

Selection of Antiepileptic Drugs in Adults

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KEYWORDS

- Epilepsy • Antiepileptic drug selection • Seizures
- Treatment • Adults

Epilepsy affects approximately 50 million people worldwide, with an annual incidence of 50 to 70 cases per 100,000 population.¹ The condition can strike at any time of life, with an immediate impact on everyday activities and routine. Key to optimal management is swift referral to an epilepsy specialist, appropriate investigation, and timely institution of antiepileptic drug (AED) therapy. In the past 20 years, the explosion of 13 new agents into the marketplace has greatly increased the potential for therapeutic intervention. This article explores the rationale for treatment selection in adults with epilepsy.

STARTING ANTIEPILEPTIC DRUG TREATMENT

The decision to start AED treatment can be based on several criteria, including the likelihood of seizure recurrence, the consequences of continuing seizures for patients, and the beneficial and adverse effects of the pharmacologic agent chosen.

Relative risk of recurrence can vary depending on the seizure type or syndrome.² Patients with epileptiform discharges on an electroencephalogram or congenital neurologic defects are at high risk (up to 90%) of recurrence. Risk of seizure recurrence is also increased in people with previous symptomatic seizures, in those with cerebral lesions, and in patients with Todd's paralysis.³

Patients' views of the situation and those of their family should be taken into consideration when instituting AED treatment.⁴ For people who are anxious not to have another seizure, early introduction of therapy may be the best option. Further seizure activity may be unacceptable for those who need to drive, continue in employment, or are responsible for vulnerable family members. Once two or more unprovoked seizures have occurred, the decision to start treatment is usually more clear-cut.

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Some patients, however, choose not to take AEDs, even after several seizures, because they dislike taking medication or view the diagnosis of epilepsy as a stigma. Treatment may be difficult in people who abuse drugs or alcohol or who have a problem complying with any therapeutic regimen. These individuals should be counseled appropriately and made aware of the implications of further seizure activity, including the risk of sudden unexpected death in epilepsy.⁵

EVIDENCE-BASED GUIDELINES

The number of available AEDs has increased rapidly in the past 20 years, giving more choice when initiating therapy. Major evidence-based guidelines have been developed during this time, assisting clinicians and patients in making appropriate treatment choices in newly diagnosed epilepsy. These include those issued by the National Institute for Clinical Excellence in the United Kingdom,⁶ the Scottish Intercollegiate Guidelines Network,^{2,7} the American Academy of Neurology/American Epilepsy Society,⁸ and the International League Against Epilepsy.⁹ These guidelines are based on the best available evidence but may not be a substitute for knowledge, skill, and experience in managing individual patients.

TREATMENT GOALS

The goals of treatment should be complete freedom from seizures with no (or acceptable) side effects and the maintenance of a normal lifestyle. When starting medication, AED monotherapy is preferred over combination regimens, as treatment with a single drug is usually associated with better compliance, fewer adverse effects, reduced likelihood of drug interactions, and lower teratogenic potential and is more cost effective.¹⁰ The choice of drug should have efficacy for the given seizure type or syndrome, with other important properties comprising safety, tolerability, pharmacokinetic properties, and formulation.¹¹

EFFICACY

The profile of activity against different seizure types and syndromes varies among the different AEDs (**Table 1**). Accurate classification, therefore, is of paramount importance. Certain epilepsy syndromes are found particularly responsive to specific agents. For example, juvenile myoclonic epilepsy responds well to sodium valproate,¹² and vigabatrin is regarded by many clinicians as the treatment of choice for infantile spasms secondary to tuberous sclerosis.¹³ Conversely, narrow spectrum drugs, such as carbamazepine,¹⁴ phenytoin,¹⁵ gabapentin,¹⁶ and oxcarbazepine,¹⁷ can worsen myoclonic jerks and absence seizures.

With the emergence of many new AEDs in recent years, there is a growing evidence base of randomized trials (**Tables 2 and 3**) and systematic reviews (**Table 4**) comparing initial monotherapy treatments for different seizure types and syndromes. AEDs currently licensed for use as monotherapy in the United Kingdom include carbamazepine, phenytoin, phenobarbital, ethosuximide, sodium valproate, lamotrigine, topiramate, oxcarbazepine, and levetiracetam. There is, however, currently no overwhelming efficacy evidence supporting the use of a particular drug. This is due to differences in study design and the absence of comparative adverse effects data at equivalent dosage. There is a dearth of properly conducted randomized controlled trials, particularly in patients with generalized tonic-clonic seizures. Recent data from the levetiracetam versus controlled-release carbamazepine trial suggest that most adults with newly diagnosed epilepsy respond to a modest dose of any

Table 1
Efficacy of antiepileptic drugs against common seizure types and epilepsy syndromes

