Currently Available Antiepileptic Drugs

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Summary: Many new antiepileptic drugs (AEDs) have become available over the past 15 years. At the same time, the emphasis on treating patients with epilepsy has grown from stopping seizures to avoiding side effects and maximizing quality of life. This review summarizes currently available AEDs, and presents general treatment principles and guidelines for

AED selection. Unfortunately, despite the increased treatment options of today, seizure freedom without side effects remains unattainable for too many patients with epilepsy. Consequently, there remains a significant need for further development of new therapies. **Key Words:** Epilepsy, seizure, antiepileptic drug, refractory, side effects.

INTRODUCTION

Over the last 15 years, a new generation of antiepileptic drugs (AEDs) has emerged for the pharmacological management of seizures. Concurrent with that development, the concept of optimum therapy for seizures has evolved to include complete control of seizures, absence of bothersome side effects, and an emphasis on maximizing quality of life.^{1,2} With the AEDs now available and access to physicians familiar with their use, patients with epilepsy have a greater chance to achieve these treatment goals than in the past.³ Nonetheless, the prospect of freedom from seizures and side effects remains elusive for a considerable number of patients with epilepsy despite concerted attempts by their physicians to utilize available pharmacotherapies to their full advantage.

This review provides an overview of the currently available AEDs that are widely used in the U.S. for the chronic treatment of epilepsy, and discusses general treatment principles, guidelines for AED selection, and treatment outcomes. Determining when to initiate and terminate treatment, assessing compliance, considering the special requirements of defined populations such as children and pregnant women, and evaluating and addressing psychosocial problems associated with epilepsy are important topics related to effective AED therapy,

but are beyond the scope of this review and thoroughly covered elsewhere.⁴⁻⁶

GENERAL TREATMENT PRINCIPLES FOR THE CURRENT AEDS

The effectiveness of the newer AEDs was determined with regulatory trials and postmarketing studies in patients with defined seizure types. Therefore, the first step in selecting among the currently available AEDs for a particular patient is to determine his or her seizure type(s). Concomitant medical conditions and medications, lifestyle, and other factors also contribute to the decision regarding choice of drug treatment. Once chosen, the AED is generally started at a low dosage and slowly titrated to the maximum-tolerated dose. If the first AED is unsuccessful because of ineffectiveness or side effects, then a second AED, also appropriate for the target seizure type(s), is generally prescribed. The second AED should be titrated to a tolerable and effective dosage before the first AED is tapered. In general, it is preferable to maintain a patient on a single AED rather than combinations of AEDs because compliance is enhanced, overall medication costs are usually less, and there are generally fewer idiosyncratic reactions, teratogenic effects, and side effects (though not invariably).⁷ Nonetheless, some patients do better on combinations of AEDs than on individual agents.

Effective management using currently available AEDs requires detailed knowledge of their pharmacodynamic and pharmacokinetic profiles, which vary significantly as shown in [Tables 1](#) and [2](#). Side effects are a major cause

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TABLE 1. *Common and Rare Side Effects of Available Antiepileptic Drugs*

