Epilepsia, **46**(Suppl. 4):31–37, 2005
Blackwell Publishing, Inc.

An Introduction to Antiepileptic Drugs

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Summary: In recent years, the number of commercially available antiepileptic drugs (AEDs) has increased steadily. Although this may complicate management choices, it also offers welcome new options to individualize treatment more effectively. Because each of the available AEDs differs from others in many clinically relevant properties, opportunities to tailor drug treatment to the characteristics of the individual patient have never been greater. Properties that are especially important in drug selection in patients with epilepsy include spectrum of efficacy in different seizure types, adverse effects profile, pharmacokinetic properties, susceptibility to cause or be a target of clinically important drug–drug interactions, ease of use, and cost. Other factors that need to be considered in tailoring drug choice include availability of user-friendly pediatric formulations, and potentially favorable effects on co-morbid conditions. In fact, a number of AEDs are efficacious and widely prescribed in additional indications, particularly psychiatric disorders, migraine prophylaxis, and neuropathic pain. Recently, advances have been made in understanding the mechanisms of actions of AEDs at the molecular level. While a fully mechanistic approach to the clinical use of these agents is not yet feasible, knowledge of mechanisms of action offers useful clues in predicting their efficacy profile and spectrum of potential adverse effects. **Key Words:** Antiepileptic drugs—Epilepsy—Drug therapy—Clinical pharmacology—Review.

Antiepileptic drugs (AEDs) are among the most commonly prescribed centrally active agents. In a recent survey of 471,873 persons carried out in Denmark, 5,426 were found to be receiving AEDs, which corresponds to a prevalence of 1.1% (1). The use of these drugs also increases with increasing age. A U.S. study of 10,168 elderly nursing home residents revealed that 1,132 (11.1%) were prescribed AEDs, and in 19% of these, the indication was unrelated to seizures or epilepsy (2). This underlines the fact that some AEDs are widely used to treat conditions other than epilepsy, including migraine, neuropathic pain, bipolar disorder, anxiety, and many other disorders (3).

MECHANISMS OF ACTION

Unlike other therapeutic classes, AEDs are not usually classified into categories according to their respective modes of actions for many reasons. First, their actions at the molecular level are not completely understood, and current knowledge indicates that most AEDs have more than one mechanism of action (Table 1), each of which may contribute to therapeutic efficacy to a variable extent depending on the condition being treated (4,5). Second, perhaps as a consequence of our incomplete understanding of how drugs interfere with the pathophysiology of the disease, the approach to the treatment of epilepsy and, indeed, most other conditions in which AEDs are being used, is not mechanism based. In other words, knowledge of the modes of action of various AEDs has limited value in predicting the therapeutic and adverse effects of these drugs in the clinic (6). Last, drug promotion in an increasingly competitive market place does little to provide balanced information on mechanisms of action, and every agent introduced into clinical use is invariably claimed, often on the basis of questionable evidence, to have additional or innovative properties not shared by preexisting drugs (7). Although these limitations should be kept in mind, a number of important mechanisms have been clearly identified, and a congruent pattern is starting to emerge whereby specific actions can be linked to specific clinical activity profiles.

Blockade of voltage-dependent sodium channels is a primary action of phenytoin (PHT), carbamazepine (CBZ), oxcarbazepine (OXC), lamotrigine (LTG), topiramate (TPM), zonisamide (ZNS), and felbamate (FBM) (4). The voltage- and use-dependent nature of this block implies that high-frequency repetitive neuronal firing is selectively prevented, thereby inhibiting spread of seizure activity without interfering with physiologic neurotransmission. Although, at therapeutic concentrations, sodium channel blockers inhibit action-potential firing without directly affecting synaptic responses, blockade of

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TABLE 1. *Main mechanisms of actions of old- and new-generation AEDs*