Antiepileptic Drug	Focal-Onset Seizures	Primary Generalized Seizures			Lennox-Gastaut Syndrome	Infantile Spasms
		Tonic Clonic	Absence	Myoclonic		
Carbamazepine	+	+	↓	↓	0	0
Phenytoin	+	+	↓	↓	0	0
Phenobarbital	+	+	+	0	?	?
Primidone	+	+	0	?	?	?
Ethosuximide	0	0	+	0	0	0
Sodium valproate	+	+	+	+	+	+
Clobazam	+	+	?	+	+	?+
Clonazepam	+	+	?	+	?+	?+
Vigabatrin	+	?+	↓	↓	?	+
Lamotrigine	+	+	+	+ ^a	+	?+
Gabapentin	+	?+	↓	↓	?	?
Topiramate	+	+	?	+	+	?
Tiagabine	+	?	↓	?	?	?+
Oxcarbazepine	+	+	↓	↓	0	0
Levetiracetam	+	+	?+	+	?	?
Pregabalin	+	?	?	?	?	?
Stiripentol	+	+	?+	+	?+	?+
Zonisamide	+	?+	?+	?+	?+	?+
Rufinamide	+	+	?+	?+	+	?
Lacosamide	+	?	?	?	?	?

^a Lamotrigine may worsen myoclonic seizures in some patients.

first-line AED.³⁶ The more pragmatic standard and new antiepileptic drugs (SANAD) trials assessing effectiveness favored lamotrigine over carbamazepine, gabapentin, topiramate, and oxcarbazepine for partial epilepsy³⁷ and sodium valproate over lamotrigine or topiramate for generalized and unclassifiable epilepsy.³⁸

SAFETY

Establishing acceptable tolerability is a crucial function of regulatory studies performed by pharmaceutical companies for licensing purposes. On occasion, an important safety issue emerges once a drug becomes available for general clinical use. This was the case with felbamate, which was found to cause hepatic failure and aplastic anemia, severely limiting its use,⁵⁸ and with vigabatrin, where peripheral visual field defects were first documented 8 years after the drug was licensed.⁵⁹ Other AEDs, such as phenobarbital, carbamazepine, phenytoin, lamotrigine, oxcarbazepine, and zonisamide, are associated with a range of rashes and hypersensitivity reactions.⁶⁰ These can be minimized by a low starting dose and slow titration schedule. The presence of a previous allergic reaction might guide clinicians away from prescribing one of the AEDs described previously.⁶¹ Recent data support a particular association

Table 2
Randomized controlled trials comparing antiepileptic drug monotherapies in patients with newly diagnosed partial-onset seizures

Reference	AEDs Compared	Study Population	Conclusions	Comments
Mikkelsen et al, 1981 ¹⁸	Carbamazepine Clonazepam	36 adults with complex partial seizures	No significant difference was found between the 2 drugs during 6 months' treatment.	Small cohorts
Ramsay et al, 1983 ¹⁹	Carbamazepine Phenytoin	87 adults with newly diagnosed partial-onset and primary GTCS	Efficacy and tolerability were the same for both drugs.	Double-blind study; small patient numbers
Mattson et al, 1985 ²⁰	Carbamazepine Phenobarbital Phenytoin Primidone	622 adults with partial and secondary generalized seizures	Control of tonic-clonic seizures did not differ between the drugs. Carbamazepine more often controlled partial seizures compared with phenobarbitone or primidone. Primidone had efficacy similar to phenobarbital, but was tolerated less well.	Multicenter study
Dam et al, 1989 ²¹	Carbamazepine Oxcarbazepine	235 adults with newly diagnosed partial-onset and primary GTCS	No significant differences in efficacy were found between the two drugs. There was a trend toward better tolerability with oxcarbazepine.	Double-blind multicenter study
Mattson et al, 1992 ²²	Carbamazepine Sodium valproate	480 adults with complex partial or secondary GTCS	Carbamazepine was superior to valproate in controlling complex partial seizures. Carbamazepine is as effective as sodium valproate in controlling secondary GTCS.	Double-blind multicenter study

Richens et al, 1994 ²³	Carbamazepine Sodium valproate	300 adults with newly diagnosed partial- onset or primary GTCS	The drugs controlled seizures equally effectively. Significantly more patients continued on valproate than carbamazepine for at least 6 months.	Open-label study
Brodie et al, 1995 ¹¹	Carbamazepine Lamotrigine	260 patients aged >13 years with untreated partial- onset or primary GTCS	Similar efficacy results were obtained for both drugs. Lamotrigine was significantly better tolerated.	Double-blind multicenter study
Christie et al, 1997 ²⁵	Oxcarbazepine Sodium valproate	249 adults with partial or GTCS	No significant differences in efficacy or tolerability found between the two drugs.	Double-blind multicenter study
Bill et al, 1997 ²⁶	Phenytoin Oxcarbazepine	287 adults with untreated partial-onset and primary GTCS	No significant differences in efficacy found between the two drugs. Oxcarbazepine was significantly better tolerated than phenytoin.	Double-blind multicenter study
Guerreiro et al, 1997 ²⁷	Phenytoin Oxcarbazepine	193 children and adolescents with epilepsy	No significant differences in efficacy found between the two drugs. Oxcarbazepine was tolerated and retained significantly better.	Double-blind multicenter study
Chadwick et al, 1998 ²⁸	Gabapentin 300 mg, 900 mg, and 1800 mg Carbamazepine	292 patients aged 12–86 years with newly diagnosed partial-onset seizures	Gabapentin at 900 mg or 1800 mg/d is as effective and as safe as carbamazepine.	Open-label study
Steiner et al, 1999 ²⁹	Phenytoin Lamotrigine	181 newly diagnosed adults with partial-onset or primary GTCS	Efficacy results were similar for the two drugs. There was a trend toward better tolerability with lamotrigine.	Double-blind study; the high rash rate with lamotrigine probably was due to high starting doses