Drug	U.S. Trade Name	Systemic Side Effects	Neurotoxic Side Effects	Rare Idiosyncratic Reactions
Carbamazepine	Tegretol, Carbatrol	Nausea, vomiting, diarrhea, hyponatremia, rash, pruritus, fluid retention	Drowsiness, dizziness, blurred or double vision, lethargy, headache	Agranulocytosis, Stevens–Johnson syndrome, aplastic anemia, hepatic failure, dermatitis–rash, serum sickness, pancreatitis
Ethosuximide	Zarontin	Nausea, vomiting	Sleep disturbance, drowsiness, hyperactivity	Agranulocytosis, Stevens–Johnson syndrome, aplastic anemia, dermatitis–rash, serum sickness
Felbamate	Felbatol	Nausea, vomiting, anorexia, weight loss	Insomnia, dizziness, headache, ataxia	Aplastic anemia, hepatic failure
Gabapentin	Neurontin	None known	Somnolence, dizziness, ataxia	Unknown
Phenytoin	Dilantin, Phenytek	Gingival hypertrophy, body hair increase, rash, lymphadenopathy	Confusion, slurred speech, double vision, ataxia, neuropathy (with long-term use)	Agranulocytosis, Stevens–Johnson syndrome, aplastic anemia, hepatic failure, dermatitis–rash, serum sickness
Lamotrigine	Lamictal	Rash, nausea	Dizziness, somnolence	Stevens–Johnson syndrome, hypersensitivity syndrome
Levetiracetam	Keppra	Anorexia	Somnolence, dizziness, headache, nervousness	N/A
Oxcarbazepine	Trileptal	Nausea, vomiting, hyponatremia, rash	Drowsiness, dizziness, headache, double vision, ataxia	Dermatitis–rash, Stevens–Johnson syndrome, toxic epidermal necrolysis
Pregabalin	Lyrica	Weight gain, peripheral edema	Dizziness, somnolence, asthenia, headache, ataxia	N/A
Primidone, Phenobarbital	Mysoline	Nausea, rash	Alteration of sleep cycles, sedation, lethargy, behavioral changes, hyperactivity, ataxia, dependence	Agranulocytosis, Stevens–Johnson syndrome, hepatic failure, dermatitis–rash, serum sickness
Tiagabine	Gabitril	N/A	Dizziness, weakness, ataxia nervousness, tremor, somnolence	N/A
Topiramate	Topamax	Anorexia, weight loss	Confusion, cognitive slowing, dysphasia, dizziness, fatigue, paresthesias	Nephrolithiasis, hypohidrosis, acute angle closure glaucoma
Valproate	Depakote	Weight gain, nausea, vomiting, hair loss, easy bruising	Tremor	Agranulocytosis, Stevens–Johnson syndrome, aplastic anemia, hepatic failure, dermatitis–rash, serum sickness, pancreatitis
Zonisamide	Zonegran	Anorexia	Dizziness, ataxia, fatigue, somnolence, confusion	Nephrolithiasis, oligohydrosis and hyperthermia

of medication intolerance and noncompliance, particularly within the first six months of therapy. Neurotoxic effects of commonly used AEDs (TABLE 1) are generally dose-related and often dose-limiting. Patients who have peak-level side effects may benefit from a modification of the treatment schedule, such as spreading out the dosage or giving proportionally more at bedtime. Notably, serum concentrations that are associated with neurotoxicity vary from one patient to another with current AEDs, and may occur within the so-called “thera-

peutic range.” Table 2 shows the variability of pharmacokinetic profiles of current AEDs, including dosing schedule, number of days needed to achieve steady state, and frequency of initial laboratory monitoring.

OLDER GENERATION AEDS

Carbamazepine

Carbamazepine (CBZ) blocks voltage-dependent sodium channels, thereby limiting rapid, repetitive neuro-

TABLE 2. *Pharmacokinetic Properties of Available Antiepileptic Drugs*

Drug	Percent Bound to Plasma Protein	Elimination Half-life (h)	Time to Steady State (days)	Frequency of Dosing	Frequency of Initial Monitoring	Therapeutic Level (ug/ml)
Carbamazepine	70–80	11–17 (chronic therapy)	3–10	bid, tid, or qid	3, 6, 9 weeks	4–12
Ethosuximide	0	40–50	6–12	qd, bid, or tid	2–3 weeks	40–100
Felbamate	25	20–23	5–10	bid or tid	See package insert for detailed instructions	32–137
Gabapentin	0	5–7; increases with decreased creatinine clearance (see prescribing information)	1–2	tid	none	2–3
Lamotrigine	50–55	10–15 with enzyme-inducing AEDs*; 40–60 with VPA	5–15	bid	None	Not established
Levetiracetam	< 10	7–8	3–4	bid	None	Not established
Oxcarbazepine	40	8–10	3–4	bid, tid	None (except sodium every 2–4 weeks in patients at risk for hyponatremia)	Not established
Phenobarbital	40–60	30–50	16–21	qd or bid	3–4 weeks	10–40
Phenytoin	90	15–30	5–15	qd or bid	2–3 weeks	10–20
Pregabalin	0	6	2	bid, tid	None	Not established
Tiagabine	96	5–9	3	bid, tid, qid	None	Not established
Topiramate	9–17	20–24	5–7	bid	none	Not established
Valproate	60–95 (decreases with serum levels over 100 ug/ml)	6–18	2–4	bid or tid	1–2 weeks	50–150
Zonisamide	40–60	50–68	12–14	qd, bid	none	Not established

AEDs = antiepileptic drugs. Bid (bis in die) = twice a day; tid (ter in die) = three times daily; qd = each day; qid = four times daily.

