When to Start and Stop Anticonvulsant Therapy in Children

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A large body of evidence has accrued in recent years, allowing a more precise estimate of the risk of seizure recurrence for children with new-onset seizures and for children who stop therapy once they are seizure-free. The primary goal for children with epilepsy is not solely freedom from seizures, but an optimal quality of life. Unless the physician can predict a recurrence risk at the extremes (0% or 100%), the nonmedical factors that affect quality of life will usually dominate the family’s decision making. Together, the physician and family should weigh the risks and benefits of treatment against the risks and benefits of withholding or stopping therapy. Antiepileptic drug treatment should be withheld from most children until they have had a second seizure. Most children who receive antiepileptic drug treatment should attempt to taper their medications after 2 years without seizures.

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Over the last 2 decades, neurologists have gradually come to realize that they may have overestimated the risks of seizure recurrence and underestimated the stigma of epilepsy and the adverse effects of epilepsy treatment. This recognition has led to a more critical assessment of both the need to initiate antiepileptic drug (AED) therapy in children with new-onset seizures and the need to continue AED therapy once it is started. The decision to start and the decision to discontinue AED therapy in children with seizures both entail a similar risk-benefit analysis in which the pros and cons of treatment and withholding treatment are evaluated.

In this decision-making process, patients and their families usually question the probability of whether a seizure will recur. Increasing scientific evidence that has accrued over the last 2 decades has led to better quantification of the likelihood of seizure recurrence.1-12 Unfortunately, many families have difficulty using this information because they do not understand risk-benefit analysis, relative risk, or probability.13 Compounding matters, there is wide variability in risk tolerance, and physicians may not always accurately judge a family’s comfort level with risk.13

The principal issue for children with seizures is quality of life; consequently, total freedom from seizures is not the sole objective.14 To optimize the quality of life, the physician, family, and patient must assess the probability and the consequences of each risk and benefit of treatment vs non-treatment. Families’ interpretations of probabilities and their views of the consequences of these risks and benefits vary widely. Psychological, social, cultural, resource, and religious factors often overshadow medical data. The physician can educate the patient and family about the medical factors affecting an individual’s likelihood of a risk or benefit. The art lies in the application of this information to a particular individual to optimize the quality of life.

STARTING AED TREATMENT

In discussing whether to start AED treatment after a first seizure, one should assume that seizures are not already recurrent or caused by a progressive neurological disorder and that they are not the response of a normal brain to an abnormal condition (i.e., acute symptomatic seizures). In fact, about 75% of patients who...
present with seizures have had more than 1 previous seizure.6 Certain seizures, such as absence or myoclonic seizures, almost always present to the physician as recurrent events and in most instances will be treated from the time they are first recognized. Patients with partial seizures without secondary generalization often have also had unrecognized prior occurrences. Because the recognition and number of nonconvulsive seizures are unreliable, most studies of first seizures are limited to patients with convulsions. Most studies have also excluded patients with progressive neurological disorders or acute symptomatic seizures. The natural history of these conditions and the seizures they cause are different than those of idiopathic or remote symptomatic seizures. Thus, the initial step in caring for the child with a first seizure is to determine whether the seizure is already recurrent or the result of an acute event or progressive neurological disorder.

WITHHOLDING AED TREATMENT: THE RISKS

Withholding therapy from a child with new-onset seizures eliminates the potential for adverse effects of treatment. Seizures, however, are clearly associated with risk. Seizures are universally perceived as an unpleasant and frightening occurrence. Very commonly, seizure occurrence results in negative social consequences for the child and family. In most parts of the world, a seizure is cause for shame or embarrassment, especially in older children. Unfortunately, the stigma of epilepsy may unfairly exclude the child from social interactions or employment. Since social consequences increase with age, adolescents and their families should be encouraged to resolve AED treatment issues prior to beginning driving, starting employment, or other major life transitions.7

Seizures may also result in psychological or physical injury or even death. As a developing being, a child is particularly vulnerable to the psychological impact of seizures. The loss of confidence, self-esteem, and self-sufficiency that may accompany seizures or their treatment may impede psychological maturation. Convulsions or other seizures associated with sudden loss of postural control may cause fractures or lacerations, risks that are lower in children than in adults.12 Prolonged convulsive seizures or status epilepticus may result in other forms of morbidity or even death. Although status epilepticus as the first seizure does not reliably predict a second seizure,4 the potential consequences may be so overwhelming that some families are unable to consider withholding treatment. Even excluding the rare deaths from status epilepticus, there is an increased risk of sudden unexpected death (SUD) for patients with epilepsy (range, 1-3 deaths per year per 1000 patients).15 The higher number of unexpected death (SUD) for patients with epilepsy from status epilepticus, there is an increased risk of sud-

