drugs are approved for a particular indication, some may be more efficacious and better tolerated than others.

### Partial Epilepsy

Prior to the availability of the new-generation AEDs, carbamazepine was generally accepted as first-line treatment for partial-onset seizures. In a multicenter, double-blind trial of 622 adults with partial and secondarily generalized tonic-clonic seizures randomized to carbamazepine, phenobarbital, phenytoin, or primidone, treatment success was highest with carbamazepine and phenytoin. Carbamazepine provided more frequent complete control of partial seizures than phenobarbital and primidone, with primidone significantly limited by side effects [11]. Similarly, in a multicenter, double-blind trial of 480 adults with partial or secondarily generalized tonic-clonic seizures randomized to carbamazepine or valproate, the agents performed equally against partial seizures with secondary generalization; however, carbamazepine was more effective for complex

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**Table 1.** FDA-Approved Indications for Primary Antiepileptic Drugs

Generic Name	Year Approved	Indications for Epilepsy Treatment	Other Approved Indications
<b>FIRST GENERATION</b>			
Carbamazepine	1968	Monotherapy/adjunctive therapy: partial or GTC May exacerbate absence or myoclonic	Trigeminal neuralgia
Clonazepam	1975	Monotherapy: akinetic, myoclonic, LGS Second-line therapy: absence Adjunctive therapy: LGS	Panic disorder
Ethosuximide	1960	Monotherapy: absence	
Phenobarbital	N/A	Predates FDA approval process; generally accepted as monotherapy for partial or GTC	Short-term insomnia; preanesthesia
Phenytoin	1953	Monotherapy: partial or GTC Prophylaxis/treatment of seizures around neurosurgery	
Primidone	1954	Monotherapy/adjunctive therapy: partial or GTC	
Valproic acid	1978	Monotherapy/adjunctive therapy: absence or partial Adjunctive therapy: multiple seizure types that include absence	Migraine prophylaxis, manic episodes associated w/ bipolar disorder
<b>NEW GENERATION</b>			
Felbamate	1993	Refractory use only, not first-line Monotherapy/adjunctive therapy in adults: partial Adjunctive therapy: LGS	
Gabapentin	1993	Adjunctive therapy in patients age > 3 yr: partial	Postherpetic neuralgia
Lacosamide	2008	Adjunctive therapy in patients age > 17 yr: partial	
Lamotrigine	1994	Adjunctive therapy in patients age > 2 yr: partial, GTC, LGS Adults: conversion to monotherapy from single enzyme-inducing AED	Maintenance treatment of bipolar disorder
Levetiracetam	1999	Adjunctive therapy: age > 4 yr: partial; age > 6 yr: GTC; age > 12 yr: JME; adults: myoclonic	
Oxcarbazepine	2000	Monotherapy in patients age > 4 yr: partial Adjunctive therapy in patients age > 2 yr: partial	
Pregabalin	2004	Adjunctive therapy in adults: partial	Diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia
Rufinamide	2008	Adjunctive therapy in patients age > 4 yr: LGS	
Tiagabine	1997	Adjunctive therapy in patients age > 12 yr: partial May exacerbate absence or myoclonic	
Topiramate	1996	Monotherapy in patients age ≥ 10 yr: partial, GTC Adjunctive therapy in patients age ≥ 2 yr: partial, GTC, LGS	Migraine prophylaxis
Zonisamide	2000	Adjunctive therapy in patients age > 16 yr: partial	

GTC = generalized tonic-clonic; JME = juvenile myoclonic epilepsy; LGS = Lennox-Gastaut syndrome.

partial seizures with fewer long-term side effects [12]. In fact, to date no AED has been shown more efficacious than carbamazepine against partial seizures. However, more recent data suggest that some new-generation AEDs may be equally effective and possibly better tolerated.

The SANAD trial [13] is the largest trial comparing new-generation AEDs with older agents. In the first arm of the SANAD trial, 1721 patients (> 85% with partial epilepsy) were randomized to carbamazepine, oxcarbazepine, lamotrigine, topiramate, or gabapentin monotherapy. Although carbamazepine was most likely to be associated with treatment failure due to side effects, it was associated with the shortest

time to 12-month remission and 24-month remission and was most likely to prevent a seizure following treatment initiation. In limited data secondary to late addition of oxcarbazepine to the trial, oxcarbazepine was comparable to carbamazepine in overall seizure control but possibly less likely to fail due to adverse effects and more likely to fail because of inadequate seizure control. Topiramate and gabapentin were associated with the longest times to 12-month remission, and topiramate, similar to carbamazepine, was most associated with treatment failure due to side effects. Lamotrigine, while intermediate in prevention of first seizure after therapy, had the fewest reported adverse events and was not significantly

inferior to carbamazepine at longer time points. In quality of life surveys, there was also a trend towards reduced depression with lamotrigine. Cost analysis using UK data suggested that lamotrigine was more cost-effective than carbamazepine in terms of cost per seizure avoided and cost per quality-adjusted life-year. Based on these data, the optimal first-choice agents for patients with partial seizures, out of those tested in this trial, were carbamazepine, oxcarbazepine, or lamotrigine. These conclusions were confirmed in a meta-analysis of 20 randomized controlled monotherapy trials suggesting these 3 agents again as the most favorable in terms of combination of seizure control and tolerability (including SANAD) [14].