* Such as carbamazepine, phenytoin, and phenobarbital

nal firing. Other mechanisms may be relevant to its anticonvulsant effect as well. Carbamazepine is a first-line treatment for partial-onset and primary generalized tonic-clonic seizures, but is ineffective against, and may exacerbate, absence and myoclonic seizures.⁸ To minimize CNS-related side effects, CBZ should be initiated at 100–200 mg daily and increased by 100–200 mg increments every 3–14 days as needed for seizure control, typically over one to two months. The final dose in part depends on the extent of autoinduction; i.e., the degree to which CBZ induces its own metabolism. Diplopia, headache, dizziness, nausea, and vomiting are the most common dose-related side effects, which typically occur two to three hours after a dose. Use of a controlled-release formulation can reduce the severity of side effects. Car-

bamazepine is also associated with idiosyncratic side effects, including a morbilliform rash in around 10% of patients, and more rarely, serious rashes such as Stevens-Johnson syndrome.⁹ Reversible mild leucopenia may occur within the first two to three months, but usually does not necessitate discontinuation of therapy. Potentially fatal hematologic and hepatic effects are very rare. An antidiuretic hormone-like action leading to hyponatremia is infrequent and usually asymptomatic.¹⁰ Carbamazepine is teratogenic, and has been associated with spina bifida in some^{11,12} but not all¹³ studies.

Hepatic metabolism is induced by CBZ; therefore, clearance of many AEDs and non-AEDs,¹⁴ including hormonal contraceptives,¹⁵ is increased when coadministered with CBZ. Likewise, drugs that inhibit CBZ me-

tabolism, such as cimetidine, dextropropoxyphene, diltiazem, erythromycin, isoniazid, verapamil, viloxazine, and fluoxetine, may precipitate CBZ-related side effects.

Ethosuximide

Ethosuximide (ESM) reduces T-type calcium currents in thalamic neurons.¹⁶ It is a first-line treatment for patients with absence seizures⁷ but ineffective against myoclonic, primary generalized tonic-clonic, and partial-onset seizures. The usual initial dose is 250–500 mg daily, with 250 mg dose increments over two to three weeks as needed for seizure control. Side effects include hiccups, nausea, vomiting, abdominal pain, anorexia, headache, dizziness, drowsiness, and unsteadiness. Allergic rashes occur in approximately 5% of patients, and drug interactions are not a significant problem.

Phenobarbital

Phenobarbital (PB) augments the inhibitory effect of GABA by prolonging the chloride-channel opening at the GABA_A receptor. Phenobarbital is effective against partial-onset seizures, primary generalized tonic-clonic seizures, and myoclonic seizures but is widely considered a second-line drug because of behavioral and cognitive effects,¹⁸ including sedation, depression, agitation, and hyperactivity in children and the elderly. Intravenous PB is useful for the treatment of status epilepticus.¹⁹ Daily maintenance dosages in adults range from 60–240 mg (2–5 mg/kg/day in children). Because the half-life of PB is four days, steady-state serum concentrations are not reached until approximately three weeks after a dosage change. Abrupt discontinuation can precipitate withdrawal seizures.²⁰ Phenobarbital is associated with a significantly increased risk of fetal abnormalities.²¹ Hepatic metabolism is induced by PB, and the clearance of concomitantly administered hepatically metabolized drugs, including hormonal contraceptives,¹⁵ is increased.

Phenytoin

Phenytoin (PHT) blocks voltage-dependent neuronal sodium channels and is a first-line treatment for partial-onset and primary generalized tonic-clonic seizures. Phenytoin is ineffective against myoclonic, atonic, and absence seizures. Intravenous PHT and fosphenytoin, a PHT prodrug, are useful for quickly providing a loading dose and for treating status epilepticus.^{22,23} In a nonurgent situation, oral treatment is often started at the anticipated maintenance dose, typically 300 mg/day administered either as a single dose or in two divided doses in adults (5–8 mg/kg/day in children). Neurotoxic side effects include ataxia, nystagmus, dysarthria, asterixis, and somnolence. Long-term use has been associated with gingival hyperplasia, hirsutism, acne, facial coarsening, and, less commonly, folate deficiency, osteopenia, peripheral neuropathy, and cerebellar atrophy. A diffuse allergic rash occurs in 5–10% of patients. Other idiosyn-

cratic reactions are rare, and include Stevens–Johnson syndrome, hepatitis, bone marrow suppression, lymphadenopathy, and a lupus-like syndrome. Phenytoin is teratogenic.²⁴

The hepatic metabolism of PHT becomes saturated at moderate-to-high serum concentrations in an age-dependent fashion, which results in nonlinear pharmacokinetics.²⁵ Phenytoin induces hepatic enzymes, reducing serum concentrations of other hepatically metabolized AEDs such as CBZ, valproate (VPA), lamotrigine (LTG), and topiramate (TPM), as well as hormonal contraceptives.¹⁵ Phenytoin is tightly bound to circulating albumin and may be displaced by other protein-bound drugs such as VPA.