	Blockade of voltage-dependent sodium channels	Increase in brain or synaptic GABA levels	Selective potentiation of $GABA_A$-mediated responses	Direct facilitation of chloride ion influx	Blockade of calcium channels	Other actions
First-generation AEDs						
Benzodiazepines	−	−	++	−	−	−
Carbamazepine	++	?	−	−	+ (L-type)	+
Ethosuximide	−	−	−	−	++ (T-type)	−
Phenobarbital	−	+	+	++	?	+
Phenytoin	++	−	−	−	?	+
Valproic acid	?	+	?	−	+ (T-type)	++
Second-generation AEDs						
Felbamate	++	+	+	−	+ (L-type)	+
Gabapentin	?	?	−	−	++ (N-, P/Q-type)	?
Lamotrigine	++	+	−	−	++ (N-, P/Q-, R-, T-type)	+
Levetiracetam	−	?	+	−	+ (N-type)	++
Oxcarbazepine	++	?	−	−	+ (N- and P-type)	+
Pregabalin	−	−	−	−	++ (N-, P/Q-type)	−
Tiagabine	−	++	−	−	−	−
Topiramate	++	+	+	−	+ (L-type)	+
Vigabatrin	−	++	−	−	−	−
Zonisamide	++	?	−	−	++ (N-,P-,T-type)	+

++, Primary action; +, secondary action; -, no action described; ?, controversial evidence; GABA, γ-aminobutyric acid. Modified from Perucca (8).

neuronal firing ultimately prevents depolarization of the nerve terminal and the consequent release of neurotransmitters, particularly glutamate. Experimental and clinical evidence indicates that drugs sharing this property are effective against partial and secondarily generalized tonic–clonic seizures and possibly also against primarily generalized tonic–clonic seizures (8). Sodium channel blockade is not considered useful for efficacy against absence and myoclonic seizures and, indeed, AEDs that have sodium channel blockade as their only primary action may even be aggravating against these seizure types (9). It should be noted that important differences may exist in the kinetics of interaction of different AEDs with sodium channels (10), and these may translate into differences in their clinical activity, including their efficacy in indications other than epilepsy.

Because γ-aminobutyric acid (GABA) is the main inhibitory transmitter in mammalian brain, it is not surprising that many AEDs suppress epileptic firing by potentiating GABAergic inhibition (5). Vigabatrin (VGB) exerts such an effect by inhibiting GABA transaminase and thereby increases the pool of GABA that can be released from presynaptic nerve terminals. Tiagabine (TGB), conversely, increases GABAergic transmission by blocking the reuptake of synaptically released GABA. In certain brain areas, GABA may have a proepileptic effect (partly by suppressing activity of inhibitory pathways), which may explain the ability of GABAergic drugs to cause paradoxical seizure aggravation in certain syndromes, particularly within the group of generalized epilepsies. VGB and TGB, specifically, although effective against partial and secondarily generalized tonic–clonic seizures, may precipitate absence and myoclonic seizures (9). Aggravation of absences by GABAergic drugs may be mediated, at least in part, by stimulation of $GABA_B$ receptors in thalamic neurons (11), which may explain why AEDs that potentiate selectively $GABA_A$-mediated responses do not appear to precipitate absence seizures. These drugs include not only benzodiazepines (BZDs), but also TPM and FBM, which exert a modulatory action at non-BZD recognition sites on the $GABA_A$ receptor–chloride channel complex (5).

Blockade of T-type calcium channels in thalamic neurons is a primary mechanism for the antiabsence effect of ethosuximide (ESM) and ZNS (4,12), and controversial evidence exists on whether such an action also contributes to the efficacy of VPA and LTG in absence epilepsy. Although effects at other voltage-gated calcium channels have been less extensively investigated, these may be important. Blockade of L-type calcium channels, for example, may contribute to the ability of CBZ to aggravate absence seizures (13), whereas modulation of excitatory transmission release through blockade of N-type and P/Q-type calcium channels appears to be responsible for the efficacy of gabapentin (GBP) and pregabalin (PGB) in epilepsy, neuropathic pain, and possibly other indications (14). Many other AEDs act at various subtypes of voltage-gated calcium channels (Table 1).

