



Antiepileptic drug therapy in younger patients: when to start, when to stop

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SUMMARY

Decisions about whether and how long to treat seizures in children and adolescents should be based on rational criteria and knowledge of the natural history of epileptic syndromes, rather than on the presumption that all seizures should be treated at any cost.

KEY POINTS

Prospective studies of children with a first unprovoked seizure suggest that the risk of recurrence is low and depends primarily on the etiology. In idiopathic seizures, abnormal electroencephalographic findings and a family history of epilepsy are valuable predictors of recurrence. In seizures associated with an identifiable brain pathology (“remote symptomatic seizures”), predictors of recurrence include a partial seizure and a history of febrile seizures. Status epilepticus presenting as a first seizure does not increase the risk of seizure recurrence. ■ Most children with a single unprovoked seizure do not require long-term antiepileptic drug (AED) therapy, since fewer than 50% will develop recurrent seizures (epilepsy). ■ Most children and adolescents with epilepsy will become seizure-free with appropriate AED treatment. Recent studies suggest that AEDs can be discontinued successfully in many after a seizure-free interval of 2 years.

INDEX TERMS: EPILEPSY; SEIZURES; RECURRENCE
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MEDICAL OPINION regarding seizures in children and adolescents is shifting to a more “hands-off” approach, in which medications are prescribed more selectively—and discontinued sooner. This change is based on evidence that some assumptions that guided clinical decision-making in the past may have been wrong. This paper will review the literature and offer guidelines for starting and stopping antiepileptic drug (AED) therapy in young patients.

HOW CURRENT CONCEPTS EVOLVED

Until recently, four axioms guided the medical management of seizures: 1) seizures are harmful and can be deadly, 2) seizures lead to more seizures, 3) AEDs prevent seizure recurrence, and 4) AEDs are harmless. Over the past two decades, these conceptions have been challenged and, to a large extent, refuted. Many early reports were based on “regrettably scanty” records and observations.¹ The bulk of these reports emanated from tertiary care institutions treating intractable epilepsy, which created a large selection bias.²

DEFINING THE TERMS

A “clinical” seizure is a sudden, abnormal neuronal discharge associated with altered behavior.³ A “provoked” seizure has a known proximate cause (eg, fever), in contrast to an “unprovoked” seizure, which has no known proximate cause.

The term “unprovoked first” seizure is often used operationally for an initial unprovoked seizure as well as for all subsequent seizures occurring within 24 hours.⁴ “Status epilepticus” is any seizure or seizures lasting 30 minutes or more, without return to baseline neurologic function.

“Epilepsy” denotes a tendency for recurrent, unprovoked seizures⁵; most clinicians reserve the term for two or more unprovoked seizures. “Remote symptomatic” seizure signifies seizures tied to a known neurologic disorder (ie, the seizures are a symptom of a disorder such as a brain malformation or cerebrovascular accident); “idiopathic epilepsy” does not have a known cause.

ARE SEIZURES HARMFUL?

The once-popular notion that seizures are dangerous and even deadly has given way to a view that they are more benign, at least for a large proportion of patients.

Physical injuries associated with seizures do occur and include falls, broken teeth, fractures, dislocations, lacerations, bruises, and burns. The overall mortality rate is increased in patients with epilepsy.^{3,6-9} However, brief seizures are probably harmless, and even prolonged seizures rarely cause brain damage unless they are associated with an acute neurologic insult.^{10,11}

While status epilepticus can cause brain damage or death,¹² and has been said to be fatal in 2.5% to 6% of patients,³ in children it is associated with a remarkably low rate of morbidity and mortality.¹¹ The degree to which patients with prolonged seizures might suffer subtle deficits in higher cognitive function is unknown. The National Collaborative Perinatal Project found no difference in mental performance between children with epilepsy and their nonepileptic siblings.¹³ No study has clearly demonstrated an adverse effect on intellectual function in most patients with epilepsy.¹⁴

Patients are rarely violent during¹⁵ or between seizures³; indeed, prisoners with epilepsy are no more likely than their nonepileptic peers to have commit-