Primidone

Primidone (PRM) is metabolized in the liver to PB and another active compound, phenylethylmalonamide.²⁶ Primidone is effective against partial-onset and primary generalized tonic-clonic seizures, but is considered second line because of dose-related neurotoxicity, the effects of which include sedation, ataxia, and diminished libido. Dosing is usually initiated with 125 mg at bedtime, and increased by 125 mg every three to five days as needed for seizure control up to 1500 mg daily. As with PB, abrupt discontinuation of PRM should be avoided.²⁰ Primidone induces hepatic metabolism and is therefore prone to the same drug–drug interactions as PB.

Sodium valproate

Sodium valproate (VPA) blocks voltage-dependent sodium channels, facilitates the effects of the inhibitory neurotransmitter GABA, and reduces low threshold (T-type) calcium currents.¹⁶ Sodium valproate is effective for virtually all seizure types.²⁷ Therapy is initiated with 500 mg once or twice daily, and titrated as needed for seizure control. An intravenous form allows for a loading dose and substitution for oral therapy when needed.^{28,29} Side effects include dose-related tremor, weight gain, and hair thinning. Though controversial, evidence suggests that VPA promotes the development of menstrual irregularities and other endocrinologic features of the polycystic ovarian syndrome.^{30–32} Thrombocytopenia and pancreatitis occur rarely, and very young children on combinations of VPA and other AEDs may develop significant hepatotoxicity. Sodium valproate is teratogenic,¹² and has been associated with neural tube defects.³³ Sodium valproate inhibits hepatic metabolism, reducing the clearance of PHT, PB, CBZ-epoxide, and LTG.

NEWER GENERATION AEDS

Felbamate

Felbamate (FBM) potentiates GABA-mediated inhibition, and blocks voltage-dependent sodium channels as well as the ionic channel at the *N*-methyl-D-aspartate

receptor.³⁴ Felbamate is effective against partial-onset seizures as well as generalized seizures (including atonic seizures) associated with the Lennox–Gastaut syndrome in children.³⁵ Dosing is titrated slowly over several weeks to minimize side effects. Side effects include insomnia, headache, nausea, anorexia, somnolence, vomiting, weight loss, and dizziness.³⁶ There is an elevated risk of aplastic anemia and fatal hepatitis,³⁷ which has dramatically curtailed the use of FBM. Routine monitoring of liver and blood counts is recommended, but does not predict potentially fatal toxicity. Consequently, FBM is now primarily used in patients with Lennox–Gastaut syndrome where the benefits of treatment outweigh the risks. Felbamate is metabolized by the liver and reduces the clearance of PHT, VPA, and CBZ-epoxide, as well as hormonal contraceptives.¹⁵

Gabapentin

Gabapentin (GBP) binds to the $\alpha 2\delta$ subunit of neuronal voltage-gated calcium channels, inhibiting calcium flow. Gabapentin is effective against partial-onset seizures but may exacerbate myoclonic and absence seizures. The typical initial dose is 300 mg daily, which is increased by 300 mg every three days, as needed for seizure control, to the maximum tolerated dose. Side effects include drowsiness, ataxia, dizziness, weight gain, and peripheral edema. Gabapentin is not metabolized and has no effect on hepatic metabolism; consequently, there are no significant drug interactions. Because GBP is eliminated by the kidneys, patients with renal insufficiency require lower dosages and less frequent dosing. A risk profile to exposed fetuses has not been established.

Lamotrigine

Lamotrigine is a sodium channel blocker that is effective against partial-onset seizures and generalized seizure subtypes, though it has been reported to exacerbate myoclonic seizures,³⁸ especially in patients with severe myoclonic epilepsy.³⁹ Dosing is started at a low dose, 25–50 mg daily, and increased slowly to reduce the likelihood of rash. Starting dosages, subsequent increments, and target maintenance dosages are reduced in patients comedicated with VPA.^{40,41} Side effects include rash, headache, nausea, insomnia, vomiting, dizziness, diplopia, ataxia, and tremor. Neurotoxic side effects of LTG are accentuated when LTG is taken simultaneously with CBZ. Severe skin reactions, including bullous erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis occur in up to 1 in 1000 adults and 1 in 100 children; the risk is reduced with slow and gradual titration⁴² as recommended in the package insert. Recent data from a pregnancy registry suggest an increased risk of isolated cleft lip or palate. The half-life of LTG is reduced during pregnancy⁴³ and by enzyme-inducing

drugs, and significantly increased by VPA, which inhibits the glucuronidation of LTG.

