INDIVIDUALIZING AED CHOICES IN ADULTS

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Selecting an antiepileptic drug
Choosing an antiepileptic drug that is optimal for an individual patient is becoming a daunting task, as more and more drugs are approved for use for epilepsy. Approximately 20 drugs have been or shortly will be approved for use in the United States (see table 1). This creates significant complexity, particularly for neurologist who must split their time between many subspecialty areas. It would be ideal if one or two antiepileptic drugs were always "First choice", after which other drugs could be tried. Unfortunately, the drugs are unique enough that there are many "first-line" drugs, and the ideal drug for a given patient will be tied to particular characteristics of that patient. Selection should be based on a number of considerations that will be asked in order of importance along the decision tree. Considerations include, among others: Epilepsy syndrome, initial versus chronic therapy, specific health issues, gender, and age. This syllabus will discuss some of these aspects of antiepileptic drug choice, and suggest some suitable drugs for particular situations. Some of the information provided below can also be found in an article in Continuum (1).

Epilepsy syndrome/seizure type:
This must be the first issue considered, since seizure control is the primary goal of therapy, and many AEDs treat only certain types of epilepsy and not others. AEDs that are “narrow spectrum”, are much more effective at controlling seizures associated with select syndromes, or within a specific category (for example focal versus generalized). Other AEDs are so-called “broad spectrum” agents, able to treat a wide variety of epilepsies and seizure types. In addition, recently several compounds have been studied in specific etiologies, rather than for seizure types or epilepsy syndromes. Examples include cannabidiol for Dravet syndrome (2) and everolimus for seizures associated with tuberous sclerosis complex (3).

Narrow-spectrum agents that treat focal epilepsy include:
Carbamazepine, oxcarbazepine, gabapentin, pregabalin, tiagabine, and eslicarbazepine. Many of these drugs may in fact exacerbate some generalized seizures, such as myoclonus and absence (4)

Vigabatrin, while generally considered a narrow spectrum drug, is exceptionally useful in the treatment of infantile spasms (often considered a generalized seizure type) due to tuberous sclerosis (5)

Narrow-spectrum agents that primarily treat generalized epilepsy syndromes include:
Rufinamide (especially for atonic seizures in LGS) and ethosuximide (specifically for absence seizures). These drugs are not typically used in the setting of partial epilepsy.

Broad-spectrum agents (suitable for treatment of both focal and generalized epilepsy) include :
Levetiracetam, lamotrigine, topiramate, felbamate, zonisamide, valproic acid, perampanel.

Levetiracetam tends to be more effective for myoclonic than absence seizures; lamotrigine can sometimes exacerbate myoclonus but can be effective in treating generalized-onset tonic-clonic seizures. Lamotrigine was inferior to valproate and ethosuximide in controlling absence seizures (6) and inferior to valproate in all generalized seizures, in randomized controlled trials (6,7) Although Phenobarbital and phenytoin are considered broad-spectrum by some, they have been associated with triggering or ineffective for absence seizures; in addition, a worsening of Lennox Gastaut Syndrome (LGS) and myoclonic epilepsies has been seen with their use (4)

Valproic Acid was inferior to carbamazepine for control of complex partial seizures, but equal to carbamazepine in its ability to control partial seizures evolving to generalized tonic-clonic convulsions (8) . Perampanel was recently found to be very effective for the treatment of primary generalized (idiopathic) tonic clonic seizures, in addition to its previously known efficacy for focal seizures.

Several newer AEDs (lacosamide, ezogabine, brivaracetam) have only been tested against focal seizures or have not been adequately explored in generalized epilepsy, and thus the spectrum of activity is currently unknown.

Studies indicate that, at the time of diagnosis, classification of focal or generalized seizures can only be made about half of the time. If a clear diagnosis cannot be made, it is wise to choose a broad-spectrum AED. More information about specific new AEDs, their efficacy profile and side effects can be found in the two AAN guideline on new AEDs (9,10). A new AED guideline is underway and close to completion.