### Table: Relative Risk (RR) of Seizure Recurrence

<table>
<thead>
<tr>
<th>Factor</th>
<th>After First Seizure</th>
<th>After Stopping Anti-epileptic Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of initial unprovoked seizure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 y</td>
<td>NS</td>
<td>1.8 (1.7-1.9)</td>
</tr>
<tr>
<td>Adolescence</td>
<td>NS</td>
<td>2.2 (1.0-4.0)</td>
</tr>
<tr>
<td>Neurologic deficits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental retardation</td>
<td>1.7 (1.1-2.3)†</td>
<td>2.1 (1.5-3.1)</td>
</tr>
<tr>
<td>Motor deficit</td>
<td>2.5 (0.6-7.0)</td>
<td></td>
</tr>
<tr>
<td>Seizures, No. before control</td>
<td>2.5 (1.7-3.3)</td>
<td></td>
</tr>
<tr>
<td>Partial seizures</td>
<td>1.4 (1.3-1.5)‡</td>
<td>0.8 (0.7-0.9)</td>
</tr>
<tr>
<td>Abnormal electroencephalogram</td>
<td>1.9 (1.6-2.1)§</td>
<td>1.9 (0.8-3.7)</td>
</tr>
<tr>
<td>Abnormal imaging</td>
<td>1.7 (1.5-2.8)</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*The RR are taken from studies of children and adults or of children alone.1-2 NS indicates not significant.
†Either motor or cognitive deficits.
‡Idiopathic seizures (no known brain abnormality; RR, 1.5 [1.3-1.6]) or remote symptomatic seizures (known brain abnormality; RR, 1.6 [1.3-2.1]).
§Idiopathic seizures (RR, 1.7 [1.2-2.2]) or remote symptomatic seizures (RR, 1.3 [1.2-1.4]).

in preventing bad outcomes is necessary before the family and patient can make an informed decision.

Fortunately, the more extreme consequences (ie, injury or death) are very unusual and most seizures are short-lived, with only transient impairments. The likelihood of these risks occurring hinges on the probability of seizure recurrence. In the past, AED therapy was usually recommended, since the probability of seizure recurrence was assumed to be high. Estimates in the literature of recurrence risk after an initial seizure vary dramatically, ranging between 23% and 71%.1,3 A recent, large, well-controlled study found the risk of seizure recurrence within 5 years after an initial unprovoked seizure to be only 33%.2 Even the occurrence of a second seizure did not guarantee additional seizures, since about 25% of these patients never had a third seizure.

Study design has also varied in important ways in investigations of first seizures. Some studies included patients with multiple seizures on the same day or status epilepticus as the first event,4 while another did not.5 Another recent study went to great lengths to exclude non-epileptic events,3 which may account for the somewhat higher 2-year relapse risk of 54%.

The major medical factors that influence the risk of recurrence after the first seizure are provided in the Table. Children with neurologic abnormalities, partial seizures, epileptiform activity on electroencephalogram (EEG) (especially generalized spikes and waves), and siblings with seizures are at the greatest risk for seizure recurrence.1,6 Patients with multiple seizures or status epilepticus are more likely to suffer a recurrence only if they have also had a prior brain insult.1,4 One study found that the occurrence of Todd paralysis increased the risk of recurrence substantially (relative risk, 3.1).4 Combinations of risk factors may be additive; for example, patients with remote symptomatic seizures and an abnormal EEG may have an especially high recurrence risk (65%).1 Sex and a family history of seizures are not consistently predictive. The physician can use the absence or pres-
ence of these risk factors to either emphasize or de-emphasize the probability of seizure recurrence when counseling the family and patient.

The consequences of a seizure recurrence must also be considered. If the first seizure occurs in someone with benign epilepsy with centrotemporal spikes, the physical consequence is probably minor, and many physicians and families may elect to withhold AED treatment. If the first seizure is status epilepticus, the consequence is more likely to be viewed by the family as major, so the family would be less likely to agree to withhold AED treatment.

**STARTING AED TREATMENT**

**The Benefits**

The presumed benefit of AED treatment is freedom from seizures, but how likely it is that a patient’s seizures will be completely controlled after therapy is started? Frequently, families wrongly assume that this is certain. In a study comparing seizure recurrence in treated and untreated children who had a single seizure, treatment significantly reduced the risk of recurrence, but 25% of children had a second seizure within 2 years of starting AED treatment.