Most AEDs have other actions in addition to those discussed earlier. For example, TPM acts on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors, FBM acts on *N*-methyl-D-aspartate (NMDA) receptors, LTG may modulate serotoninergic transmission, and LTG and LEV may differentially affect potassium currents (4,15,16). In the case of LEV, recent data suggest that its primary action is

related to modulation of SV2A, a synaptic vesicle protein involved in vesicle exocytosis (17). Some actions may be more relevant in explaining specific adverse effects than therapeutic activity. For example, the antidiuretic action of OXC and CBZ is responsible for the possible occurrence of hyponatremia and water intoxication in patients treated with these drugs (18), whereas inhibition of carbonic anhydrase is the mechanism by which TPM and ZNS may induce paresthesias and urolithiasis (19).

Considerable debate has occurred on the role of many of the mechanisms described in underlying the therapeutic effects of AEDs in other conditions, particularly psychiatric disorders. An analogy, for example, has been drawn between the kindling process (a widely used model and paradigm for epileptogenesis) and the development of recurrent manic–depressive episodes (20). It would seem likely that the clinical efficacy of many AEDs in affective disorders is related to multifactorial mechanisms, including changes in intracellular signaling processes (21).

Efficacy spectrum

AEDs vary in their spectrum of activity against different seizure types (Table 2). VPA, BZDs, LTG, TPM, phenobarbital (PB) and, probably, LEV and ZNS have broad-spectrum activity, being efficacious against partial seizures (with or without secondary generalization) and various generalized seizure types (8). Conversely, ESM is efficacious only against absence, continuous spike–waves during slow sleep (CSWS), and possibly myoclonic seizures, whereas the remaining agents are useful mainly in the management of partial epilepsies and may even have an aggravating effect on absence and myoclonic seizures. Among "broad spectrum" drugs, however, some notable differences are found in efficacy spectrum: in particular, PB is ineffective (and may even aggravate) absence seizures (9), and LTG may worsen various seizure types associated with severe myoclonic epilepsy of infancy (22).

Distinct differences in effectiveness are seen between the various AEDs in disorders unrelated to epilepsy (Table 2). As discussed in the previous section, these differences are likely to reflect the diverse and complex mechanisms of action of these agents, although at the current state of knowledge, mechanistic information is insufficient to make reliable predictions on the potential usefulness of any individual drug in indications other than epilepsy.

Clinical pharmacokinetics and therapeutic drug monitoring

Knowledge of pharmacokinetic properties is essential for a rational use of AEDs (8,23). An especially important parameter is the elimination half-life (Table 3), not only because it determines the time to reach steady state after a dose change (as a rule of thumb, 4 half-lives are required) but also because it affects fluctuations in serum drug concentration during a dosing interval (24). Drugs

TABLE 2. *Main indications of antiepileptic drugs in the treatment of seizure disorders and other conditions*

Drug	Main indications in seizure disorders	Main indications in other conditions
First-generation AEDs		
Benzodiazepines	Status epilepticus. Partial and generalized seizures	Anxiety, insomnia, spasticity
Carbamazepine	Partial seizures (with and without secondary generalization) and primarily generalized tonic–clonic seizures	Trigeminal neuralgia, bipolar disorder
Ethosuximide	Absence seizures, continuous spike—waves during slow sleep (CSWS).	
Phenobarbital	Partial and generalized seizures (ineffective against absence seizures). Status epilepticus	
Phenytoin	Partial seizures (with and without secondary generalization) and primarily generalized tonic–clonic seizures. Status epilepticus.	
Valproic acid	Partial and generalized seizures	Bipolar disorder, migraine
Second-generation AEDs		
Felbamate	Severe epilepsies, particularly Lennox–Gastaut syndrome, refractory to all other AEDs	
Gabapentin	Partial seizures (with and without secondary generalization)	Neuropathic pain
Lamotrigine	Partial and generalized seizures (may aggravate severe myoclonic epilepsy of infancy)	Bipolar depression
Levetiracetam	Partial and, probably, generalized seizures	
Oxcarbazepine	Partial seizures (with and without secondary generalization) and primarily generalized tonic–clonic seizures.	
Pregabalin	Partial seizures (with and without secondary generalization)	Neuropathic pain, generalized anxiety disorder
Tiagabine	Partial seizures (with and without secondary generalization)	
Topiramate	Partial and generalized seizures (efficacy against absence seizures not proven)	Migraine
Vigabatrin	Infantile spasms (West syndrome). Partial seizures (with and without secondary generalization) refractory to all other AEDs.	
Zonisamide	Partial and, probably, generalized seizures	