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Table 2
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Reference	AEDs Compared	Study Population	Conclusions	Comments
Brodie et al, 1999 ³⁰	Carbamazepine Lamotrigine	150 patients aged ≥ 65 years with newly diagnosed epilepsy	No difference was found between the 2 drugs in time to first seizure. More patients continued with lamotrigine than with carbamazepine.	Lamotrigine: carbamazepine treatment ratio was 2:1
Chadwick, 1999 ³¹	Carbamazepine Vigabatrin	459 patients aged 12–65 years with partial-onset seizures	All efficacy outcomes favored carbamazepine and failed to show equivalence between the two drugs. Time to first seizure was significantly greater with carbamazepine. Vigabatrin was associated with more psychiatric symptoms.	Double-blind multicenter study
Brodie et al, 2002 ¹¹	Lamotrigine Gabapentin	309 adults with partial-onset seizures or primary GTCS	The drugs were similar in efficacy and tolerability.	Double-blind multicenter study
Privitera et al, 2003 ³²	Carbamazepine Sodium valproate Topiramate	621 children and adults with newly diagnosed partial-onset seizures or primary GTCS	No significant differences in efficacy were found between the three drugs.	Double-blind multicenter study
Gilliam et al, 2003 ³³	Topiramate 50 mg/d, 200 mg/d, or 500 mg/d	Patients aged ≥ 3 years with partial-onset seizures	Seizure-free rates were significantly higher and time to first seizure was significantly longer with 200 mg/d and 500 mg/d.	Double-blind multicenter study
Arroyo et al, 2005 ³⁴	Topiramate 50 mg/d or 400 mg/d	Patients ≥ 6 years old with untreated partial-onset or GTCS	The higher dose was significantly more likely to produce seizure freedom than the lower dose. More patients on the higher dose discontinued treatment.	Multicenter study

Rowan et al, 2005 ³⁵	Carbamazepine Lamotrigine Gabapentin	593 patients aged ≥ 65 years with newly diagnosed epilepsy	Seizure control outcomes were similar for the three drugs. Significantly more patients came off carbamazepine due to adverse events compared with gabapentin and lamotrigine.	Double-blind multicenter study
Brodie et al, 2007 ³⁶	Controlled release carbamazepine Levetiracetam	579 patients ≥ 16 years with ≥ 2 partial-onset or GTCs in the past year	Seizure free rates were equivalent for both drugs.	Double-blind multicenter study
Marson et al, 2007 ³⁷	Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Topiramate	1721 adults with partial-onset seizures	For time to treatment failure, lamotrigine was significantly better tolerated than carbamazepine, gabapentin or topiramate. For time to 12-month remission, carbamazepine was significantly better tolerated than gabapentin.	Multicenter study
Marson et al, 2007 ³⁸	Sodium valproate Lamotrigine Topiramate	716 adults with newly diagnosed epilepsy	Valproate was significantly better than topiramate in time to treatment failure. For patients with idiopathic generalized epilepsies, valproate had significantly better efficacy than topiramate or lamotrigine. Valproate was significantly better tolerated than topiramate.	Multicenter study
Saetre et al, 2007 ³⁹	Controlled release carbamazepine Lamotrigine	186 patients aged ≥ 65 years with newly diagnosed epilepsy	Effectiveness was comparable for both drugs. There was a trend toward higher seizure free rates with carbamazepine and for better tolerability with lamotrigine.	Double-blind multicenter study

Abbreviation: GTCs, generalized tonic-clonic seizures.

Table 3

Randomized controlled trials comparing antiepileptic drug monotherapies in patients with generalized tonic-clonic seizures