There are currently insufficient data about the effectiveness of several other of the new-generation AEDs in initial monotherapy for partial seizures, namely levetiracetam, tiagabine, pregabalin, zonisamide, rufinamide, and lacosamide. Pregabalin and zonisamide have not yet been compared for monotherapy in randomized clinical trials. There is a recent multicenter, double-blind trial of 579 adults with newly diagnosed epilepsy (> 85% with partial seizures) randomized to levetiracetam or controlled-release carbamazepine [15] that showed similar seizure-free rates at 6 months and 1 year, with nonsignificant differences in treatment failure due to side effects. Despite the lack of evidence, these agents are gaining popularity, and levetiracetam in particular is often used off-label as monotherapy because of its availability in oral and intravenous forms, rapid titration schedule allowing starting doses to be therapeutic, relatively benign side-effect profile, and lack of significant interactions with other medications.

### Generalized Epilepsy

In comparison to partial seizures, there are less data about initial optimal AED therapy in generalized-onset seizures and a lack of trials on generalized seizure subtypes other than tonic-clonic or absence. Further, studies on generalized seizures have been confounded by possible classification errors (classifying patients with partial seizures as having generalized seizures). In addition, study design frequently uses a heterogeneous population of patients with partial and generalized seizures, with the study population skewed towards those with partial seizures. Out of 20 controlled trials comparing various AEDs, only 28% of the patients had generalized seizures [14].

Historically, valproate has been known as broad-spectrum and has been the drug of choice in patients with generalized-onset tonic-clonic seizures or those with multiple seizure types. This was based predominantly on case reports and series and not randomized controlled data [16]. Other drugs considered more narrow-spectrum for partial seizures, such as carbamazepine, have been avoided because of possibly worsening of certain generalized seizure types including

absence, atonic, and myoclonic seizures [17,18]. Recently, randomized data seem to agree with the choice of valproate as first-line therapy in generalized and unclassified epilepsy types. In the second arm of the SANAD trial [19], valproate was compared with new-generation AEDs thought to have broad-spectrum activity. Specifically, patients (> 60% with generalized epilepsy) were randomized to valproate, topiramate, or lamotrigine monotherapy. In the study, lamotrigine was least likely to be associated with treatment failure due to side effects but was most likely to be associated with treatment failure due to inadequate seizure control. Topiramate was most likely to be associated with treatment failure due to side effects. Valproate was least likely to be associated with overall treatment failure showing shortest time to 12-month and 24-month remission and longest time to first seizure after therapy, particularly when examining the subgroup of patients with idiopathic generalized epilepsy. Similarly, a meta-analysis of 20 randomized clinical trials (including SANAD) confirmed the choice of valproate as first-line therapy for most patients with generalized-onset tonic-clonic seizures in terms of seizure control (although contraindicated in certain populations such as in women of childbearing age). However, there was a nonsignificant trend towards shorter time to 12-month remission and longer time to first seizure after treatment with phenytoin [14], a drug typically used in partial seizures and possibly even associated with worsening of certain generalized seizure types similar to carbamazepine, thus likely emphasizing the classification error in these studies.

In addition to the data on generalized-onset tonic-clonic seizures, there is also limited evidence regarding the treatment of absence seizures; however, a Cochrane review in 2005 [20] found not enough evidence to recommend the optimal drug treatment of absence seizures. Ethosuximide and valproate currently have FDA indications as monotherapy in patients with absence seizures, and the AAN also backs the use of lamotrigine in monotherapy in these patients. Ethosuximide, unlike valproate or lamotrigine, does not have broad-spectrum activity and likely will not be sufficient in patients with generalized seizure types other than purely absence.

### Other Factors Influencing Choice of Antiepileptic Therapy

While carbamazepine, oxcarbazepine, and lamotrigine may be most favorable in terms of seizure control and tolerability across the entire population of patients studied for partial seizures, and valproate may be most favorable for generalized seizures, therapy must be further tailored to individual patients, at times possibly leading to another drug as initial choice in a given patient. The choice of optimal antiepileptic therapy should be a dynamic process that considers not only the patient's seizure type as above but also considers multiple other factors to most benefit and least harm the

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**Table 2.** Pharmacologic Properties of the Antiepileptic Drugs (AEDs)

