



A Proposed Strategy for Selecting an Antiseizure Medication

With efficacy distinctions hard to come by, neurologists must rely on secondary factors. Here's how to weigh several when choosing a medication.

The medications used to treat seizures are commonly referred to as “antiepileptic drugs,” or AEDs. However, there is growing support to call them “anti-seizure drugs” instead. This is due to the fact that they suppress seizures, and have never been shown to literally prevent the occurrence of epilepsy. As the neuroprotective properties of medicines become better defined, this distinction may be an important one. However, at present there are no medicines which fall clearly into this category. In other words, physicians use the terms antiepileptic drug and anti-seizure medication interchangeably.

Over the past decade, there has been a proliferation of antiseizure drugs. This offers people with epilepsy a greater number of treatment possibilities, and holds promise for an improved quality of life. However, physicians are now faced with a longer list of choices: selecting the most appropriate medication is more challenging than ever before. To add to this confusion, there are very few trials that compare the effectiveness of antiseizure agents, particularly the newer agents. Because there is such little information in this area, physicians have looked at the rate of seizure freedom reported in early trials for these medications and are forced to conclude that the medications are roughly equally efficacious.

If we assume that all antiseizure medications are about equally effective, then what determines the treatment choice? The selection of an agent is based on seizure type (or epilepsy type), side effect profile, potential drug interactions and co-existing medical conditions.

Seizure Type and/or Epilepsy Syndrome

Identification of the person's seizure type or epilepsy syndrome (Table 1) is the most critical factor in selecting the most appropriate agent. But how does one know what kind of epilepsy a person has? A detailed history of the person's events is the first step.

If the patient experiences a “warning” or aura before there is loss of awareness, the seizure likely began in a focal region of cerebral cortex, and is therefore partial in onset. As the seizure propagates, it may become complex partial (consisting of loss of awareness, possibly with oral or manual automatisms or both). Finally, if the seizure that started focally spreads to involve the entire brain, it will clinically appear as a generalized tonic-clonic seizure. In instances where a partial seizure becomes a generalized tonic-clonic seizure, it is called a secondarily generalized tonic-clonic seizure. An EEG would show an electrical discharge which began focally, spread to adjacent cortex and then through interhemispheric connections to both hemispheres.

By contrast, generalized seizures (Table 1) involve the entire cerebral cortex from their onset. There are several types of generalized seizures, each with its own electrical signature pattern. Because they involve both hemispheres from onset, there is immediate loss of awareness. In other words, there is no warning or aura. Here again, a detailed history is likely to help narrow the differential.

With the exception of ethosuximide, which works well in absence seizures, all of the AEDs have been shown to be effec-

tive against partial seizures. A shorter list of agents has demonstrated effectiveness against generalized from onset seizures: these medications also work for partial seizures, and are therefore often referred to as broad spectrum agents (see Table 2). Once the diagnosis of either partial or generalized epilepsy has been made, an agent must be selected from one of these lists. However, this still leaves a long list of possible choices, especially when partial seizures have been identified.

Mechanism of Action

For many AEDs, at least some elements of their mechanism(s) of action have been studied. This may be an issue when either combining AEDs or when switching from one agent to another. For instance, if the primary mechanism of the first agent was sodium channel blockade, and this was ineffective in controlling the person's seizures, it seems logical to select a second agent that has a different mode of action. Similarly, if two agents were needed, it seems reasonable to combine two that have differing modes of action.

This seems to be an elegant way to choose an AED; however there are at least two pitfalls to this reasoning. First, most medicines have more than one mechanism of action. Although the primary mode of action may be similar for two agents, they may still be complementary based on secondary mechanism(s). Second, we do not know all of the possible modes of action for all of the available AEDs. Because our understanding is so incomplete, it is not possible to anticipate, based on this aspect of the medication, which combinations are optimal.



EPILEPSY ESSENTIALS

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Adverse Events/Side Effects

If the medications are roughly equal in efficacy, perhaps we can choose between them based on possible side effects. There are side effects which seem to be common to this entire class of medicines: drowsiness, dizziness, diplopia and imbalance. However, valproate and gabapentin are known to cause weight gain. Others (felbamate, zonisamide and topiramate) have been associated with weight loss. Some agents have been reported to help with mood and depression: lamotrigine is the best studied, but valproate and carbamazepine also have been reported to help with mood stabilization. There are many other subtleties which we could list. For instance, the selection of an AED may depend on other, concurrent illness(es) the patient is experiencing.

Drug-to-Drug Interactions

The selection of an AED may ultimately depend on what other medications a person is taking. For instance, some AEDs induce the metabolism of other medications, thereby lowering their serum levels. This may directly affect the efficacy of the other medicine. For instance, phenytoin induces the metabolism of warfarin. If a person were taking Coumadin, and Dilantin was added, the INR may be reduced to a subtherapeutic value.

In this instance, either another AED should be selected or the Coumadin dose should be adjusted upwards to offset the effect of Dilantin on its metabolism. Valproate has the opposite effect, inhibiting hepatic metabolism of many drugs.

If the person were taking Coumadin and added valproate, the INR would go up, potentially leading to serious consequences if left unchecked. In some instances, interactions are mild; in others, quite serious. This is a critical factor to take into account when choosing an AED.

Table 1: Seizure Types

Seizures with Partial Onset

- Simple partial seizures
- Complex Partial seizures
- Secondarily generalized tonic-clonic seizures

Seizures with Generalized Onset

- Absence seizures (typical and atypical)
- Myoclonic seizures
- Tonic seizures
- Clonic seizures
- Atonic seizures
- Generalized tonic-clonic seizures

Table 2: AEDs and Seizure Types (Narrow vs. Broad Coverage)

Seizures Types	Antiseizure Drug
Broad Spectrum: <i>all</i> seizure types (generalized from onset and partial onset seizures)	felbamate, lamotrigine, levetiracetam, topiramate, valproate, zonisamide
Narrow spectrum: (simple partial, complex partial, and secondarily generalized seizures)	carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, phenytoin, topiramate, tiagabine, oxcarbazepine, phenobarbital, primidone, valproate, zonisamide
Absence (a type of generalized seizure)	ethosuximide
Infantile Spasms	topiramate, valproate, vigabatrin (not available in the US), zonisamide

Hepatic or Renal Disease

Many AEDs are either metabolized by the liver, excreted by the kidneys, or both. In a person with hepatic or renal disease, it may be necessary to avoid certain AEDs or to adjust the dose accordingly. For instance, gabapentin is excreted by the kidneys. If a person has renal impairment, lower the dose. If the person has renal failure, and is on dialysis, it may only be necessary to administer a dose after each dialysis.

Gender

Much is now known about the effects that certain AEDs may have on the female reproductive cycle, oral hormones (contraceptives) and fertility. AEDs that are hepatic enzyme inducers will erode the effectiveness of oral contraceptives. The hepatic enzyme inhibitor valproate

may cause polycystic appearing ovaries, and therefore contribute to impaired hormonal cycles and impaired fertility. Although not absolutely contraindicated, these factors must be weighted when choosing an AED.

Summary

As the list of AEDs grows, it becomes increasingly difficult to select the most appropriate one for a given patient. Since we do not have head-to-head comparative data for many of these agents, we must base our selection of AED on other factors. Seizure type (or epilepsy syndrome), mechanism of action, side effect profile and potential drug interactions are but a few. Hopefully, further research will improve our understanding of how to best select an antiseizure medication or a combination of antiseizure drugs. **PN**