TABLE 1

RISK FACTORS FOR RECURRENCE AFTER A FIRST, UNPROVOKED SEIZURE IN CHILDREN AND ADOLESCENTS

Definite risk factors
Neurologic abnormality
Risk factors within subgroups
Abnormal electroencephalographic findings (idiopathic cases)
Partial seizures (remote symptomatic cases)
Febrile seizures (remote symptomatic cases)
Family history (idiopathic cases and with abnormal electroencephalographic findings)
Minimal or no effect
Age
Todd's paresis
Duration of seizure
Status epilepticus
Antiepileptic drug prescription (on intention-to-treat analysis)

ted serious crimes.¹⁶ All seizure types can lead to motor vehicle accidents; predisposing factors include long driving periods, driver fatigue, and photic stimulation.¹⁷ In one study, the accident rate for seizure patients was slightly greater than for the general population.¹⁸

DO SEIZURES BEGET SEIZURES?

In studies of epilepsy in Rochester, Minn, the percentage of patients seizure-free for 5 years steadily increased over time: 42% within 6 years of diagnosis, 61% within 10 years, and 70% within 20 years.¹⁹⁻²¹ A survey of 122 adults and children found that, 15 years after seizure onset, more than 80% had been seizure-free for 2 or more years.^{22,23} These numbers indicate relatively high rates of long-term remission.

Risk of recurrence after a first unprovoked seizure

In various studies, the overall likelihood of a child having a second seizure ranged from 27% to 62%,^{2,24-29} but the high estimates came from studies that included children who already had recurrent seizures.^{26,28} Retrospective studies of first seizures have reported a recurrence risk of 48% to 52%.^{25,27} The risk in prospective studies that excluded children with previous seizures ranged from 27% to 40%,^{24,29} and these figures seem the most accurate. *Table 1* summarizes the risk factors for recurrence after a first seizure. The combination of more than one risk factor may have prognostic importance.

An ongoing Italian study is trying to determine whether starting AED therapy after a first seizure will improve the long-term prognosis in some types of epilepsy.³⁰ The predominant view at present, however, is that the risks outweigh the benefits. As Camfield and Camfield¹⁷ point out: “Regardless of the risk of recurrence, however, the potential adverse effects of daily medication in children who have had only one seizure outweigh concerns of injury or psychosocial consequences.” Currently, neurologists rarely recommend starting AEDs after only one seizure. However, if the patient or family would be emotionally unable to cope with a second seizure, some physicians would prescribe an AED “to treat the parents’ concerns,” and gradually taper the dosage after several seizure-free months.

Seizures recurring within a short interval require prompt assessment and treatment. One should also bear in mind that the study by Shinnar et al²⁹ deliberately excluded several types of epilepsy, including neonatal seizures, absence epilepsy, infantile spasms, Lennox-Gastaut syndrome, and myoclonic epilepsy. These types present as multiple seizures, and treatment, when indicated, is begun at the first opportunity. However, in general it is safe to conclude that, in children, there is a low recurrence risk after a first unprovoked seizure, contrary to the historical notion that seizures beget seizures. Long-term AED therapy may not be necessary in many cases.

Risk of recurrence after two or more unprovoked seizures

By the time patients come to a physician, 60% or more have already experienced two or more seizures.¹⁹ After two unprovoked seizures, the recurrence risk is 80% to 90%.^{24,27} The predominant view is that this high recurrence rate does not reflect seizures inducing further seizures, but rather indicates that some individuals are seizure-prone and are aptly described as having epilepsy. Because the recurrence risk is high, AED therapy is indicated in most children or adolescents who have had two or more unprovoked seizures.

DO AEDs PREVENT SEIZURE RECURRENCE?

Prescribing medication after an unprovoked first seizure does not significantly lower the recurrence rate in children or adults.^{24,27-29} In fact, in some studies, the risk of seizure recurrence has been higher in

persons for whom AEDs were prescribed.^{20,25} How could this be?