Generic Name	Trade Name	Formulations	Titration	Half-Life	Adult Dosing
Carbamazepine	Carbatrol, Epitol, Tegretol, Equetro	PO		25–65 hr initially, then 12–17 hr after 3–5 wk secondary to auto-induction	200 mg bid, increase 200 mg/d every week to maximum 1600 mg/d divided bid
Clonazepam	Klonopin	PO		30–40 hr	0.5 mg tid, increase 0.5–1 mg/d every 3 days to maximum 20 mg/d divided tid
Ethosuximide	Zarontin	PO			500 mg/d, increase 250 mg/d every 4–7 days to goal 20–30 mg/kg/d
Felbamate	Felbatol	PO		20–23 hr	400 mg tid, increase 600 mg/d every 2 wk to maximum 3600 mg tid (other AEDs must have dose reduced)
Gabapentin	Neurontin, Gabarone	PO		5–7 hr	300 mg tid, increase up to 3600 mg tid
Lacosamide	Vimpat	PO, IV		15–23 hr	50 mg bid, increase 100 mg/d to 200–400 mg/d
Lamotrigine	Lamictal	PO		13–60 hr, heavily impacted by concomitant AED use	Variable, depending on other drug therapy
Levetiracetam	Keppra	PO, IV	May be rapidly loaded	6–8 hr	500 mg bid, increase 1000 mg every 2 wk to target 1500 mg bid
Oxcarbazepine	Trileptal	PO		2 hr; metabolite 9 hr	300 mg bid, increase 300 mg/d every 3 days to goal 600–1200 bid
Phenobarbital	Luminal	PO, IV, IM	May be rapidly loaded	2–5 d	2–3 mg/kg/d, divided dosing not required
Phenytoin	Dilantin	PO, IV	May be rapidly loaded	7–30 hr	300–600 mg/d, usually tid
Primidone	Mysoline	PO		3–23 hr; metabolites extended	100–125 mg every night for 3 nights, increase 100–125 mg/d every 3 days to goal 250 mg tid
Pregabalin	Lyrica	PO		6 hr	75 mg bid, increase to maximum 600 mg/d divided bid–tid
Rufinamide	Banzel	PO		6–10 hr	400–800 mg bid, increase 400–800 mg/d every 2 days to maximum 1600 mg bid
Tiagabine	Gabatril	PO		7–9 hr	4 mg/d, increase 4–8 mg/d every wk to maximum 56 mg/d divided bid–qid
Topiramate	Topamax	PO		21 hr	25 mg bid, increase 50 mg/d every wk to goal 200 mg bid (for monotherapy, increase by 100 mg/wk on wk 5 and 6 of titration schedule)
Valproic acid	Depakene, Stavzor, Depacon	PO, IV	May be rapidly loaded	9–16 hr	15 mg/kg/d bid, increase 5–10 mg/kg/d every wk to maximum 60 mg/kg/d
Zonisamide	Zonegran	PO		63 hr	100 mg/d, increase by 100 mg every 2 wk to goal 400 mg/d, not divided or bid

bid = twice daily; BUN = blood urea nitrogen; CBC = complete blood count; IM = intramuscularly; IV = intravenously; LFTs = liver function tests; PO = by mouth; qid = 4 times daily; TFTs = thyroid function tests; tid = 3 times daily; U/A = urinalysis. (Data from Micromedex Healthcare Solutions. Proprietary database. [www.micromedex.com/products/hcs/](http://www.micromedex.com/products/hcs/).)

individual patient. These factors include (1) other FDA-approved indications helpful in treating comorbid conditions, (2) pharmacologic properties including formulation, titration rate, half-life, metabolism, and need for monitoring,

(3) common and serious side effects as well as contraindications to use, and (4) drug metabolism and effects on hepatic enzymes that lead to interactions with other prescribed medications. These properties can also affect patient

**Monitoring**

Serum levels: target 4–12 µg/mL, continue to measure for 3 mo because of autoinduction  
 Routine CBC, platelets, Na, LFTs, U/A, BUN, TFTs, eye exams

No therapeutic level established  
 Routine CBC, LFTs

Serum levels: target 40–100 µg/mL  
 Routine CBC, LFTs, U/A

No therapeutic level established (usu 40–100 µg/mL)  
 Routine CBC, platelets, retic counts, LFTs

No therapeutic level established (usu < 5 µg/mL)

No therapeutic level established

No therapeutic level established (usu 4–15 µg/mL)

No therapeutic level established (usu trough 10–30, peak 40–70 µg/mL for maximum)

No therapeutic level established (usu 8–35 µg/mL for metabolite)  
 Routine Na

Serum levels: target 15–40 µg/mL, correlate with AED effect

Serum levels: target 10–20 µg/mL (free 0.1–2.0), correlate with AED effect

Regular dental check-ups

Serum levels: target 5–12 µg/mL  
 CBC/chem 12 every 6 mo

No therapeutic level established

No therapeutic level established

No therapeutic level established

No therapeutic level established (usu 10–35 µg/mL)  
 Routine serum bicarbonate; ammonia if lethargy, vomiting, change in mental status  
 Follow body weight

Serum levels, target 50–100 µg/mL  
 Routine LFTs, ammonia, platelets, coagulation studies; amylase if abdominal pain, nausea, or vomiting

No therapeutic level established (usu < 40 µg/mL)

compliance, and noncompliance with AEDs is a major factor in breakthrough seizures in patients with epilepsy [21,22].