First line therapies

Several antiepileptic drugs within the broad-spectrum and narrow spectrum category can be considered to be "first-line". In other words, they are more appropriate for initial therapy for patients who are newly diagnosed with epilepsy. The appropriateness for first-line therapy relates to a number of characteristics. Efficacy will not be a particularly important characteristic for selection of first-line therapy. This is because there are few well-documented differences in efficacy between anti-epileptic drugs in this population. Many head-to-head studies have been performed that have failed to show efficacy differences (11) This may relate to the fact that patients with newly diagnosed epilepsy have seizures that are often more easy to control than those with chronic epilepsy, and their overall prognosis is good. Since many efficacious drugs exist, this population should be treated with a drug that is known to be safe and well tolerated, as there are many choices that fit this description. Several drugs have been approved in the last few years, (ezogabine, perampanel, brivaracetam) and their safety and efficacy in this population has not yet been completely established. Recent studies have indicated that 37 % of patients with newly diagnosed epilepsy will become seizure free on the initial therapy (12). A seizure free patient may be unwilling to attempt a change in therapy, even in the presence of side effects. A clinician is also less likely to risk a medication conversion in a seizure-free patient as they may become destabilized. This is particularly relevant if the patient has resumed activities such as driving. Therefore, there may be only one chance to select the optimal therapy. Drugs of the second generation that have undergone head-to-head trials confirming similar efficacy, and equal or better tolerability than standard drugs in focal epilepsy, include, lamotrigine, topiramate, oxcarbazepine, zonisamide lacosamide and levetiracetam (9, 13-16) Vigabatrin and tiagabine were inferior to carbamazepine in head to head trials (17), gabapentin was inferior to carbamazepine for efficacy in one pragmatic trial (14), and pregabalin was inferior to lamotrigine for efficacy (18) Topiramate was less well tolerated than valproate or lamotrigine for generalized seizures in one pragmatic trial (7) Eslicarbazepine acetate was comparable to controlled release carbamazepine as initial monotherapy (results only published in abstract form to date)(19).

Table 1: Antiepileptic drugs: Spectrum of activity. Drugs considered "first line" are in bold

Narrow spectrum (appropriate for established focal epilepsy only)	Narrow spectrum (appropriate for established generalized epilepsy only)	Broad spectrum	Appropriate for focal epilepsy, otherwise spectrum unknown
carbamazepine	**ethosuximide** (absence)	**levetiracetam**	**lacosamide**
oxcarbazepine	rufinamide	**lamotrigine**	ezogabine
gabapentin		**zonisamide**	brivaracetam
pregabalin		**valproic acid (first line for generalized epilepsies)**	
tiagabine		topiramate	
vigabatrin (also effective in infantile spasms)		felbamate	
Eslicarbazepine acetate		(phenytoin)	
		(phenobarbital)	
		perampanel	

Selecting an AED to be added to an existing regimen

When selecting a drug that will be added on to an existing regimen, a number of factors should be considered. One issue is whether the addition of the drug will lead to pharmacokinetic interactions. Pharmacokinetic interactions are those that will alter measurable serum concentrations of either the drug that is being added, or the background drug. They are not a contraindication to combining drugs, but they must be recognized and addressed, to avoid potential for toxicity (20) . Equally important as pharmacokinetic interactions is the potential for positive and negative pharmacodynamic interactions. Pharmacodynamic interactions can be defined as the situation in which coadministration of drugs causes more than additive toxicity or benefit, without a change in serum concentrations. Negative pharmacodynamic interactions may happen because side effect profiles of the coadministered drugs are too similar. This is probably the explanation behind the pharmacodynamic interaction between lamotrigine and carbamazepine, carbamazepine and phenytoin, and lacosamide and sodium channel blockers. These drug combinations, although in some cases beneficial, should probably not be used as a first choice. Some pharmacodynamic interactions are favorable, and in this case a drug combination may provide more benefit than either drug alone. One combination, valproate/lamotrigine, while increasing some safety and tolerability concerns, has been noted to be favorable in terms of efficacy in some patients (21,22) . Some of the newer drugs, such as levetiracetam, gabapentin and pregabalin seem to be particularly well tolerated as add-on therapy, due to lack of pharmacodynamic interactions.

Selecting an AED in patients with underlying comorbidity/medical issues

Hypersensitivity: Patients with a prior history of rash or hypersensitivity to AEDs or other agents should have a drug selected that is not likely to produce such a reaction. Lamotrigine would not be an optimal choice. One should keep in mind that there is cross-sensitivity between phenobarbital, carbamazepine, and phenytoin. Drugs such as levetiracetam, gabapentin, pregabalin and valproate have a low risk of hypersensitivity and could be a good choice. *Weight:* Drugs that produce weight gain, such as valproic acid, gabapentin, pregabalin, carbamazepine and the new AEDs retigabine and perampanel might not be an optimal choice in obese patients; topiramate and zonisamide, which can cause weight loss, might be preferred in this patient population, but should be avoided in patients who are too thin, or have eating disorders.

Renal calculi: Topiramate and zonisamide predispose patients to stone development. They should be avoided in patients with renal calculi, unless there is a specific reason for use.