Indications reflect the author's assessment and do not necessarily imply regulatory endorsement. For detailed information, refer to recent reviews and monographs (3,7,8,51,52).

TABLE 3. *Main pharmacokinetic parameters of antiepileptic drugs in adults*

Drug	Oral bioavailability	Half-life (h)		Main routes of elimination
		Patients not comedicated with enzyme inducers	Patients comedicated with enzyme inducers	
First-generation AEDs				
Carbamazepine	≤85%	10–25	5–12	Oxidation. The 10,11- epoxide metabolite may contribute to activity
Clobazam	Nearly complete	15–50	<30	Oxidation. Active *N*-desmethyl-metabolite contributes to activity
Ethosuximide	Nearly complete	40–60	20–30	Oxidation
Phenobarbital	Nearly complete	75–125	75–125	Oxidation, conjugation, and renal excretion
Phenytoin	Nearly complete	10–100 (increases with increasing dosage)	10–100 (increases with increasing dosage)	Oxidation
Valproic acid	Nearly complete	10–20	6–12	Oxidation and glucuronide conjugation
Second-generation AEDs				
Felbamate	Nearly complete	14–23	10–20	Oxidation and renal excretion
Gabapentin	≤60% (decreases with increasing dose)	5–7	5–7	Renal excretion
Lamotrigine	Nearly complete	15–30 (30–90 when comedication is valproic acid)	8—20 (15–30 when valproic acid is also present)	Glucuronide conjugation
Levetiracetam	Nearly complete	6–8	5–8	Renal excretion and hydrolysis
Oxcarbazepine	Prodrug of the monohydroxy derivative (MHD)	8–15 (MHD)	7–12 (MHD)	Keto-reduction followed by glucuronide conjugation of the active MHD derivative
Pregabalin	Nearly complete	5–7	5–7	Renal excretion
Tiagabine	Nearly complete	4–13	2–3	Oxidation
Topiramate	Nearly complete	20–30	10–15	Renal excretion, oxidation
Vigabatrin	60–70%	5–8	5–8	Renal excretion
Zonisamide	≥65%	50–70	25–35	Glucuronide conjugation, acetylation, oxidation, and renal excretion

Enzyme inducers include carbamazepine, phenytoin, phenobarbital, and primidone. For more information, refer to recent reviews (8,53).

with short half-lives, particularly GBP, TGB, CBZ, and VPA may need multiple daily doses to avoid excessively high blood concentrations (associated with adverse effects) at the time of peak or excessively low concentrations, with the attendant risk of breakthrough seizures, at the time of trough. In the case of CBZ and VPA, sustained-release formulations have been developed to allow reduction of the frequency of administration, which is advantageous in terms of convenience and compliance. LEV, PGB, and VGB are usually administered twice daily despite their short half-lives, because their duration of action can be longer than anticipated on the basis of their rate of elimination (24).

Some AEDs exhibit nonlinear pharmacokinetics. PHT, in particular, shows Michaelis–Menten kinetics because of progressive saturation of the liver enzymes responsible for its metabolism (25). As a result, small increments in PHT dosage can result in marked, disproportionate increases of the serum drug concentration at steady state, possibly precipitating clinical toxicity. CBZ, conversely, undergoes dose-dependent enzyme induction, and increments in CBZ dose can result in less than proportional increases in drug concentration (26). GBP also has nonlinear kinetics, due to a progressive decrease in extent of gastrointestinal absorption with increasing dosage (8).