Many of these important properties are outlined in **Table 2**, **Table 3**, and **Table 4**.

**Special Populations**

Certain populations also deserve mention when considering optimal choice of antiepileptic therapy; specifically, these include women who are pregnant or of childbearing age and persons of advanced age.

**Women with Epilepsy**

The AAN recently published practice parameters for the management of women with epilepsy, specifically focusing on pregnancy [23,24]. These parameters are based on a review of the evidence in the literature. Key conclusions regarding teratogenicity include (1) valproate is implicated in increased risk of major congenital malformations and should be avoided when possible, (2) polytherapy is associated with increased risk of major congenital malformations, and (3) there is probably a relationship between the dose of valproate and lamotrigine and the risk of development of major congenital malformations. Drugs associated with specific malformations include phenytoin (cleft palate), carbamazepine (cleft palate), valproate (neural tube defects, facial clefts, hypospadias), and phenobarbital (cardiac malformations). In additions, there is an association of valproate, phenytoin, and phenobarbital with possible reduced cognition in offspring of women with epilepsy. There is currently insufficient evidence to assess the risks of the other AEDs. The North American Pregnancy Registry is an ongoing study with a primary goal of determining the frequency of major malformations in the infants exposed to AEDs during pregnancy ([www.massgeneral.org/aed](http://www.massgeneral.org/aed) and 1-888-233-2334), and pregnant women with epilepsy should be encouraged to enroll.

There is limited information about breast-feeding and AEDs [24]. However, in general, breast-feeding is encouraged. Levetiracetam appears to penetrate into breast milk in potentially clinically important amounts as does gabapentin, lamotrigine, and topiramate. Valproate, phenobarbital, phenytoin, and carbamazepine probably do not penetrate into breast milk in potentially clinically important amounts.

The interaction of AEDs and hormonal contraception is of key importance in treating women with epilepsy. The AEDs that reduce the efficacy of hormonal contraception are carbamazepine, felbamate, phenytoin, phenobarbital, primidone, oxcarbazepine, and topiramate (at > 200 mg/d). Use of hormonal contraception increases the metabolism of lamotrigine, requiring an increased dose often greater than 100% to achieve the same level.

Bone health is an important consideration in treatment in women as well as men. Osteopenia and osteoporosis occur at a higher frequency after long-term exposure to the older AEDs. Less is known about the newer agents. Induced vitamin D metabolism and direct effects on bone metabolism may play a role. Calcium and vitamin D and dual-energy x-ray absorptiometry screening are often recommended.

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**Table 3.** Common and Serious Side Effects of Antiepileptic Drugs and Contraindications to Use

Generic Name	Common Side Effects	Serious Side Effects
Carbamazepine	Hyper/hypotension, N/V, dizziness, nystagmus, diplopia, somnolence	AV block, CHF, syncope, SJS/TEN, hypocalcemia, hyponatremia, acute intermittent porphyria, aplastic anemia, hepatitis, acute renal failure, angioedema
Clonazepam	Excessive salivation, dizziness, ataxia, somnolence, seizures, abnormal behavior, respiratory depression	
Ethosuximide	Decreased appetite, abdominal symptoms, ataxia, dizziness, headache, somnolence, hiccoughs	Aplastic anemia, SJS, SLE, seizures
Felbamate (requires patient registration to prescribe)	Decreased appetite and weight loss, abdominal symptoms, purpura, photosensitivity, dizziness, headache, insomnia	Aplastic anemia and hepatic failure (both may be fatal), SJS, seizures
Gabapentin	Peripheral edema, myalgias, dizziness, nystagmus, somnolence, abnormal thoughts/behavior. Rarely, myoclonus	SJS, coma, seizures
Lacosamide	Diplopia, dizziness, headache	Syncope, suicidal behavior, hypersensitivity reactions
Lamotrigine	Ataxia, dizziness, asthenia, abdominal symptoms, tremor, diplopia, dysmenorrhea, rash	Rare life-threatening SJS (higher risk with fast titration, age < 16, or use with VPA), hepatic failure, renal failure, DIC
Levetiracetam	Decreased appetite, vomiting, asthenia, dizziness, headache, somnolence, abnormal behavior, irritability, cough	Pancytopenia, liver failure, suicidal behavior
Oxcarbazepine	Abdominal symptoms, ataxia, dizziness, nystagmus, vertigo, diplopia, URI	Hyponatremia (> elderly or on diuretics), SJS/TEN, angioedema
Phenobarbital	Somnolence, dizziness, irritability, headache, constipation, N/V. In children, hyperactivity.	Thrombophlebitis, scaling eczema, SJS, agranulocytosis, megaloblastic anemia, thrombocytopenia, liver failure, osteopenia, rickets
Phenytoin	Lethargy, abnormal movements, confusion, headache, nystagmus, ataxia, dysarthria, encephalopathy, N/V, constipation, pruritus, rash Chronic use: gingival hyperplasia, "dilantin facies," osteoporosis, hirsutism, cerebellar atrophy, peripheral neuropathy	Hepatic failure, aplastic anemia, lupus erythematosus, SJS/TEN, scaling eczema, purpuric rash, bullous dermatosis
Pregabalin	Peripheral edema, increased appetite and weight gain, constipation, xerostomia, ataxia, dizziness, somnolence, blurred vision, diplopia, euphoria	Angioedema
Primidone	N/V, ataxia, dizziness, somnolence	Thrombocytopenia, megaloblastic anemia
Rufinamide	Shortened QT interval, nausea/vomiting, dizziness, headache, lethargy	Suicidal behavior
Tiagabine	Pruritus, increased appetite, abdominal symptoms, confusion, ataxia, dizziness, paresthesias, pharyngitis	Seizures, status epilepticus, sudden death
Topiramate	Decreased appetite and weight loss, abdominal symptoms, confusion, decreased psychomotor performance, cognitive impairment, diplopia, nystagmus, fatigue	Renal stones, metabolic acidosis, open angle glaucoma, liver failure, SJS/TEN, hyperammonemia, hypohydrosis, hyperthermia, suicidal behavior
Valproic acid	Increased appetite and weight gain, alopecia, peripheral edema, rash, abdominal symptoms, asthenia, dizziness, ataxia, diplopia, nystagmus, respiratory symptoms, somnolence, tremor	Hyperammonemia, pancreatitis, liver failure, palpitations, thrombocytopenia (dose-related), ototoxicity
Zonisamide	Abdominal symptoms, ataxia, confusion and memory impairment, dizziness, nystagmus, diplopia, fatigue, decreased appetite and weight loss, renal stones	Aplastic anemia, SJS/TEN, schizophreniform disorder

