The epilepsy specialist always has two equally important endpoints in mind when plotting a treatment strategy for a patient: controlling seizures and minimizing the adverse effects of medications. The second point is the impetus for many practitioners to direct their patients towards monotherapy and be slow and cautious when considering adding a second or third AED to the regimen. Most of the time this philosophy proves to be the best course for the patient, as it leads to the maximum seizure suppression while minimizing drug exposure. However, when a patient achieves seizure freedom, is it reasonable to reduce or stop some of the anti-epileptic medications?

When a withdrawal plan is started, most physicians are concerned about recurrent seizures, and losing the ability to control them in the future. However, studies have shown that maintaining AED therapy does not necessarily alter the long-term prognosis, and the risk of serious injury or status epilepticus is low. Therefore, in a controlled trial the risks to the patient should be outweighed by the potential benefits.
In this article, we’ll look at some of the concerns that come with reducing AEDs, and how to avoid them. We will also discuss some of the factors which place certain patients at higher risk for recurrence.

Reasons to Taper
There are likely to be many reasons behind the decision to taper AEDs. Some of these may involve the desire for a permanent end to medication use; others may only concern a temporary withdraw. The rationale may directly tie back to the patient’s physical health, it may be done with the intent to improve the patient’s self-image, or it may be a purely financial consideration.

One of the primary concerns is the long-term toxicity associated with some of the older AEDs. These include cerebellar toxicity with phenytoin, polycystic ovarian syndrome with valproic acid, and osteopenia with enzyme-inducing AEDs, to name a few. At present, there are no data about the long-term effects of newer agents such as topiramate, gabapentin and lamotrigine.
Tapering AEDs

While the risks associated with an AED taper may vary from patient to patient, the guidelines behind what makes a good candidate are fairly well established.

The available literature indicates those most likely to maintain seizure freedom without medication are individuals who have been seizure free for at least two years. A 2001 study found a higher seizure recurrence risk if anti-epileptics were withdrawn prior to two years in pediatric patients. Unfortunately, there are no data for adults since the largest randomized trial, the 1991 MRC Study, had an exclusion criteria of less than two years. Based on the available literature, there is no definite benefit with longer seizure-free periods.

However, many patients may start asking about taking fewer medications after they have been free from seizures for six months to a year. You may need to explain the risk of recurrence if medications are reduced before the two-year mark. If the patient insists, it may be prudent to start the weaning process after documenting that the physician recommended a longer period of seizure-freedom and has discussed the risk of recurrence. Here, the withdrawal is done gradually, under a physician’s supervision, which could prevent a persistent patient from abruptly stopping medications.

Women considering conception and family planning should also be viewed as candidates for a taper, even if they have not been seizure-free for two years. A discussion regarding the risks of seizure recurrence versus the risk of fetal malformations and neural tube defects should take place so that an informed decision can be made. However, if the woman has failed a past trial or has a condition with a high risk of recurrence, such as focal epilepsy with a structural lesion and EEG abnormalities, then changing to an alternative monotherapy that is not associated with teratogenicity may be the best course of action.

Children with benign conditions, such as benign rolandic epilepsy or benign occipital epilepsy, may also prove successful in a tapering trial. In fact, it may be best to get children off AEDs when possible since these treatments often suppress normal brain activity, and may impact long-term cognitive outcomes. Also, since children do not drive and tend to be in a relatively safe environment, there are fewer safety concerns than when attempting treatment withdrawal for an adult.

Calculating the Risks
The overall risk of a recurrent seizure either during the taper or after medications have been stopped is between 25 and 40 percent, depending on which study you read. A meta-analysis completed in 1994 calculated a pooled risk of 25 percent at one year and 29 percent at the end of two years. However, the majority of recurrences will occur within the first year after AED withdrawal.