Reference	AEDs Compared	Study Population	Conclusions	Comments
Shakir et al, 1981 ⁴⁰	Sodium valproate Phenytoin	33 adults with epilepsy	Sodium valproate was as effective as phenytoin.	Small cohort
Turnbull et al, 1982 ⁴¹	Phenytoin Sodium valproate	88 adults with untreated partial-onset or primary GTCS	No significant differences in efficacy between the drugs. Both were more effective for GTCS than partial seizures.	
Ramsay et al, 1983 ¹⁹	Carbamazepine Phenytoin	87 adults with newly diagnosed partial-onset and primary GTCS	Efficacy and tolerability were the same for both drugs.	Small patient numbers
Turnbull et al, 1985 ⁴²	Phenytoin Sodium valproate	140 patients aged >16 years with partial or tonic-clonic seizures	No significant differences in efficacy between the two drugs.	Single-center study
Callaghan et al, 1985 ⁴³	Carbamazepine Phenytoin Sodium valproate	181 adults with untreated epilepsy	All the drugs were highly effective in controlling generalized seizures but less effective in controlling partial seizures.	Single-center study
Dam et al, 1989 ²¹	Carbamazepine Oxcarbazepine	235 adults with newly diagnosed partial-onset and primary GTCS	No significant differences in efficacy were found between the two drugs. There was a trend toward better tolerability with oxcarbazepine.	Double-blind multicenter study
Aikia et al, 1992 ⁴⁴	Phenytoin Oxcarbazepine	37 adult patients with newly diagnosed epilepsy	No significant differences in efficacy between the drugs.	Single-center double-blind study; small cohort

Placencia et al, 1993 ⁴⁵	Carbamazepine Phenobarbital	192 patients aged aged between 2 and 60 years with 2 or more untreated seizures	Both drugs had equal efficacy.	Community-based study
Richens et al, 1994 ²³	Carbamazepine Sodium valproate	300 adults with newly diagnosed partial-onset or primary GTCS	The drugs controlled seizures equally effectively. Significantly more patients continued on valproate than carbamazepine for at least 6 months.	Multicenter open-label study
Pulliainen et al, 1995 ⁴⁶	Carbamazepine Phenytoin	43 adults with newly diagnosed partial-onset or primary GTCS	No significant differences in efficacy between the drugs.	Single-center open-label study
Heller et al, 1995 ⁴⁷	Phenobarbital Phenytoin Carbamazepine Sodium valproate	243 patients aged >16 years with untreated epilepsy	No significant differences in efficacy between the drugs. More patients stopped phenobarbital due to side effects.	Two-center randomized study
Kalviainen et al, 1995 ⁴⁸	Carbamazepine Vigabatrin	100 patients aged 15 to 64 years with untreated epilepsy	Significantly more patients remained seizure-free with carbamazepine than with vigabatrin. The former was withdrawn more often due to adverse effects. The latter was statistically more often stopped due to lack of efficacy.	Single-center open-label study
Brodie et al, 1995 ²⁴	Carbamazepine Lamotrigine	260 patients aged >13 years with untreated partial-onset or primary GTCS	Similar efficacy results were obtained for both drugs. Lamotrigine was significantly better tolerated.	Double-blind multicenter study

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Table 3
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Reference	AEDs Compared	Study Population	Conclusions	Comments
Reunanen et al, 1996 ⁴⁹	Carbamazepine Lamotrigine	343 patients aged >12 years with untreated partial or GTCS	Carbamazepine and lamotrigine were equally efficacious, with a trend to better tolerability with lamotrigine.	Multicenter randomized study
Bill et al, 1997 ²⁶	Phenytoin Oxcarbazepine	287 adults with untreated partial-onset and primary GTCS	No significant differences in efficacy between the drugs. Oxcarbazepine was significantly better tolerated than phenytoin.	Double-blind multicenter study
Christie et al, 1997 ²⁵	Oxcarbazepine Sodium valproate	249 adults with partial or generalized seizures	No significant differences in efficacy or tolerability found between the two drugs.	Double-blind multicenter study
Steiner et al, 1999 ²⁹	Phenytoin Lamotrigine	181 untreated adults with partial-onset or primary GTCS	Efficacy results were similar for the two drugs. There was a trend toward better tolerability with lamotrigine.	The high rash rate with lamotrigine probably was due to high starting doses.
Brodie and Kwan, 2002 ⁵⁰	Lamotrigine Gabapentin	309 adults with partial-onset seizures or primary GTCS	The drugs were similar in efficacy and tolerability.	Double-blind multicenter study

Privitera et al, 2003 ³²	Carbamazepine Sodium valproate Topiramate	621 children and adults with newly diagnosed partial-onset seizures or primary GTCS	No significant differences in efficacy were found between the three drugs.	
Arroyo et al, 2005 ³⁴	Topiramate 50 mg/d, or 400 mg/d	487 patients aged ≥ 6 years with untreated partial-onset or GTCS	The higher dose was significantly more likely to produce seizure freedom than the lower dose. More patients on the higher dose discontinued treatment.	Double-blind multicenter study
Marson et al, 2007 ³⁷	Sodium valproate Lamotrigine Topiramate	716 adults with newly diagnosed epilepsy	Valproate was significantly better than topiramate in time to treatment failure. For patients with IGEs, valproate had significantly better efficacy than topiramate or lamotrigine. Valproate was significantly better tolerated than topiramate.	Multicenter, randomized study

Abbreviations: GTCS, generalized tonic-clonic seizures; IGEs, idiopathic generalized epilepsies.