AV = atrioventricular; CHF = congestive heart failure; DIC = disseminated intravascular coagulation; MAOI = monoamine oxidase inhibitor; N/V = nausea and vomiting; SJS = Stevens-Johnson syndrome; SLE = systemic lupus erythematosus; TCA = tricyclic antidepressant; TEN = toxic epidermal necrosis; URI = upper respiratory infection; VPA = valproic acid. (Data from Micromedex Healthcare Solutions. Proprietary database. [www.micromedex.com/products/hcs/](http://www.micromedex.com/products/hcs/).)

**Contraindications**

Bone marrow suppression, use of MAOI within 14 d, use of nefazodone, TCA hypersensitivity, +HLA-B\*1502 allelic variant

Acute narrow angle glaucoma, significant liver impairment

History of blood dyscrasia or liver disease

Relative: severe hepatic impairment, AV block, severe cardiac disease

Porphyria, significant liver impairment, respiratory disease (dyspnea or obstruction)

Porphyria, barbituate hypersensitivity  
Familial short QT syndrome

Urea cycle disorders, significant liver impairment

Sulfonamide hypersensitivity

A recent study showed decreased bone density after only 1 year of phenytoin use in young women [25].

**Elderly Patients**

Treatment of epilepsy in the elderly has unique challenges, and the incidence of epilepsy is highest in those aged 75 years or older. Nearly 25% of all persons with epilepsy are elderly, and of all new seizures, 25% to 50% occur in the elderly [26,27]. In addition, up to 18% of elderly nursing home residents have epilepsy, and most are treated with first-generation AEDs [28]. The average community-dwelling elderly person takes 5 medications daily; the average nursing home resident takes 5 to 10 medications daily [29]. Elderly patients are also more sensitive to drug interactions and adverse events because they have reduced hepatic and renal clearance, reduced protein binding, and altered gastrointestinal absorption. Phenytoin and valproate are highly protein bound and may lead to a higher free fraction in the elderly, contributing to adverse events. Even in a controlled setting with stable dosage, phenytoin levels within an elderly individual may vary as much as two- to threefold [30]. Cognitive changes and gait dysfunction are common side effects of many AEDs. These symptoms may be attributed to other known problems, and the patient may not be able to recognize these side effects. The newer AED agents may overcome some of these problems [31,32].

As new-onset seizures in this age-group are readily controlled with modest dosages, the selection of an initial AED for an elderly patient should consider tolerability and potential side effects as much as efficacy of the agent. The VA Cooperative Study assessed the efficacy and tolerability of 3 AEDs for new-onset seizures in patients older than 60 years: gabapentin (1500 mg), lamotrigine (150 mg), and carbamazepine (600 mg). There was no significant difference in efficacy among these agents. However, carbamazepine was associated with significantly more adverse events (27.3%) compared with gabapentin (17.4%) and lamotrigine (10%) [33]. Several agents are recently recognized as being associated with an increased risk of osteoporosis (carbamazepine, phenobarbital, primidone, phenytoin). Gabapentin, lamotrigine, levetiracetam, and valproate have fewer cognitive side effects. Gabapentin and levetiracetam are often selected for initial treatment in the elderly. Both agents can be titrated to a therapeutic dose quickly and may even be started at a therapeutic dose. They have no serious side effects and no drug-drug interactions. Lamotrigine has a positive cognitive profile and is generally safe. Oxcarbazepine is associated with an increased risk of hyponatremia in the elderly (6%–7% of patients will have sodium levels  $\leq 125$  mEq/L) but has much less risk of leukopenia and aplastic anemia and fewer drug interactions when compared with carbamazepine. Topiramate and zonisamide may have more cognitive side effects, and both agents can be associated with anorexia and weight loss.