A marked interindividual and intraindividual variability occurs in pharmacokinetics of AEDs under the influence of genetic background, age-related factors (children, as a general rule, eliminate drugs faster compared with adults), other physiologic influences (e.g., pregnancy), associated diseases (particularly those affecting the liver and the kidney), and drug interactions. As a result, patients receiving the same dosage exhibit a large variation in serum drug concentrations, which, in turn, translates into important differences in clinical response. For a number of AEDs, optimal ranges of serum drug concentrations have been reported, which may provide a useful reference for the individualization of dosage (23). Therapeutic serum AED concentration ranges, however, should be interpreted flexibly. Because some patients respond optimally at concentrations outside these ranges, dose adjustments should be made only when a clinical need exists, irrespective of the

level of the drug in the blood. The measurement of serum drug concentrations (therapeutic drug monitoring) is especially valuable as a check for compliance, in assessing the causes for an inadequate response, or in adjusting therapy in situations in which pharmacokinetic alterations are expected (e.g., after adding or removing an interacting drug). Although optimal concentrations ranges have not been identified for second-generation AEDs, the argument that therapeutic drug monitoring is unhelpful for these drugs has been challenged (27). Indeed, it is usually possible to identify empirically a concentration at which individual patients exhibit a good response and use this information as a reference in the subsequent clinical management of the same individual.

Adverse-effect profiles

The tolerability profiles of available AEDs differ substantially from one drug to another, and the likelihood of appearance of specific adverse effects represents the most important consideration in selecting the drug to be prescribed in the individual patient.

Adverse effects can be broadly classified into those that are reversible and dose dependent (e.g., ataxia, sedation, dizziness, cognitive dysfunction), those that are chronic and nonrapidly reversible (e.g., changes in body weight, hirsutism, gingival hyperplasia), and those that are idiosyncratic (e.g., skin rashes, blood dyscrasias, liver toxicity) (28). Although this classification may have didactic value, a precise distinction between these categories is not always possible. Serious side effects are especially common with FBM (1:6,000 risk of aplastic anemia, and 1:26,000 risk of fatal liver toxicity) (29) and VGB (~30% risk of irreversible visual field defects) (30). Therefore these agents are used only as a last resort, although in the case of VGB, first-line use may be justified for the treatment of infantile spasms (31).

Because AEDs have a narrow therapeutic ratio, adverse effects are not infrequently observed at doses (and serum concentrations) within the recommended range. Optimal management often involves achieving the best compromise between the objective of ensuring complete control of symptoms and the need to minimize toxicity (32). With some AEDs, slow dose titration is recommended, because certain side effects can be attenuated or avoided altogether by a gradual introduction of the medication (24). This applies not only to CNS side effects, as in the case of TPM, TGB, and many other agents, but also to idiosyncratic reactions such as skin rashes, as in the case of CBZ, PHT, and LTG (24,33).

An attempt should be made to tailor the expected side-effect profile of the drug to the characteristics of the individual: for example, a drug causing weight loss may be a good choice for the obese patient, and a drug likely to cause hirsutism is best avoided in female patients. An additional concern for female patients of childbearing potential is the risk of adverse drug effects on the fetus. Intake of first-generation AEDs during the first trimester of pregnancy has been associated with a two- to threefold increase in the risk of fetal malformations (34), with some studies suggesting a higher risk in association with VPA exposure (35–37). Whether second-generation AEDs are associated with a lower teratogenicity risk has not yet been determined.

In patients who are not well controlled at the initial maintenance regimen, the dosage should be increased gradually until a full therapeutic effect is obtained, or intolerable side effects appear (24). In persons with difficult-to-treat epilepsy, particularly in those receiving polytherapy, the risk of overtreatment is a serious one, and a patient should never be made to suffer more from the side effects of treatment than from the consequences of the disease (38).