Although medications are usually successful in suppressing seizures, if AED treatment were shown to alter the natural history of epilepsy, we would have a compelling reason to initiate AED therapy early. It is frequently speculated that seizures may be self-perpetuating, which leads one to question whether AED treatment could interrupt the process. Unlike rodents, there is little evidence that something akin to a kindling phenomenon occurs in most seizures in humans. Focal seizures in the limbic system may display a course that is similar to kindling in rodents. In these cases, we know that uncontrolled seizures do have a course of worsening seizures and progressive behavioral and cognitive problems. Unfortunately, even in the animal model of kindling, most of the older AED therapies do not prevent kindling, even if they suppress kindled seizures. Treatment of patients with head injuries with AED therapy prevents seizures but does not prevent the development of later epilepsy. Among patients with up to 10 seizures prior to initiating AED treatment, the number of seizures before starting AED therapy did not affect the likelihood of becoming seizure-free, the number of seizures after starting AED therapy, or the seizure recurrence rate after discontinuation of AED therapy. For these reasons, if kindling occurs in humans, it occurs only with uncontrolled partial seizures, it may require more than 10 seizures, and current AED treatment may not prevent its occurrence. Current evidence would not support the risk of kindling as a justification for AED therapy.

**The Risks**

The risks of AED treatment include unpleasant physical effects, adverse cognitive and behavioral changes, and potential teratogenicity. In addition, all medications are expensive, stigmatizing, and a nuisance. For some patients, certain medications (especially the newer drugs) may not be options at all, owing to their prohibitive cost.

The probability that a patient will experience adverse effects is uncertain, but the consequences of these effects are usually minor and infrequently necessitate stopping medication. Rarely, patients experience catastrophic adverse effects, such as hypersensitivity reactions or bone marrow or liver failure. For some families, even a tiny risk of catastrophic consequences eliminates a medication from consideration.

Frequently, the diagnosis of epilepsy remains uncertain after initial investigation. Given the low probability of injury, the real possibility of bothersome consequences of AED treatment, and the remote possibility of catastrophic consequences of AED treatment, most patients with possible seizures can be observed off therapy until the diagnosis is clear, rather than embarking on a diagnostic trial of therapy.

**CONTINUED AED TREATMENT**

**The Benefits**

Having made the judgment to treat and having reached seizure remission, one should then reassess the need to continue therapy. This decision is made largely on the basis of the risk-benefit analysis described above. With continued treatment there is a certain comfort and security of the known; however, there is a significant risk of seizure recurrence even while receiving AED treatment. In a recent study, 22% of patients who had been seizure-free for at least 2 years when randomized to continued treatment had additional seizures over the subsequent 2 years. Thus, one cannot be certain that ongoing therapy will ensure freedom from seizures, even if seizure recurrence is less likely with continued treatment.

**The Risks**

The risks of continued treatment include some of the risks of taking AEDs that were cited above, except that rather than estimating the likelihood of adverse effects, a patient and family have real experience with effects of an AED. However, some adverse effects may only become apparent in retrospect after drug therapy is stopped. Some idiosyncratic adverse events that were possible at the outset, such as drug allergy, are no longer of concern when considering discontinuation of AED therapy.

**STOPPING AED TREATMENT**

**The Benefits**

The benefits of stopping treatment may be large or small depending on a particular patient’s experience. Most of the benefits are obvious. A patient will no longer carry the stigma of epilepsy and will no longer be burdened by the costs, inconveniences, and adverse effects of treatment. For the adolescent, stopping treatment is a bridge toward independence.
The primary risk of stopping AED treatment is the risk of seizure recurrence. Compared with the initiation of AED treatment, there are more data regarding the likelihood of relapse on discontinuation. Although it was once thought to be high, there is now agreement that the likelihood of seizure recurrence is rather low (30%) for patients who have been seizure-free for at least 2 years. Longer periods without seizures before the tapering of AED treatment are associated with a declining risk of relapse. For most patients, the small reduction in the seizure recurrence rate after a 3- or 4-year period without seizures does not justify the risks of extended treatment and may even make the tapering of AED therapy at a later time more difficult.

Most studies indicate that it may be possible to define a more precise risk for a particular patient that is either substantially above or below the general risk. Unfortunately, the studies do not always agree on the significant factors required for relapse. The same factor predicts relapse or successful AED therapy withdrawal or is insignificant in different studies. This should not be terribly surprising considering the differences in inclusion criteria and patient mix. General agreement has been reached on the predictive value of only a few risk factors for seizure recurrence after the tapering of AED therapy.