Levetiracetam

Levetiracetam (LEV) binds to synaptic vesicle protein and has actions on neuronal GABA- and glycine-gated currents, as well as voltage-dependent potassium currents, though its exact mechanism of action is unknown. Levetiracetam is effective against partial-onset seizures⁴⁴ as well as generalized seizure types, including myoclonic and absence seizures. Dosing is initiated at 500–1000 mg daily and titrated at 1000 mg increments every two weeks as tolerated and needed for seizure control. Common side effects are somnolence, headache, anorexia, and nervousness.⁴⁵ Less frequently, patients or families may report agitation, aggression, anxiety, or depression. Teratogenicity has not been established. There are no pharmacokinetic interactions with other drugs, including oral contraceptives.^{46–48} Clearance is reduced in patients with renal insufficiency.

Oxcarbazepine

Oxcarbazepine (OXC) is the prodrug for its active metabolite, 10,11-dihydro-10-hydroxycarbazepine, which blocks voltage-dependent sodium channels, and modulates calcium and potassium currents. Oxcarbazepine is the 10,11 keto analogue of CBZ, and has a similar spectrum of efficacy against partial-onset⁴⁴ and primary generalized tonic–clonic seizures. Dosage is usually initiated at 150–600 mg daily in adults and titrated every one to two weeks as needed to control seizures and as tolerated. Common side effects are drowsiness, dizziness, headache, diplopia, nausea, vomiting, and ataxia.⁴⁹ An allergic rash is infrequent and instances of Stevens–Johnson syndrome and toxic epidermal necrolysis are rare.⁵⁰ Hyponatremia, which is usually asymptomatic, occurs more commonly than with CBZ.³ The teratogenic risk has not been determined. Oxcarbazepine induces the metabolism of hormonal contraceptives¹⁵ and may increase PHT serum concentrations through inhibition of the cytochrome P-450 isoenzyme 2C19.

Pregabalin

Pregabalin (PGB) binds with high affinity to the $\alpha 2\delta$ subunit of neuronal voltage-gated calcium channels and inhibits calcium flow, an action similar to GBP.⁵¹ Pregabalin is effective against partial-onset seizures and is six to eight times more potent than GBP.⁵² The usual initial dose is 150 mg daily, with subsequent titration every five to seven days to an effective and tolerable maintenance dose. Side effects include dizziness, somnolence, asthenia, headache, ataxia, weight gain, and peripheral edema. Teratogenicity has not been fully evaluated. Pregabalin has no pharmacokinetic interactions with other drugs and is excreted by the kidneys. Conse-

quently, dosage reduction and less frequent dosing are recommended for patients with renal insufficiency.

Tiagabine

Tiagabine (TGB) inhibits neuronal and glial reuptake of GABA, which increases the availability of GABA to inhibit postsynaptic neurons.⁵³ Tiagabine is effective against partial-onset seizures, but has been reported to rarely precipitate absence stupor.⁵⁴ Treatment is initiated with 4–8 mg daily, and increased weekly by 4–8 mg as needed for control of seizures and as tolerated.⁵⁵ Side effects include dizziness, asthenia, muscle weakness, nervousness, tremor, impaired concentration, lethargy, and depression,⁵⁶ which may be lessened by taking TGB with food. The risk of teratogenicity has not been established. Tiagabine is hepatically metabolized, and its clearance is increased when TGB is coadministered with hepatic enzyme-inducing AEDs. Doses should be reduced in patients with significant hepatic impairment.⁵⁷

Topiramate

Topiramate blocks sodium channels and high voltage-activated calcium channels, attenuates the effects of excitatory neurotransmitters, enhances GABAergic neurotransmission, and inhibits carbonic anhydrase, though the relevance of this last mechanism to its anticonvulsant effect is uncertain. Topiramate is used for partial-onset, primary generalized tonic-clonic and myoclonic seizures. The initial dose is 25–50 mg daily, which is increased by 25–50 mg every one to two weeks as needed for seizure control. Side effects include word-finding disturbance, cognitive slowing, ataxia, poor concentration, dizziness, fatigue, paresthesia, somnolence, reduced appetite, and weight loss.^{58, 59} In addition, there is a small increased risk of kidney stone formation, hypohydrosis,⁶⁰ and acute angle closure glaucoma.³ Effects on exposed fetuses have not been determined. Topiramate increases the metabolism of hormonal contraceptives¹⁵ and infrequently inhibits the metabolism of PHT. The clearance of TPM is increased by CBZ and PHT.⁶¹