Drug interactions

Drug interactions are a major consideration in the clinical use of AEDs, for a number of reasons: (a) AEDs are usually prescribed for prolonged periods, often for a lifetime, and the probability of coadministration with medications used to treat comorbid conditions is considerable; (b) polypharmacy is relatively common, both in epilepsy and in other indications; (c) many AEDs interfere with the activity of cytochromes P450 (CYP) and glucuronyltransferases, and many also are substrates of these enzymes; (d) because of the narrow therapeutic ratio of AEDs, interactions resulting in changes in serum drug concentration can easily result in toxicity or in loss of response; and (e) given the partly overlapping mechanisms of action of these agents, a potential exists for pharmacodynamic interactions (39,40).

A major group of interactions result from enzyme induction. CBZ, PHT, PB, and primidone (PRM) are potent enzyme inducers, and they may decrease by this mechanism the half-life of several concomitantly administered AEDs (Table 3), thereby decreasing their concentration in serum and increasing their dosage requirements (39). Enzyme induction may also affect response to a wide variety of concomitantly prescribed agents, including several psychotropic drugs (41), oral contraceptives (42), anticancer drugs (43), and many other agents (40). Second-generation AEDs are mostly devoid of enzyme-inducing properties, although OXC, LTG, FBM and, at doses >200 mg/day, TPM, may all selectively stimulate the metabolism (and thereby reduce the efficacy) of steroid oral contraceptives (40).

Interactions resulting from enzyme inhibition also are relatively common. VPA, in particular, may inhibit the metabolism of PB and LTG, resulting in increased serum concentration of the latter drugs and potential toxicity. Other examples of interactions mediated by enzyme inhibition include the increase in serum PHT levels by

OXC and FBM, the increase in serum CBZ levels by erythromycin, diltiazem, and verapamil, and the marked elevation in serum CBZ-10,11-epoxide levels by valpromide, a VPA derivative prescribed in some countries mainly as a psychotropic drug (44).

Interactions caused by displacement from plasma protein binding sites usually are not clinically significant, but they should be kept in mind because they alter the relation between total serum drug concentration and clinical response. For example, VPA displaces PHT from plasma protein binding sites, and in the presence of VPA, therapeutic and toxic effects of PHT may be observed at unusually low total serum PHT concentrations (39).

Pharmacodynamic interactions can be adverse or beneficial. For example, the occurrence of neurotoxic symptoms in some patients given LTG in combination with CBZ has been ascribed to reciprocal potentiation of their sodium channel–blocking effects (45). Conversely, the favorable "synergistic" responses sometimes reported in patients receiving a combination of LTG and VPA has been ascribed to "complementary" mechanisms of action of these drugs (46,47). Use of the latter combination, however, usually also requires an adjustment in LTG dosage and dose titration rate, to account for the concomitant occurrence of a pharmacokinetic interaction.

CONCLUSIONS

In recent years, the number of commercially available AEDs has increased steadily. Although this may complicate management choices, it also offers welcome new options to individualize treatment more effectively. Because each of the available AEDs differs from others in terms of pharmacologic properties, efficacy spectrum, side-effect profile, interaction potential, and cost, opportunities to tailor drug treatment to the characteristics of the individual patient have never been greater. Although in most situations, first-generation drugs still represent the best choice, increasing evidence shows that in many conditions, newer agents may be fully justified for initial treatment. For example, LTG may represent a valuable first-line therapy in the elderly because of its favorable tolerability profile in this age group (48), and it may also be preferred to VPA in childbearing-age women with generalized epilepsy, in whom VPA may be considered undesirable because of risks for the offspring (49). GBP may be the most rational choice to treat partial-onset seizures in a patient with acute intermittent porphyria (8), and VGB is often a preferred choice for infantile spasms secondary to tuberous sclerosis (31). The effectiveness of many AEDs against comorbid conditions also influences therapeutic choices.

In line with the steady improvement in our understanding of the modes of action, efficacy spectrum, and side-effect profiles of AEDs in different patient groups and indications (50), we can look forward to a more rational use of these agents in the years to come.

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