All studies of AED therapy withdrawal have found that the presence of a cognitive or motor handicap or an abnormal EEG at the time of discontinuation increases the likelihood of seizure relapse (Table). Even for children with cerebral palsy, however, AED therapy withdrawal may not always be associated with a greatly increased risk of seizure relapse. In a recent study, the overall seizure relapse risk in children with cerebral palsy and seizures was only 40% after AED therapy withdrawal following a 2-year period without seizures. Children with spastic diplegia had only a 14.3% relapse rate after AED therapy withdrawal. Children with the onset of seizures before age 2 years or in adolescence also have a higher likelihood of relapse. This is probably because the onset of epilepsy before age 2 years may be associated with structural or metabolic disorders that have strong epileptogenic effects. It is unclear why adolescents have a higher probability of recurrence, although part of this increased risk may be attributed to juvenile myoclonic epilepsy, which has a low potential for remission. Later investigations have not confirmed the effect of some factors on seizure recurrence risk that was suggested in earlier studies, including seizure type, sex, family history, and the number, type, or serum levels of AEDs.

For the minority of patients in whom it is possible, classification by epileptic syndrome may provide the best prediction of relapse risk. Eventually, all patients with benign epilepsy with centrotemporal spikes will have seizure remission. In these patients, age is the most important factor in considering when to discontinue AED therapy. Conversely, nearly all patients with juvenile myoclonic epilepsy will have seizure recurrence if AED therapy is discontinued. No other factor is as robust across studies or predicts such a clear recurrence risk (Table).

Patients with the greatest number of risk factors have the highest rate of relapse. Scoring systems have been devised to assess a particular patient’s risk. These scales have not been widely validated in independent populations and are not often used, which may reflect the limited effect relapse probability has on a family’s decision to stop AED therapy. Unless the predicted risk is at the extremes (0% or 100%), many patients and families are not influenced by these statistics. For most patients, psychological, social, resource, and cultural factors play the most prominent role in decision making, in addition to seizure type and severity.

The discontinuation of treatment almost always induces anxiety, but it is reassuring to know that no deaths or significant morbidity have been reported after AED therapy was stopped. Previously controlled seizures rarely become intractable after the tapering of AED treatment. When a decision is made to discontinue AED treatment, traditionally, medications are tapered. The effect of the duration of the tapering of AED therapy on the likelihood of seizure relapse has been a point of debate. It is clear that barbiturates and benzodiazepines may provoke seizures when abruptly withdrawn, but the evidence to support such a phenomenon with other medications is less certain. Even if it were safe to abruptly discontinue medications, many families would find it more comfortable to gradually wean themselves from the security of AED treatment. We recently showed that the probability of seizure recurrence after a relatively short, 6-week tapering of medication is equivalent to the risk after a longer, 9-month period of medication tapering. The advantages of a shorter period of medication tapering include lower medication expenses, a shorter period of restriction, and a more expedient adjustment to whatever the outcome may be.

CONCLUSIONS

Many questions remain about starting or stopping AED therapy in children with seizures. There is some evidence that the requirement that a child be without seizures for 2 years before AED therapy withdrawal could be reduced to 1 year or 6 months for some patients. Individual factors or improved scoring systems may be devised to more precisely predict the need for AED treatment after the first seizure and to predict when one should consider tapering a medication. The precise prognosis predicted by a diagnosis of benign epilepsy with centrotemporal spikes or juvenile myoclonic epilepsy encourages further work with epilepsy syndrome classification. Perhaps clinical neurophysiological techniques can be developed to better identify epileptogenic potential and therefore the need to start or continue AED therapy. The development of a treatment that alters the natural history of epilepsy would revolutionize our approach to therapy. For patients who suffer adverse effects, it would be useful to know that the dosage of medications could be reduced without jeopardizing seizure control once epilepsy has gone into remission. Answers to these questions and a more precise definition of the risks and benefits of AED treatment will require large, collaborative multicenter studies, which have rarely been performed.
It is clear that the decision to start or stop AED therapy must be individualized. For patients with most seizure types, treatment is usually deferred until the second seizure has occurred. Even then, AED therapy may be deferred if there has been a long interval between seizures or if the seizure type is known to be benign. Treatment is typically continued for 2 years in a patient who is seizure-free, at which point medications are tapered over 6 weeks. Perhaps a shorter duration of treatment can be recommended for patients with bothersome adverse effects, for a benign seizure type, or for a family with a high tolerance for risk, as well as for patients whose conditions are easily controlled and who have few risk factors for recurrence. A longer duration of treatment may be necessary for those with extraordinary risk for recurrence or low tolerance for risk.

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REFERENCES