



When and How to Discontinue AED Therapy in People with Epilepsy

It's more risky than many patients realize. Here's a look at the prospects and perils.

Anti-epilepsy drugs have been the mainstay of treatment for seizure disorders for over 70 years, with the widespread use of phenobarbital and then over two dozen other agents since the 1930s. When a person becomes seizure-free with treatment, inevitably one question arises: can the person stop taking their seizure medication(s)? Patients are often the first to raise this question, as they are eager to taper and ultimately discontinue medication(s). Once asked, the clinician must carefully weigh the risks of continued treatment against the recurrence of seizures. Of course, this also raises the concerns about the morbidity and mortality in the untreated state.

The Scope of the Problem

Currently, there is very little evidence from either randomized or prospective trials (class I evidence) to help clinicians answer this question confidently. Much evidence is derived from a single randomized, prospective study performed in children.¹ Since there have been no randomized trials in adults, this information is often applied to adults. As we will see, this may be a problematic use of data. As a result, the clinician is forced to combine the available prospective data with retrospective data and his or her own experience in order to formulate a clinical opinion.

There are many reasons for discontinuing medications. The first is to eliminate short-term or long-term side effects due to AEDs. For instance, many studies have shown that patients are unhappy with their medications. Often, it is the daily medication side effects, such as cognitive slowing, that erode a person's quality of life.² In addition, the clinician must consider the cumulative effects of treatment:

long-term use of phenytoin, for instance, has been associated with bone loss such as osteopenia and osteoporosis.³

Women, during all phases of their reproductive lives, face unique concerns with respect to AED usage. The medical literature provides little about the effects of AEDs during puberty and menopause. However, much is known about the complex interaction between AEDs and hormones in adulthood (see *Epilepsy Essentials*, June 2005 and May 2007, available online at www.practicalneurology.net/PN_archive.htm). For instance, hepatic enzyme-inducing drugs increase the rate of contraceptive pill failure. AEDs are potentially teratogenic and may affect the development of infants and children. Discontinuation of AEDs has obvious benefits in this group.

People with epilepsy face many social, psychological and economic factors. There is a stigma associated with epilepsy. By definition, a person has epilepsy if they have experienced two or more unprovoked seizures in their lifetime. In other words, people who become seizure-free still carry this diagnosis. However, the longer a person remains seizure-free, the less likely they are to see themselves as "ill." This can have a direct impact on his or her self-perception. Finally, people with epilepsy carry the financial burden of the cost of medication. Discontinuation of medications can have an impact on all of these factors.

Despite patient willingness to stop medications, individuals may under-report their events. Patients may have impaired memory or be unaware of the events. In addition, patients may fear the repercussions of seizure reporting. For instance, people who experience a return of seizures may have to stop driving. Seizure relapse

may have workplace consequences. Here, the family can help to fill in the gaps and provide a secure environment.

When Should You Stop Anti-seizure Medications?

Though information in the medical literature is again vague in this area, there are several general "rules" regarding the discontinuation of medications.⁴ More specifically, there are several statements that can be made regarding the likelihood of relapse during medication withdrawal. Many of these "rules" are likely to be related to the kind of epilepsy that the person develops. Unfortunately, most studies do not address the issue of epilepsy syndrome. Instead, many available studies look at the rates of remission (or relapse) in "all-comers." In other words, the type of epilepsy does not factor into the equation.

Generally, onset of epilepsy in infancy seems to carry a worse prognosis. This is likely due to the cause of seizures in this age group. In many instances, the seizures are due to an injury to the central nervous system. This could have occurred during fetal development, or may have occurred during a traumatic labor and delivery.

One example of this is Lennox-Gastaut Syndrome (LGS). This is a debilitating kind of epilepsy that is due to severe brain injury. Not only do many types of seizures occur, but LGS is associated with significant intellectual disability. One study showed that if a person had multiple seizure types (as occurs in LGS), the chance of remaining seizure-free off medications was low. Another indicated that if a child was mildly mentally "retarded," there was a 38 percent chance of relapse; if severely mentally retarded, the chance of relapse was 51 percent.⁴

Seizures that begin in childhood have the best prognosis. This may be due to the kinds of epilepsy that are most likely to develop in this age group. For instance, childhood absence epilepsy (CAE) and benign epilepsy with centrotemporal spikes (BRECTs) arise during childhood. These are thought to be genetic syndromes. About 80 to 90 percent of these syndromes remit spontaneously by puberty.

Seizures that begin in adolescence have a two-fold greater relapse rate than those beginning in childhood. Here again, we must consider the kinds of epilepsy that arise in this age group: juvenile absence epilepsy (JAE) and juvenile myoclonic epilepsy (JME). These are also thought to be genetic syndromes. Limited retrospective studies have shown that 100 percent of people with JME relapse after discontinuing AEDs; expert opinion widely supports this finding. In short, if the person has this type of epilepsy, there is a very high likelihood of relapse.

The nomenclature for seizures and epilepsy syndromes was restructured by the International League Against Epilepsy in the late 1980s. Since then, there has been greater recognition of the importance of identifying the specific syndrome. This applies not only to the selection of medications, but also to prognosis. When it comes to discontinuation of medications, identification of the epilepsy syndrome is essential, and helps the clinician to better predict the chance of remission or relapse.