Table 4
Systematic reviews of antiepileptic drug monotherapy comparison studies

Reference	Antiepileptic Drugs Compared	Study Population	Conclusions	Comments
Marson et al, 2000 ⁵¹	Carbamazepine Sodium valproate	Children and adults with partial-onset seizures or generalized-onset tonic-clonic seizures	Some evidence supported use of carbamazepine for partial-onset seizures. No evidence to support use of valproate in generalized-onset seizures.	Misclassification of epilepsy may have confounded results.
Tudur Smith et al, 2001 ⁵²	Phenytoin Sodium valproate	Children and adults with partial-onset or primary generalized tonic-clonic seizures	No significant differences in efficacy outcomes between the two drugs.	
Tudur Smith et al, 2003 ⁵³	Carbamazepine Phenobarbital	Adults and children with partial-onset or primary generalized tonic-clonic seizures	Drugs were equally effective at controlling focal-onset and primary generalized tonic-clonic seizures.	
Taylor et al, 2003 ⁵⁴	Phenobarbital Phenytoin	Adults and children with partial-onset or primary generalized tonic-clonic seizures	Phenobarbital was significantly more likely to be discontinued than phenytoin. No difference in time to 12-month remission or first seizure.	Differences in study design made comparisons difficult.
Posner et al, 2005 ⁵⁵	Ethosuximide Sodium valproate Lamotrigine	Children and adolescents with absence seizures	Evidence was insufficient to make conclusions regarding efficacy.	Trials included were of poor methodologic quality with small patient numbers.
Muller et al, 2006 ⁵⁶	Phenytoin Oxcarbazepine	Children and adults with epilepsy	For patients with partial-onset seizures, oxcarbazepine is significantly less likely to be withdrawn. Data did not allow efficacy comparisons.	Misclassification of epilepsy types may have confounded results.
Gamble et al, 2006 ⁵⁷	Carbamazepine Lamotrigine	Children and adults with partial-onset seizures or generalized seizures with or without other seizure types	Carbamazepine may be superior to lamotrigine in terms of seizure control for time to first seizure.	Studies of a longer duration are required to assess long-term outcomes.

between the HLA-B* 1502 allele and AED-induced cutaneous reactions in Han Chinese.⁶²

TERATOGENICITY

The incidence of minor and major fetal malformations is higher in women with epilepsy than in the general population, even if they are untreated.⁶³ Commonly cited percentages are 3% to 6% for women with epilepsy compared with 2% to 3% in the general population.⁶⁴ The risk increases disproportionately with the number of AEDs taken, approximately 3% for one drug (similar to background risk), 5% for two, 10% for three, and greater than 20% in women taking more than three AEDs. A syndrome initially ascribed to hydantoins, including phenytoin (fetal hydantoin syndrome), but now known to occur with other AEDs, including carbamazepine and valproate, consists of facial dimorphism, cleft lip and palate, cardiac defects, digital hypoplasia, and nail dysplasia.⁶⁴

Current evidence suggests that the risk of major congenital malformations is 2 to 4 times higher with the use of valproic acid compared with other AEDs, such as carbamazepine and lamotrigine, although this may be minimized by keeping the daily dose at or below 1000 mg.⁶⁵ Absolute rates have ranged from 6% to 11%. Exposure to high-dose valproic acid in utero may impair later cognitive function.⁶⁶ The risk of major malformations with high-dosage lamotrigine remains to be resolved.⁶⁷

TOLERABILITY

For an AED to be effective, it must be well tolerated and have efficacy. AEDs are commonly associated with unwanted dose-related central nervous system effects, such as dizziness, drowsiness, and ataxia. As with idiosyncratic reactions, these can be minimized by a low starting dose and slow titration schedule. Several of the newer agents show superior tolerability over established AEDs,^{21,24,26,48,49} although seizure freedom may still be unattainable due to the development of dose-related adverse effects in some patients.

Cognitive impairment is common in patients with epilepsy, particularly in those with focal epilepsies.⁶⁸ Of the established AEDs, phenobarbital perhaps has the greatest potential for cognitive and behavioral toxicity. Dose-related impairment occurs in attention and vigilance, reaction time, short-term memory, and performance IQ.^{69,70} Phenobarbital also may produce hyperactivity and aggravation of behavioral disorders.⁷¹ Phenytoin can cause a decline in concentration, memory, mental speed, visuo-motor functions, and intelligence.⁷² The adverse cognitive and psychomotor effects found with carbamazepine likely are caused partly by the active metabolite carbamazepine-epoxide.⁷² When studied in older patients, valproic acid generally had minimal cognitive impact,⁷³⁻⁷⁵ although the drug occasionally can impair attention, visuo-motor function, complex decision making, and psychomotor speed. Comparing the cognitive effects of carbamazepine, phenobarbital, phenytoin, and primidone, a Department of Veterans Affairs cooperative study found few pre- to post-AED treatment neuropsychologic changes in patients with new-onset epilepsy.²⁰ A second Veterans Administration study found mild cognitive changes using carbamazepine and valproic acid as monotherapy for the initial treatment of partial-onset seizures, although there were no significant differences between the two drugs.⁷⁴