Based on the Medical Research Council Antiepileptic Withdrawal Study Group in 1991, the following factors are
associated with a higher risk of recurrence:

- Age 16 years and older (1.75 relative risk, 95 percent confidence interval 1.30 to 2.35).
- AED polytherapy (1.83 RR, 1.40 to 2.39 CI)
- A history of seizures after starting antiepileptic drug treatment (1.56 RR, 1.19 to 2.04 CI).
- A history of tonic-clonic seizures, primary or secondarily generalized (1.56 RR, 1.09 to 2.22 CI).
- A history of myoclonic seizures (1.84 RR, 1.13 to 3.01 CI).
- An abnormal electroencephalogram in the previous year (1.32 RR, 1.01 to 1.73 CI).

In their 1994 meta-analysis of the literature, Berg and Shinnar3 found an increased risk of recurrence with adolescent (1.79 relative risk, 1.46 to 2.19 confidence interval) and adult (1.34 relative risk, 1.00 to 1.81 confidence interval) onset epilepsy compared to cases that begin in early childhood. In patients with remote symptomatic epilepsy (1.55 relative risk, 1.21 to 1.98 confidence interval) compared to idiopathic epilepsy, and in children with obvious motor deficits, the relative risk increased to 1.79 (1.13 to 2.83 confidence interval). The authors also noted that an abnormal EEG reading was associated with a relative risk of 1.45 (1.18 to 1.79 confidence interval). The definition used here included both epileptiform

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**Tapering Trials in Clinical Practice**

**Case 1:** The patient is a 17-year-old male with a diagnosis of juvenile myoclonic epilepsy (JME) that began at age 13. He has been seizure free on Depakote monotherapy 1000mg TID. He and the parents ask if the medication can be stopped before he begins attending college next year. The only adverse effect from the therapy was a 15-pound weight gain.

What are the issues and risks for this patient? He has been seizure free for greater than three years with monotherapy. Other than the weight gain, he is tolerating the medication. An EEG reveals 4-5 Hz generalized spike and wave complexes.

Patients with JME have one of the highest recurrence risks according to the existing literature, despite it being a readily treatable epilepsy syndrome. Therefore, I would tell the patient and family that he is at extremely high risk for seizure recurrence due to his underlying condition, age of onset and abnormal EEG. However, I also understand the patient’s desire to attempt to stop the medication before attending college. If they wished to proceed despite the increased risk, I would recommend weaning the Depakote by 500mg per week. If he fails, or they decide not to attempt a weaning trial, I would recommend changing to Depakote ER due to the BID dosing, which may improve compliance while at college.

**Case 2:** The patient is a 26-year-old female with a history of complex partial seizures that started at age 15. She has a history of a complicated febrile seizure that started when she was one year old and was treated with phenobarbital for two years. She was seizure-free until she was 15, when she began to have spells associated with an aura of an uneasy sensation in her stomach. These would last for a few seconds and were followed by a period of unresponsiveness, staring and occasionally distal manual automatisms. She was initially treated with phenytoin and carbamazepine; the treatment failed. She currently is controlled with Lamictal monotherapy and has been seizure-free for a year and a half. She presents to the clinic for follow-up and states she is considering having a baby.

What are the issues and risks for this patient? Based on the seizure description, she is suffering from localization-related partial epilepsy, most likely of the temporal lobe. Her EEG reveals intermittent slowing within the left temporal region, and her MRI is normal.

Based on her underlying epilepsy syndrome and short seizure-free interval, she is at an increased risk for recurrence. This conclusion is supported by the abnormal EEG, despite there being no epileptiform activity. However, since she is considering conception a weaning trial should be considered.

The patient needs to be informed of the risks associated with both teratogenicity and seizure recurrence. Luckily, she is controlled with Lamictal monotherapy, which at the present time appears to have the best evidence for minimizing AED toxicity. I typically would reduce Lamictal by 100mg per week and would encourage her to wait several months (the AAN guideline calls for six months) after the medication has been discontinued before attempting conception. If the trial fails or she does not wish to wean her medication, she should continue with her current dose of Lamictal and also take folic acid supplementation.
Tapering AEDs

and non-epileptiform abnormalities. Those with a low incidence of status epilepticus had a high probability of regaining control over their seizures if a recurrence happens.