Zonisamide

Zonisamide (ZNS) blocks voltage-dependent sodium channels as well as T-type calcium channels, and inhibits carbonic anhydrase. Zonisamide is effective against partial-onset seizures and generalized seizure subtypes, tonic-clonic, tonic, atonic, atypical absence, and myoclonic seizures.^{44,62} The recommended initial dose is 100 mg daily for adult patients and 2 mg/kg/day for children in two divided dosages. Because steady state is reached slowly, doses should be increased at two-week intervals to the target maintenance dose. Side effects include anorexia, dizziness, ataxia, fatigue, somnolence, confusion, and poor concentration. Less than 5% of patients develop renal stones.⁶³ Oligohydrosis and hyperthermia have been rarely reported in children.⁶⁴ The risk of teratoge-

nicity has not been determined. Zonisamide has no effect on hepatic metabolism, but its half-life is reduced by enzyme-inducing AEDs.⁶⁵ Patients with renal dysfunction have reduced clearance.

AED SELECTION: GUIDELINES AND EXPERT OPINION

The treatment of epilepsy has become increasingly complex with the introduction of new AEDs, new formulations of older AEDs, and the vagus nerve stimulator. Ideally, the selection of therapy should be based on experimental evidence. Recently published AED treatment guidelines from the American Academy of Neurology and the American Epilepsy Society for the use of GBP, LTG, TPM, TGB, OXC, LEV, and ZNS in the treatment of new-onset and medically refractory seizures are based on evidence of efficacy, tolerability, and safety in adults and children.^{66,67} However, while clinical practice is ideally evidence-based, there are clinical situations requiring AED selections for which there are few if any relevant clinical studies.⁶⁸ For example, there are few head-to-head studies of currently available AEDs as initial therapy for specific seizure types or age groups. In such circumstances, where data is incomplete or unavailable, expert opinion can provide some direction to the clinician. A technique for assessing expert opinion based on the Rand method has been applied to determining consensus among a group of epilepsy experts with regard to selection of AEDs for particular clinical situations. The most recent expert consensus was based on data survey results obtained in 2004 from 48 American epilepsy specialists covering all of the newer AEDs excepting pregabalin. The methodology, inherent limitations, and complete findings are described in the full report.⁶⁹

OUTLOOK FOR THERAPEUTIC SUCCESS WITH CURRENT AEDS

A long-term observational study of previously untreated adolescent and adult patients with newly diagnosed epilepsy, published in 2000 (before all the newer AEDs were marketed), indicated that nearly 50% of patients became seizure free with the initial AED.⁷⁰ Among the remaining patients, approximately one in three patients became seizure free with additional treatment. Therefore, a significant proportion of patients under the care of epilepsy experts did not achieve full seizure control with available AEDs. The question of whether the situation is substantially different today requires a randomized, controlled trial to fully determine an answer, but significant difference appears unlikely, given the findings of another study⁷¹ that showed fewer than 25% of patients with medically refractory epilepsy who

were then started on LTG, GBP, and TPM were expected to continue on those agents for more than five years.

Current AEDs suppress seizures, but there is no evidence that any are antiepileptogenic; i.e., capable of preventing the onset of seizures in patients at high risk or inducing a permanent remission of seizures in patients with epilepsy.⁷²⁻⁷⁵

CONCLUSIONS

In a majority of patients with epilepsy, an accurate diagnosis of seizure type and the appropriate selection and utilization of currently available AEDs will lead to therapeutic success. However, there is no current treatment that is proven to prevent the onset or progressive course of epilepsy; many patients with epilepsy will continue to have seizures and/or distressing side effects, and current AEDs are often problematic to use by patients and to manage by physicians. Fortunately, new chemical entities and derivatives of current AEDs are in development,^{76,77} and with further understanding of the mechanisms underlying pharmacoresistance, systemic effects, neurotoxicity, and epileptogenesis,⁷⁸ effective, completely safe, easy to use, and tolerable AEDs, as well as potentially antiepileptogenic therapies, may eventually become widely available.¹⁷

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