The Risks of Stopping AEDs

Successful AED discontinuation has potential benefits; however, discontinuation also carries potentially grave risks. In general, approximately 40 percent of people who stop AEDs experience a relapse in the first year of stopping medication(s). That number climbs during subsequent years.¹ It would seem that merely restarting therapy would return the patient to remission, but in fact regaining seizure control may not be so readily achieved. Often, higher doses and even additional medica-

tions may be required to return the patient to a seizure-free state.

Furthermore, a single event (no matter how brief) may have a profound effect in limiting routine activities, from work demands to driving, or even participating in sports. If a relapse does occur, it may result in serious injury. Seizures can cause fractures, aspiration, burns and drowning.

In addition to the morbidity associated with seizures, there is also the issue of mortality. There are two issues of concern: the increased risk of status epilepticus and the risk of sudden unexpected death in epilepsy (SUDEP) in people whose seizures are not completely controlled. Prior history of status epilepticus increases the risk of a prolonged seizure with taper, but absence of this history does not ameliorate the risk. In older series, the mortality of generalized status epilepticus ranges from five to 50 percent. More recent series have quoted a mortality of 10 to 12 percent; however, this number often is higher in hospital-based studies compared with community-based studies,⁵ perhaps reflecting the complexity of cases that are treated in the hospital setting.

The causes of SUDEP remain poorly understood. However, in persons who continue to experience seizures, the incidence is somewhere between 1 in 500 to 1 in 1000. More recent studies suggest that this risk is even higher.⁶ When a person stops medications, they are not only at risk for having a return of seizures, but also an increased risk of SUDEP.

Finally, people who have poorly controlled epilepsy have a four-fold risk of committing suicide compared to age matched controls. In addition, this group also has an increased rate of all mood disorders, with depression being the most common (see *Epilepsy Essentials*, October 2005 and July 2007).

How to Stop Medications

Controversy surrounds the duration of AED taper. Recommendations vary widely: some say that the taper should occur

over six weeks, and others recommend a taper over nine months. The only prospective randomized study which was performed in children suggests that a six week taper is sufficient for all medications.

While some evidence exists to suggest that the rate of taper should not be dictated by the agent, the majority of retrospective evidence supports the notion that specific AED pharmacokinetics should in fact dictate taper. It is generally thought that barbiturates and benzodiazepines require a prolonged, slow taper (>6 months). Phenytoin deserves specific mention owed to its unique zero-order kinetics. Safe withdrawal requires a slow down titration in the initial phase of taper with an escalation in the titration rate in the final phase.

In one retrospective study,⁷ the authors looked at the rate of AED and the rate of seizure recurrence. They compared tapers that were completed in less than three months versus tapers longer than three months. They could find no difference in the rates of seizure relapse between the two groups. They concluded that factors such as sample size and patient heterogeneity played a role in their result of "no difference." They recommended further study.

Tennison's prospective study in 133 children looked at the rate of relapse after discontinuation of AEDs. Here the rate of taper was six weeks versus nine months. With a six-week AED taper, 43 percent relapsed. After a nine-month AED taper, 39 percent experienced a recurrence of seizures. In other words, there was no difference in the rate of relapse with a slow AED taper versus a faster one.

How Does EEG Help?

Although EEG testing, both routine and prolonged, is commonly used, no definitive study has been done which conclusively shows that EEG helps determine the rates of seizure relapse during AED withdrawal. For instance, a normal EEG prior to taper has not been shown to predict seizure freedom. Even rare sharp waves on EEG show no definite correlate with rates



EPILEPSY ESSENTIALS

By Nishi Rampal, MD and Steven Karceski, MD

of relapse. Generally speaking, if there is slowing or epileptiform discharges on EEG, the rate of relapse is 22 percent. If there is a positive photoparoxysmal response, the rate of relapse is 60 percent.⁴

Here again, identification of the epilepsy syndrome may be important. People with idiopathic generalized epilepsy are more likely to have the photoparoxysmal response. Adolescent-onset idiopathic syndromes are very unlikely to remit. In other words, the presence of the photoparoxysmal response on EEG may be an indicator of something with which we are already very familiar: that adolescent-onset idiopathic epilepsies are unlikely to remit.

There is a single randomized, prospective study in childhood that tried to address this question. The authors reported that the presence of spikes on EEG prior to taper was an unfavorable predictor of sustained remission. Repeat EEG after medication taper has also not been rigor-

ously studied, but there appears to be no definite predictive value of this finding either. While there are no hard and fast rules for the use of EEG before, during, and after AED taper, one must decide how to proceed and counsel a patient should suspicious findings arise. For example, if a standard EEG demonstrates a single interictal discharge, does this preclude the initiation of a medication taper?

Conclusions

Neurologists who treat people with epilepsy will inevitably face the issue of stopping AEDs. The clinician must weigh many benefits and risks when considering a medication withdrawal. It is important to consider the strength of the patient-health care provider relationship: close monitoring and open reporting is essential for patient safety. The individual's occupational needs and demands should be weighed as well, as the risk to the patient or

bystanders may preclude withdrawal. Paramount to this decision is a discussion of the individual goals of the patient. **PN**

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Nishi Rampal, MD is a Fellow in Critical Care and Epilepsy at Columbia University, after completing neurology residency at Yale University.

Steven Karceski, MD is Assistant Clinical Professor of Neurology at the College of Physicians & Surgeons of Columbia University and Director of the Columbia Epilepsy Center at the Atlantic Neuroscience Institute.