Some of the newer AEDs with multiple mechanisms of action have a poorer neuropsychiatric profile than drugs that block voltage-dependent sodium channels, such as phenytoin, carbamazepine, oxcarbazepine, and lamotrigine. Vigabatrin is associated with agitation, ill temper, disturbed behavior, and depression.⁷⁶ Levetiracetam can

increase irritability in some patients,⁷⁷ although others may experience positive behavioral effects.⁷⁸ Depression also may be more common with this AED.³⁶ Topiramate produces somnolence, slowing, memory problems, and language difficulties.⁷⁹ When the cognitive effects of levetiracetam and topiramate were compared in patients with refractory epilepsy, no significant differences were found between the two drugs.⁸⁰ Lamotrigine has mood-stabilizing properties as adjunctive and monotherapy in patients with bipolar depressive disorder.^{81–83} Adjunctive lamotrigine significantly improved anger-hostility subscale scores compared with adjunctive levetiracetam in patients with partial seizures.⁸⁴ Zonisamide may impair learning⁸⁵ and is associated with aggression, depression, or mood swings in some patients.⁸⁶ Animal studies suggest the drug may have antiparkinsonian properties, linked to its facilitation of dopamine transmission.⁸⁷ A few patients taking each of these drugs have developed paranoid and psychiatric symptoms, although this seems most likely to occur in patients treated with topiramate.⁸⁸

Awareness of a patient's medical history may bring to light endocrine signs and symptoms that can influence choice of AED monotherapy. Epilepsy itself may be responsible for reproductive endocrine abnormalities.⁸⁹ The situation surrounding metabolic influences of AEDs is complex and not yet fully understood. Because many of the data are derived from research conducted in small cohorts, with designs that may bias outcomes, results need to be interpreted with caution. Weight gain is associated with sodium valproate,⁹⁰ vigabatrin,³¹ gabapentin,⁹¹ and pregabalin.⁹² Conversely, treatment with topiramate⁷⁹ and zonisamide⁹³ may result in weight loss in some patients.

There is particular interest in the relationship between polycystic ovary syndrome (PCOS) and epilepsy. Changes associated with PCOS occurred in up to 64% of Finnish women taking valproic acid.^{94,95} Indian researchers reported weight gain (40%), hirsutism (20%), and PCOS (20%) in 25 women taking valproic acid for 1 year.⁹⁶ Similar results were reported in a Korean study, affecting 42% of women.⁹⁷ In other studies, PCOS has been found in 7.7%,⁹⁸ 9.1%,⁹⁹ 11.1%,¹⁰⁰ 28%,¹⁰¹ and 48.6%¹⁰² of women with epilepsy. Some researchers report PCOS changes in 5.7% to 16.7% of patients with carbamazepine monotherapy.^{99–102} A recent Finnish analysis found sodium valproate a predictor for development of PCOS, polycystic ovaries, and hyperandrogenism.¹⁰³

A history of sexual dysfunction may also affect choice of AED. Hepatic enzyme-inducing AEDs, such as carbamazepine, phenytoin, and phenobarbital, can stimulate production of sex hormone-binding globulin, a binding site for testosterone, where the latter, testosterone, is physiologically inactive.¹⁰⁴ These drugs also may induce the metabolism of testosterone. Daily doses of oxcarbazepine greater than 900 mg exert a similar effect on sex hormone-binding globulin as carbamazepine.¹⁰⁵ Erectile dysfunction also is reported with pregabalin.¹⁰⁶

Osteomalacia and osteoporosis are linked with chronic AED treatment.^{107–109} Phenobarbital, primidone, phenytoin, and carbamazepine increase the breakdown of vitamin D, leading to secondary hyperparathyroidism, osteomalacia, and increased bone turnover, although not all studies back such a hypothesis.¹⁰⁷ Other mechanisms include a direct effect of AEDs on osteoblasts, osteocytes, and osteoclasts; resistance to parathyroid hormone; inhibition of calcitonin secretion; and impaired calcium absorption.¹¹⁰ Research has shown an association between elevated homocysteine, reduction in bone mineral density, and increased fracture incidence.¹¹¹ In all, six AEDs (phenytoin, carbamazepine, phenobarbital, primidone, oxcarbazepine, and lamotrigine) have known antifolate properties, thus, the potential to increase homocysteine concentrations.

Chronic dosing with phenytoin can produce gum hypertrophy,¹¹² which is minimized with continuing attention to dental hygiene. Long-term treatment with phenobarbital may be associated with a range of fibrosing disorders, such as reflex sympathetic dystrophy, shoulder-hand syndrome, frozen shoulder, and Dupuytren's contracture.¹¹³

PHARMACOKINETIC PROPERTIES

Ideally, an AED should be absorbed fully, have low protein binding, and undergo linear pharmacokinetics, with clearance unaffected by renal impairment.¹¹⁴ It should neither induce nor inhibit hepatic monooxygenase or conjugating enzymes, interact with concomitant medication, or produce neurotoxic or other adverse effects. A long elimination half-life is advantageous, allowing once or twice daily dosing. A well-established target dose should be achievable without or with limited titration. Many older AEDs undergo hepatic metabolism with renal elimination of inactive metabolites (Table 5). Phenytoin pharmacokinetics are complex. With increasing doses, the eliminating enzyme system becomes progressively saturated. Thus, a small increase in dose can result in a large rise in plasma concentration and neurotoxicity.¹¹⁵