To detect the presence of these complicating factors, I perform a two-to-three hour EEG on all patients prior to AED withdrawal. This allows me to evaluate the epileptiform and non-epileptiform activity; the results provide invaluable assistance with patient counseling. A structural image, such as an MRI scan, can demonstrate possible epileptic lesions in patients with focal epilepsy, which would indicate a higher risk of recurrence. And an abnormal neurologic examination would increase the risk of recurrence, since it indicates an underlying structural lesion.

Opening Arguments for the Trial

When the candidate is selected, it is important to discuss the risk factors mentioned above with both the patient and the family or caregiver. You should also stress that these are the risks for patients who have been free of seizures for more than two years, and that those who have tapered their regimen after a shorter period may have a greater chance of recurrence. Ultimately, the patient and his or her family will be the ones who weigh the risks of a taper against the consequences of extended treatment and make the decision.

In addition to the effects of medication, many adult patients will be concerned about the possibility of seizure recurrence and its impact on quality of life. You will need to discuss fears of complications that could arise from an episode. This should be weighed against the benefits of discontinuation: no future blood monitoring, no more cognitive side effects associated with AEDs, as well as the loss of other side effects such as weight gain. Patients who complain of their AEDs affecting their sleep or mood should be told how the weaning process could help them regain control over these areas as well.

Patients who are employed and have to drive to their job—and particularly those whose profession involves driving, such as bus drivers, since they are responsible for other people's lives—need to consider the implications seizure recurrence will have on their quality of life and employment. Since most of our patients in this country live in areas with inadequate public transportation, seizure recurrence can trigger mandatory driving restrictions, which would have financial and social implications. You can reassure patients by checking your state laws, as most states have clauses that permit someone to experience a seizure during AED withdrawal and will allow them to continue driving if they resume their medications. I personally ask patients not to drive for several weeks towards the end of the medication withdrawal and immediately after they stop taking the AED, even though I have no evidence to support this practice. A recurrence may impair a patient's ability to perform the primary functions of his or her job and could result in termination, depending on the individual's profession and the employer's understanding of this condition.

After this discussion, some patients ultimately do not want to accept the risks associated and decide to continue treatment. To improve quality of life, the minimum effective dose of a single AED should be prescribed. If long-term toxicity is a concern, this would be a good time to consider changing the patient to a medication with a better outcome or even one of the newer agents.

When a patient on polytherapy says “yes” to a tapering trial, it is best to remove one AED at a time. Most of the drugs (excluding primidone, phenobarbital and benzodiazepines) can be withdrawn over a period of one to two months. I typically withdraw medications such as phenobarbital or benzodiazepines first. These usually take a number of months to stop, depending on the dose. I then begin withdrawing the other agents. I also ask patients to observe seizure precautions and attempt to limit risky behavior for three to six months after the medications have been discontinued.

If a seizure recurs, the trial should be terminated immediately and medications resumed. This assumes the physician initiated a controlled, carefully monitored medication withdrawal. Occasionally, a slower weaning process may be attempted on a second occasion for patients taking phenobarbital.

Controversies and Clear Answers

There are many reasons to have patients on as few AEDs as possible, but unfortunately there are little data that can help us quantify when, exactly, the risk outweighs the problems caused by adverse effects. Until clinicians have more data to work with, the reasons behind tapering will remain controversial and vigorously debated. It often comes down to the patient's individual decision and full awareness of recurrence risks and what a seizure after a period of freedom would mean to them.

When one looks at the complications involved with tapering, it becomes clear that perhaps the best approach is a preventive one—that is, keep the patient on as few AEDs as possible. The fewer treatments needed, the fewer complaints about adverse effects and costs they will have during the course of therapy. PN


Christopher Skidmore, MD is a new addition to the Comprehensive Epilepsy Center at Thomas Jefferson University Medical Center in Philadelphia. His interests include evaluation and treatment of seizures, with specific interests in epilepsy surgery and imaging of epilepsy.