One answer is that many studies described the physician’s intent to treat, not actual treatment.⁴ In many cases, an apparent therapeutic failure may be caused by an inadequate serum level of the AED.³¹ Yet in one study of 82 children with newly diagnosed epilepsy, 42% had recurrent seizures despite good medical compliance.²⁷ Of 622 adults with previously untreated epilepsy, only 38% attained complete control within the first year of medication.³²

On the other hand, Mussico and colleagues³³ found that AEDs reduced the incidence of recurrent seizures. In a randomized study in Italy of 397 subjects who had a first tonic-clonic seizure, the recurrence risk at 2 years was 2.8 times higher in untreated patients.³⁰ In another, small study, in which children received maintenance AED therapy with “therapeutic” blood levels, carbamazepine lowered the recurrence risk after a first unprovoked seizure compared with no medication.³⁴

It is unclear whether the type of medication has a major influence on recurrence risk. Employing the drugs of choice for certain seizure types presumably could lower the recurrence rate.

ARE AEDs HARMFUL?

The most frequent adverse effects of AEDs are neurotoxic and are seen when the drug is started, when the dosage is rapidly escalated, or shortly after the drug is ingested.³⁵ These include sedation, behavioral changes, tremor, vertigo, diplopia, nystagmus, ataxia, dysarthria, and gastrointestinal complaints. About 15% of all patients have a reaction to the first AED sufficient to warrant stopping the drug.^{27,32} The estimated risk of a truly severe reaction to an AED—including unpredictable, idiosyncratic reactions—is about 1 in 30 000.¹⁷ In these cases, another AED may need to be used, bringing with it another, new set of side effects.

Different risk factors may apply for different age groups. For example, children younger than 2 years who take valproic acid may be at increased risk of hepatotoxicity. Metabolic rates are different at different ages.³⁶ Epileptic children have an average intelligence quotient 10 points lower than do children without epilepsy, but this is primarily due to antecedent neurological abnormalities.³⁷ Nevertheless, the effects of AEDs on cognitive function and behavior appear to be largely deleterious.³⁸⁻⁴⁴

Teenage girls have a high rate of unplanned pregnancy, and AEDs typically exert their teratogenic effects in the initial weeks of gestation, before the pregnancy is detectable.^{45,46} Ironically, some AEDs may inhibit the action of oral contraceptives. AEDs cause malformations in 4% to 6% of pregnancies,⁴⁷ most commonly cleft lip or palate, spina bifida, and urogenital anomalies. In addition, AEDs have been implicated in causing mutagenic malformations in offspring of epileptic men.³ The degree of this risk for adolescent males is uncertain.

GUIDELINES FOR INITIATING AED THERAPY

After a first unprovoked seizure

A diagnostic workup is essential to firmly establish that the event was in fact a seizure (since many treatable disorders mimic seizures),^{48,49} to search for treatable causes (eg, arteriovenous malformation), to classify the seizure type (for eventual AED selection),⁵⁰ and to determine the prognosis. The basic diagnostic workup should include a history and physical examination and laboratory tests (when indicated). The key to the diagnosis and treatment of epilepsy is the patient's history.⁵¹ Initial laboratory tests might include EEG monitoring,⁵² brain neuroimaging (if focality is suspected),⁵³ blood tests, and special tests.

We do not treat a first seizure per se. Nearly all children and most adolescents should *not* start long-term AED therapy after a first seizure. Status epilepticus or flurries of seizures will prompt short-term AED therapy, but this can often be discontinued without untoward effect. However, long-term treatment of a first seizure should be considered in special situations (*Table 2*).

After two or more unprovoked seizures

AED therapy should almost always be recommended after two or more unprovoked seizures, as the recurrence rate is high in this situation. However, there are certain possible exceptions. Very infrequent seizures may not merit long-term AED therapy. Benign rolandic epilepsy carries a relatively good prognosis, and many neurologists feel comfortable withholding medication for this condition. Some physicians might not want to recommend AEDs for all simple partial seizures, but many of these focal-onset seizures subsequently show evidence of generalization.¹⁷ Finally, strong patient or parental objection may veto AED therapy.