## ANTIEPILEPTIC TREATMENT

**Table 4.** Antiepileptic Drug (AED) Metabolism and Effects on Hepatic Enzymes

Generic Name	Serum Protein Binding, %	Metabolism	Excretion	Effect on CYP Isoenzymes
Carbamazepine (CBZ)	75	Hepatic, autoinduces own metabolism; CYP3A4, metabolite by epoxide hydrolases	> 70% renal; dialyzable	Broad-spectrum inducer including CYP1A2, CYP2C9, CYP2C19, CYP3A4, UGT, epoxide hydrolases
Clonazepam (CZP)	85	Hepatic; CYP3A4	Renal	None
Ethosuximide (ESM)	0	Hepatic; CYP3A4	Renal	None
Felbamate (FBM)	25	50% hepatic (other unchanged); inducible CYP isoforms	90% renal	Induces CYP3A4 (weak/tissue-specific) Inhibits CYP2C19
Gabapentin (GBP)	0	None	Renal	None
Lacosamide (LCM)	< 15	60% hepatic (other unchanged); CYP2C19	Renal; dialyzable (~50% removed)	None
Lamotrigine (LTG)	55	Hepatic; glucuronyl transferase (UGT1A4 > 1A3)	95% renal	Induces UGT (weak)
Levetiracetam (LEV)	0	25% hepatic (other unchanged); enzyme hydrolysis	Renal; dialyzable (~50% removed)	None
Oxcarbazepine (OXC)	40	> 50% hepatic (other unchanged); glucuronyl transferase	> 95% renal	Induces CYP3A4 (weak/tissue-specific) Inhibits CYP2C19 (weak)
Phenobarbital (PB)	55	Hepatic; CYP2C9, CYP2C19	Renal; dialyzable	Broad-spectrum inducer including CYP1A2, CYP2C9, CYP2C19, CYP3A4, UGT, epoxide hydrolases
Phenytoin (PHT)	90	Hepatic; CYP2C9, CYP2C19	Renal	Broad-spectrum inducer including CYP1A2, CYP2C9, CYP2C19, CYP3A4, UGT, epoxide hydrolases
Pregabalin (PGB)	0	< 10% hepatic (other unchanged)	Renal; dialyzable (~ 50% removed)	None
Primidone (PM)	10	Hepatic, metabolized to PB and PEMA by CYP450	Renal	Broad-spectrum inducer including CYP1A2, CYP2C9, CYP2C19, CYP3A4, UGT, epoxide hydrolases
Rufinamide (RFM)	34	Hepatic; carboxylesterase hydrolysis	Renal; dialyzable (~ 30% removed)	Induces CYP3A4 (weak) Inhibits CYP 2E1 (weak)
Tiagabine (TGB)	96	Hepatic; CYP3A4	Fecal > renal	None
Topiramate (TPM)	15	30% hepatic (other unchanged); inducible CYP isoforms	Renal; dialyzable	Induces CYP3A4 (weak/tissue-specific) Inhibits CYP2C19 (weak)
Valproic acid (VPA)	90	Hepatic; mitochondrial oxidase, glucuronyl transferase, minor CYP450	> 70% renal; dialyzable (~ 20% removed)	Inhibits CYP2C9, UGT, epoxide hydrolases
Zonisamide (ZNS)	50	> 50% hepatic (other unchanged); CYP 3A4, N-acetyl transferase	> 95% renal	None

Adapted from references 36–38.

**Treatment Strategy if Initial Monotherapy Fails**

In general, drug monotherapy is the ideal strategy for seizure control. Since the majority of treatment-responsive patients can be managed on a single drug, an initial approach to breakthrough seizures first involves maximizing the initial drug of choice before switching to alternative agents. Then, if complete control is not achieved, a second and possibly third agent should be tried in monotherapy before trying adjunctive therapy. Although there is a theoretical benefit to combining drugs with different channel and receptor activities (perhaps allowing synergistic drug effects), this benefit has never been realized in clinical trials. Rather, in practice, combining medications typically results in complex and additive side effects, and even though the new-generation AEDs tend to cause fewer severe drug-drug interactions, side effects are still common.