Phenobarbital, primidone, phenytoin, and carbamazepine induce the metabolism of lipid-soluble drugs, such as the combined oral contraceptive pill,¹¹⁶ cytotoxic agents, antiretrovirals, statins, warfarin, and cardiac antiarrhythmics.¹¹⁴ Newer AEDs are less

Table 5 Pharmacokinetic interactions between antiepileptic drugs				
AED	Undergoes Hepatic Metabolism	Affects Hepatic Cytochrome P450 Enzymes	Affects Metabolism of Other AEDs	Metabolism Affected by Other AEDs
<i>Established AEDs</i>				
Carbamazepine	Yes	Yes	Yes	Yes
Clobazam	Yes	No	No	Yes
Clonazepam	Yes	No	No	Yes
Ethosuximide	Yes	No	No	Yes
Phenobarbital	Yes	Yes	Yes	Yes
Phenytoin	Yes	Yes	Yes	Yes
Primidone	Yes	Yes	Yes	Yes
Valproate	Yes	Yes	Yes	Yes
<i>Modern AEDs</i>				
Felbamate	Yes	Yes	Yes	Yes
Gabapentin	No	No	No	No
Lacosamide	Yes	No	No	No
Lamotrigine	Yes	No	No	Yes
Levetiracetam	No	No	No	Yes ^a
Oxcarbazepine	Yes	Yes	Yes ^a	Yes
Pregabalin	No	No	No	No
Tiagabine	Yes	No	No	Yes
Topiramate	Yes	Yes	Yes ^a	Yes
Vigabatrin	No	No	Yes ^a	No
Zonisamide	Yes	No	No	Yes

^a Effect modest; see text.

likely to interfere with hepatic metabolism, although oxcarbazepine,^{117,118} felbamate,¹¹⁹ and higher doses of topiramate¹²⁰ can induce the oestrogenic component of the combined oral contraceptive pill.^{121,122} Lamotrigine reduces levonorgestrel concentrations by an, as yet, unknown mechanism.¹²³

Where there is a linear relationship between dose and plasma concentration, concentration monitoring can be helpful in assessing side effects and compliance and in establishing the most effective concentration in seizure-free patients.¹²⁴ Routine measurement of plasma levels of newer AEDs is not recommended, as they do not correlate well on a population basis with efficacy or side effects.¹²¹ Therapeutic drug monitoring can play a useful role in individualizing clinical management, provided that drug concentrations are measured at an appropriate time in appropriate patients with a clear indication and are interpreted correctly. The availability of concentration monitoring may be the reason that one AED is chosen over another for a particular patient.

FORMULATION

Readily identifiable and palatable formulations can help to improve adherence, thus seizure control. Several AEDs are available in alternative formulations to tablets, such as syrup and sprinkles, which can be useful in patients with swallowing difficulties and for those with percutaneous endoscopic gastrostomy tubes. Parenteral formulations are invaluable in the rapid treatment of status epilepticus and in other circumstances where oral access is not available. The use of rectal diazepam to abolish prolonged seizure activity is now superseded by the administration of buccal or nasal midazolam.^{125,126} Intravenous formulations are available for sodium valproate, levetiracetam, and lacosamide in addition to phenytoin, fosphenytoin, phenobarbital, and the benzodiazepines, clonazepam, diazepam, lorazepam, and midazolam.

COST

Despite the introduction of several novel agents, price remains a factor in determining the global use of antiepileptic medication. With few differences in efficacy amongst AEDs, the low costs of older drugs, such as phenobarbital and phenytoin, make these agents an attractive option for developing nations. One thousand generic 100-mg phenobarbital tablets currently cost \$6.16.¹²⁷ This is considerably less than treatment with any of the new AEDs.

COMBINING ANTIEPILEPTIC DRUGS

Approximately 59% of people with newly diagnosed epilepsy become seizure-free on a single AED.¹²⁸ Another 5% require combination therapy to gain complete control of their seizures. Patients with symptomatic or cryptogenic epilepsy more likely are medication resistant than those with idiopathic epilepsy.^{129–131} The British National General Practice Study of Epilepsy reported 69% of people with idiopathic generalized epilepsies as having 5 years' seizure freedom at 9-year follow-up compared with 61% for those with remote symptomatic epilepsy.¹³²

There may be several different rationales for choosing drug combinations for patients not responding to AED monotherapy. Along with considering seizure type and syndrome classification, factors such as age, gender, comedication, and comorbidity should be taken into account.¹³³ It also seems sensible to combine drugs with different mechanisms of action, although it is becoming increasingly apparent that several AEDs act in multiple ways that are not yet understood fully.¹³⁴ There is,

however, clinical and laboratory evidence to suggest that additive or synergistic effects are seen with regimens, such as sodium valproate with ethosuximide for absence seizures,¹³⁵ sodium valproate with lamotrigine for focal-onset and generalized seizures,^{136,137} and lamotrigine with topiramate¹³⁸ for a range of seizure types. In patients with localization-related epilepsy, higher seizure freedom rates were reported in adults taking combination therapy.¹³⁹ Of 135 patients taking duotherapy, 37 (27%) were controlled, whereas 5 (10%) of 50 patients taking three AEDs were seizure-free.