Renal insufficiency: Patients with renal insufficiency, or who require dialysis, often require lower doses of renally-excreted AEDs; extra doses may be administered following dialysis treatments. AEDs which are almost exclusively renally cleared include levetiracetam, gabapentin and pregabalin. Information about renal dosing is usually found in the package insert. It is not necessary to alter the dosing of the new drug brivaracetam, in patients with renal impairment.

Hepatic insufficiency: It is preferable to avoid potentially hepatotoxic agents, such as valproate and felbamate, in patients with known hepatic disease; similar to patients with renal insufficiency, those with reduced hepatic function may require lower doses of medications that are hepatically metabolized. AEDs that often elevate measured hepatic enzymes (for example phenytoin, carbamazepine, phenobarbital, valproate) might cause difficulty in monitoring patients with underlying hepatic disease.

Chronic medical conditions: Strongly enzyme inducing AEDs (eg phenytoin, carbamazepine, phenobarbital, and primidone) should typically be used with caution in patients with chronic medical conditions other than epilepsy, since 2/3 of drugs will undergo increased clearance as a result of enzyme induction, including the antiarrhythmic drugs, calcium channel blockers, propranalol, amiodarone, digoxin, lipid-lowering agents ,warfarin , antiretroviral agents, many antifungals, chemotherapeutic agents, immunosuppressives, and psychiatric medications including some antidepressants and antipsychotics. (23) .

Behavioral/Psychiatric co-morbidity: Some drugs are more likely to produce behavior problems, while others with mood-stabilizing properties might be helpful in patients with concomitant psychiatric illness. Carbamazepine, lamotrigine, oxcarbazepine, and valproate in particular are known for their mood-stabilizing effect. Levetiracetam (and phenobarbital in children) can produce irritability, perampanel can produce irritability and aggression, and topiramate, phenobarbital, mysoline and vigabatrin can cause depressed mood (24). Drugs which can produce stimulation (such as lamotrigine or felbamate) may produce anxiety or insomnia.

Gender-based selection of AEDs

There are special considerations when antiepileptic drugs, either new or old, are given to women, particularly during their child-bearing years. Choices of therapy for women during their childbearing years may be influenced by the potential impact of treatment on hormonal function, sexuality, and pregnancy.

Many antiepileptic drugs, as noted above, alter the metabolism of other drugs and intrinsic compounds metabolized through the liver, including other drugs, steroid hormones and vitamins. The most potent inducers are phenytoin, carbamazepine, and the barbiturates. Oxcarbazepine and eslicarbazepine minimally induce hepatic metabolism. Sodium valproate inhibits hepatic metabolism. The strongly inducing/inhibiting drugs are particularly troublesome in the treatment of women, because the hormonal milieu may be affected, leading to alteration in the menstrual cycle and ovulation. Induction of Vitamin D metabolism may lead to increased risk of osteomalacia. Vitamin D and calcium supplementation, while advisable in all young women, are particularly important when strongly enzyme-inducing antiepileptic drugs are prescribed (25). The estrogen component of oral contraceptive pills (OCP) and the components of depo-forms of steroid hormones are also affected. Therefore, women on enzyme inducing AEDs (including oxcarbazepine and eslicarbazepine) should avoid such preparations, unless OCPs contain 50 μg. of estrogen. TPM, although not an inducer in general, has a weak inducing effect on OCPs and similar precautions may be warranted (26, 27) .

Major and minor anomalies, including cardiac defects, cleft lip and palate, microcephaly, and developmental delay may occur with AED exposure during pregnancy (28) . Neural tube defects have been reported with the use of carbamazepine (0.5% risk) and sodium valproate (1.0% risk). Several recent pregnancy registries in women with epilepsy have demonstrated an increased risk of teratogenicity associated with valproate when compared to other AEDs (28) . Lamotrigine was identified as having an increased risk of cleft lip/cleft palate in a single pregnancy registry (29). However follow-up data from separate registries have revealed a lower risk than that originally presented; Topiramate demonstrated a higher risk of cleft lip/palate compared to lamotrigine in the more recent North American AED Pregnancy registry findings (30). A recent AAN guideline suggested that avoidance of Valproic acid and polytherapy was advisable to reduce risks of birth defects. (28). The same guidelines identified a risk of poor cognitive outcomes among children born to women taking valproate. Notably, brain development occurs up to the third trimester, so avoidance of valproate should be considered beyond the first trimester. The effects of valproate are dose-related, so if a woman needs valproate, she should be maintained on the lowest dose possible, and if possible on monotherapy. Data from pregnancy registries are constantly being gathered, and it might be a while before we know for certain what the exact risks are for each drug. No specific anomalies have been associated with the other newer AEDs, but too few data are available to determine if they are safe.

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