Previous studies suggest that approximately 50% of newly diagnosed patients become seizure-free on the first drug initiated and approximately 70% with switching to a second or third drug [34,35]. Approximately half of patients in whom the initial drug produces intolerable side effects or an idiosyncratic reaction become seizure-free with changing to another drug; however, many less respond if the first drug was ineffective [35]. This later group represents part of the approximately 20% to 30% of people with residual seizures and chronic epilepsy even with medical treatment. Overall, persistent seizures are more common in patients with structural lesions or cryptogenic seizures than in patients with idiopathic epilepsy. Patients with persistent seizures despite medical treatment should be referred to epilepsy-specialized care, which will allow for further evaluation of the events with video-EEG monitoring as well as consideration of other therapies such as vagus nerve stimulation, the ketogenic diet, or possibly epilepsy surgery.

**Interactions with Other Medications**

As in the general population, patients with epilepsy may have comorbid medical conditions, and as many as 30% will require multiple AEDs. Therefore, it is likely that patients with epilepsy will at some point be taking multiple medications. For optimal epilepsy treatment, serum AED levels must remain within a sometimes narrow therapeutic range, with an increased risk of seizures or side effects with levels outside this range. Unfortunately, the serum level of most AEDs affects or is affected by other medications, including other AEDs. This requires that prescribers understand the potential for drug-drug interactions for patients on chronic AED therapy.

The interactions between AEDs and other medications are complicated and require an understanding of drug absorption, metabolism, and excretion [36]. Changes in drug distribution are also important, as might be seen with

Common Drugs That Affect This AED	Common Drugs That Are Affected by This AED
<ul style="list-style-type: none"> <li>↑ CBZ: diltiazem, verapamil, clarithromycin, erythromycin, fluoxetine, INH, omeprazole</li> <li>↓ CBZ: FBM, PB, PHT, RFM, CBZ (autoinduction)</li> </ul>	<ul style="list-style-type: none"> <li>↓: FBM, LTG, TGB, TPM, ZNS, OCPs, antipsychotics, CCBs, cyclosporine, protease inhibitors, theophylline, warfarin</li> </ul>
<ul style="list-style-type: none"> <li>↑ CZP: cimetidine, erythromycin, omeprazole</li> <li>↓ CZP: CBZ, PB, PHT, rifampin</li> </ul>	<ul style="list-style-type: none"> <li>Generally does not affect other drugs</li> </ul>
<ul style="list-style-type: none"> <li>↑ ESM: possibly VPA, INH</li> <li>↓ ESM: CBZ, PB, PHT</li> <li>↑ FBM: VPA</li> <li>↓ FBM: CBZ, PB, PHT</li> </ul>	<ul style="list-style-type: none"> <li>Generally does not affect other drugs</li> <li>↑: CBZ epoxide, PB, PHT, VPA</li> <li>↓: CBZ, OCP</li> </ul>
<ul style="list-style-type: none"> <li>↓ GBP 20%: antacids</li> <li>None</li> </ul>	<ul style="list-style-type: none"> <li>None</li> <li>None</li> </ul>
<ul style="list-style-type: none"> <li>↑ LTG: sertraline, VPA</li> <li>↓ LTG: CBZ, OXC, PB, PHT, PRM, OCPs, rifampin</li> <li>None</li> </ul>	<ul style="list-style-type: none"> <li>↓: VPA 25%</li> <li>None</li> </ul>
<ul style="list-style-type: none"> <li>↓ Active metabolite: CBZ, PB, PHT</li> </ul>	<ul style="list-style-type: none"> <li>↑: PHT</li> <li>↓: OCPs (at high doses)</li> </ul>
<ul style="list-style-type: none"> <li>↑ PB: FBM, VPA</li> <li>↑ or ↓ PB: PHT</li> </ul>	<ul style="list-style-type: none"> <li>↓: CBZ, FBM, LTG, PHT, RFM, TGB, TPM, VPA, ZNS, antipsychotics, CCBs, OCPs, protease inhibitors, steroids, theophylline, tricyclics, warfarin</li> </ul>
<ul style="list-style-type: none"> <li>↑ PHT: FBM, OXC, PB, TPM, VPA, amiodarone, cimetidine, diltiazem, fluconazole, fluoxetine, isoniazid, omeprazole, ritonavir</li> <li>↓ PHT: CBZ, PB, antacids, ciprofloxacin, sucralfate</li> <li>None</li> </ul>	<ul style="list-style-type: none"> <li>↓: CBZ, FBM, LTG, RFM, TGM, TPM, VPA, ZNS, antipsychotics, CCBs, cyclosporine, narcotics, OCPs, statins, steroids, theophylline, tricyclics, ↑ or ↓ warfarin</li> <li>None</li> </ul>
<ul style="list-style-type: none"> <li>Similar to PB</li> </ul>	<ul style="list-style-type: none"> <li>Similar to PB</li> </ul>
<ul style="list-style-type: none"> <li>↓ RFM: CBZ, PB, PHT</li> </ul>	<ul style="list-style-type: none"> <li>↑: PB, PHT, PRM, VPA</li> <li>↓: CBZ, LTG, OCPs</li> </ul>
<ul style="list-style-type: none"> <li>↓ TGB: CBZ, PHT, PB</li> <li>↓ TPM: CBZ, PHT, PB</li> </ul>	<ul style="list-style-type: none"> <li>None</li> <li>↑: Metformin, PHT 25%</li> <li>↓: OCPs (at high doses)</li> </ul>
<ul style="list-style-type: none"> <li>↑ VPA: FBM, ASA, fluoxetine, isoniazid</li> <li>↓ VPA: CBZ, LTG, PB, PHT, ritonavir</li> <li>↓ ZNS: CBZ, PB, PHT</li> </ul>	<ul style="list-style-type: none"> <li>↑: CBZ epoxide, FBM, LTG, PB, free PHT, CCBs, tricyclics, warfarin, zidovudine</li> <li>None</li> </ul>