With more information becoming available on seizure pathophysiology, three broad mechanisms of AED action are recognized: (1) modulation of voltage-dependent ion channels, (2) enhancement of inhibitory neurotransmission, and (3) attenuation of excitatory neurotransmission (**Table 6**). It is becoming increasingly apparent, however, that many AEDs have multiple cellular effects.¹⁴⁰ Exploration of these mechanisms will allow better understanding of the pathophysiology of seizure propagation and spread and should lead ultimately to improved management of people with refractory epilepsy.¹⁴⁰

Antiepileptic Drug	↓ Na ⁺ Channels	↓ Ca ²⁺ Channels ^c	↑ GABA Transmission	↓ Glutamate Transmission
<i>Established</i>				
Benzodiazepines			++	
Carbamazepine	++			
Ethosuximide		++ (T-type)		
Phenobarbital		?	++	?
Phenytoin	++			
Valproate	?	? (T-type)	+	?
<i>Modern</i>				
Felbamate	+	?	+	+
Gabapentin	?	++ (α2δ)	+	
Lacosamide	+ ^a			
Lamotrigine	++	?		
Levetiracetam ^b		?	?	?
Oxcarbazepine	++			
Pregabalin		++ (α2δ)		
Rufinamide	++			
Stiripentol			?+	
Tiagabine			++	
Topiramate	+	+	+	+
Vigabatrin			++	
Zonisamide	+	+ (T-type)		

Abbreviations: GABA, gamma-aminobutyric acid; ++, primary action; + probable action; ?, possible action.

^a Lacosamide also binds to collapsin-response mediator protein 2.

^b Levetiracetam acts by binding to synaptic vesicle protein 2A.

^c Unless otherwise stated, action on high-voltage-activated calcium channels.

PRACTICAL CONSIDERATIONS

The first consideration when choosing a monotherapy in newly diagnosed epilepsy is that the drug of choice has efficacy for a patient's seizure type or syndrome (**Table 1**). If the classification is unclear, an AED with a broad spectrum of action, such as sodium valproate or levetiracetam, may be selected. For patients taking other drugs, the possibility of pharmacokinetic interactions may come into play. Enzyme inducers are probably best avoided in patients taking other lipid-soluble agents, as discussed previously. For the majority of patients, AEDs are started in a low dose and slowly titrated according to efficacy and tolerability. In those who develop adverse effects, or with compliance issues, plasma concentration monitoring can aid decision making.¹²¹ For untreated patients with a high seizure density, a drug that can be rapidly titrated to therapeutic dosing, such as levetiracetam, should be preferred. For patients with swallowing difficulties, AEDs marketed in formulations, such as syrups, liquids, crushable tablets, and sprinkles, can make adherence easier.

Sodium valproate is associated with fetal malformations,¹⁴¹ cognitive problems in offspring,⁶⁶ weight gain,⁹⁵ and PCOS.⁹⁴ This drug, therefore, generally is not recommended in girls and women of childbearing age. There are, however, some young women with difficult-to-control idiopathic epilepsy syndromes, whose seizures seem responsive to sodium valproate only.

Older people generally respond well to AED therapy, with seizure freedom rates of up to 80% in individuals who develop seizures later in life.¹⁴² When starting an older person on treatment, a slow titration schedule should be used with a low target dose, given that there are age-related changes in pharmacokinetics and pharmacodynamics, together with the likelihood of complications from comorbidities and interactions with comedications.¹⁴³ Well-tolerated AEDs with a low potential for drug interactions, such as lamotrigine, levetiracetam, and gabapentin, are generally selected for these individuals.¹⁴⁴

In some patients, an AED can be used with the aim of ameliorating more than one problem. For example, in patients with partial-onset seizures and generalized anxiety disorder, adjunctive pregabalin may have efficacy for both conditions.^{145,146} Clobazam also can be a useful adjunctive therapy in this setting.¹⁴⁷ Pregabalin and gabapentin can be prescribed in patients with partial-onset seizures and neuropathic pain.^{148,149} For individuals with seizures and migraine, treatment with topiramate is an option.^{79,150,151}

Using these strategies, a seizure-freedom rate of 60% to 70% can be attained in patients with newly diagnosed epilepsy.¹²⁸ With accurate classification of seizure type or syndrome, timely investigation, and appropriate pharmacologic management, the outlook for individuals with newly diagnosed epilepsy has never been more positive. In coming years, genomic research may shed further light on seizure pathophysiology and the reasons underlying refractoriness and adverse drug reactions. As such, it is hoped this may allow a more precise selection of AED treatment, and greater potential for seizure freedom.

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