weight changes (a common side effect of AED therapy), pregnancy, or impaired nutritional states (changes in albumin concentration may impact the total level of highly protein bound drugs, such as phenytoin). Drug absorption may be impacted by changes in gastrointestinal motility or food intake. For example, while the bioavailability of phenytoin is slightly reduced by simultaneous food intake, concomitant parenteral feeding may significantly reduce phenytoin uptake. Therefore, parenteral feeds should be timed around enteral phenytoin administration. Drug metabolism can be a factor of hepatic or renal clearance or some combination. Many drugs are metabolized through hepatic enzyme pathways, which typically include the family of cytochrome P-450 (CYP) enzymes. Table 4 outlines the mechanism of individual AED metabolism, including the isoform of the CYP enzymes most responsible for the clearance of each drug. It can be readily seen that an increase in metabolic enzyme activity may lead to reduced serum drug levels (as the drug is more rapidly metabolized), while reduced activity may lead to increased drug levels. This is an important consideration, since many drugs alter the activity of the CYP enzymes (either increasing or decreasing activity, through the induction, inhibition, or down regulation of enzyme levels).

Unfortunately, even with an understanding of the pharmacokinetics of individual AEDs, it is often difficult to predict drug-drug interactions in individual patients. With some AEDs, interactions can become quite complicated, since alterations in enzyme levels may impact the drug causing these changes. For example, carbamazepine levels should be monitored for the need to increase doses after initiation, since it induces the enzymes responsible for its own metabolism. Table 4 lists common interactions for convenience, but patients should be monitored for drug side effects, seizures, and possibly serum drug levels during changes to their medication regimen [36–38].

### **Quality of Life in Epilepsy**

While medical therapy is the mainstay of epilepsy management, it is only one factor in the successful treatment of epilepsy. A more holistic approach to the treatment of epilepsy is critically important. AEDs can influence health-related quality of life (HRQOL), mood, and cognitive function [39–41]. HRQOL may differ between AEDs. Monotherapy with lamotrigine was found to be superior to carbamazepine in patients with newly diagnosed epilepsy when HRQOL was used as an outcome measure [42], although a previous study did not show a statistically significant difference between these 2 drugs when effectiveness was used as an outcome [43].

Further, factors including quality of life influence health care utilization of patients with epilepsy. Bautista et al [44] correlated demographic variables, seizure frequency, and quality of life in epilepsy (QOLIE-10) survey results

with AED use, clinic visits, emergency department (ED) visits, and inpatient admissions. Higher seizure frequency correlated with higher AED use, increased ED visits, and increased inpatient admissions. In addition, each point increase (worsening) in the QOLIE-10 score was associated with a 4% increased chance of 5 or more clinic visits, a 5% increased chance of more inpatient admissions, and a 7% increased chance of more ED visits in 1 year.

The QOLIE-10 evaluates 3 main factors: epilepsy effects, including memory and physical and mental effects of medication; mental health, including energy, depression, and overall quality of life; and role functioning, including seizure worry, work, driving, and social limits [45]. Of these factors, mood disorders are common in epilepsy and are potentially treatable. Approximately one-third of epilepsy patients endorse depressive symptoms [46]. Depression in epilepsy is likely multifactorial but is likely influenced by the sporadic nature of epilepsy leading to fear and lifestyle limitations as well as perceived or real social stigma resulting in isolation [47]. Patients with epilepsy also experience more unemployment or underemployment [48–51] related to general tonic-clonic seizures [52], adverse side effects of drugs, low self-esteem, passive coping style, and low self-efficacy [53,54]. Self-efficacy, in turn, is most negatively impacted by depressive symptoms and improved by satisfaction with epilepsy care [55]. Not surprisingly, satisfaction with epilepsy care is correlated with improved quality of life assessed by the QOLIE-10. However, seizure frequency alone is not significantly correlated with satisfaction with care, suggesting that patients are seeking more than simply seizure treatment. Therefore, this argues that quality of life should be addressed by physicians, and modifiable factors such as mood disorders should be treated. This is likely to not only improve patient satisfaction but also translate into reduced health care utilization. Furthermore, improved quality of life and reduced seizure frequency may help reduce lost work days, unemployment, and the perceived stigma of epilepsy.

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