TABLE 2
WHEN TO CONSIDER
ANTIPILEPTIC DRUGS FOR A FIRST SEIZURE

Short-term therapy
Prolonged seizures
High-risk patients
Long-term therapy
When recurrence would be hazardous (eg, in an adolescent driver)
Parental insistence
Neurodegenerative disease
Terminal illness
Absence epilepsy*
Myoclonic epilepsy
Infantile spasms
Lennox-Gastaut syndrome*

*Typically present after multiple seizures

When AEDs are indicated, one must select the appropriate agent, bearing in mind the seizure type, drug efficacy, and potential side effects for the particular patient. Certain AEDs necessitate baseline tests such as a complete blood count and liver function tests.

Patient and parent education

As McNaughton⁵⁴ noted, "Whenever a diagnosis of epilepsy has been made, there is need for an intelligent, long-term view of the problem by the patient and his or her family. A little time given to general discussion and the answering of questions at the onset of treatment may save [one from] serious mistakes and misunderstanding later." *Table 3* summarizes important points to discuss with the patient and the family.

AED therapy: the first few weeks

Many neurologists start with a relatively low dose of an appropriate AED, gradually increasing and adjusting it as necessary. Monotherapy is highly preferable to polytherapy.^{34,55} Doses of drugs such as carbamazepine need to be increased slowly to allow hepatic enzymatic induction.⁵⁶ Although some neurologists check the serum level of an AED early in the course of therapy,⁵⁷ we rarely recommend this unless the patient is continuing to have seizures or if noncompliance is suspected.³¹ Indeed, the optimal plasma level may vary for different patients and may even fall outside the therapeutic range.⁵⁸

Side effects, when they do occur, often appear early in AED therapy. The physician must be aware of diagnostic and therapeutic measures for severe

TABLE 3
GUIDELINES FOR PATIENT AND PARENT EDUCATION

Provide reassurance
Use understandable terms
Give specific and clear instructions
Explain the risks and benefits of treatment
Discuss side effects
Mention advantages of brand name vs generic drugs
Caution against using another person's AED
Discuss relative interactive effects
Address compliance issues
Warn against discontinuing AEDs suddenly
Suggest wearing an identifying bracelet
Give information about driving
Talk about informing others
Minimize limitations
Give sources for further education (Epilepsy Foundation of America: 800-EFA-1000)

reactions such as Stevens-Johnson syndrome or valproic acid-induced hepatotoxicity.³⁵ High-risk patients should be followed up closely.

Factors other than drug manipulation can be of great importance early in the course of treatment. As Holmes⁵⁹ points out: "...the pharmacological treatment of children with epilepsy is only one component of the management. Psychological, educational, and social complications in epilepsy are just as important as treating the patients. Failure to address these problems will result in a treatment program failure, regardless of whether seizures are controlled."

Prognosis

Whether early and ongoing medication and seizure control can alter the long-term prognosis is controversial. The longer active epilepsy remains uncontrolled, the worse the outlook.^{60,61} Only about 60% of patients whose seizures remain uncontrolled 1 year after diagnosis will become seizure-free, declining to about 10% of patients whose seizures remain uncontrolled for more than 4 years,⁶⁰ and to fewer than 5% of patients whose seizures remain less than fully controlled after 10 years.¹⁴ Frequent generalized tonic-clonic seizures and multiple seizure types are associated with lower remission rates.^{21,62} Monotherapy will suffice in about 70% of patients, and another 10% to 25% can achieve control with

polytherapy.^{3,14,63} Prompt referral of patients who have intractable seizures to tertiary epilepsy centers for medical or surgical therapy or both may improve their long-term prognosis.⁶⁴⁻⁷⁰

WHEN TO STOP AED TREATMENT

General considerations

Hauser¹⁴ reviewed the literature and concluded that 60% to 70% of all patients with epilepsy will enter remission, and AEDs can be withdrawn in 40% to 90% of them without seizures recurring. Gross-Tsur and Shinnar² found that seizure-free children whose medications are withdrawn stand a 65% to 90% chance of remaining seizure-free.

Continuing AED therapy in seizure-free patients for very long periods exposes them to long-term drug side effects without clear benefit. Interestingly, certain behaviors and functions may actually improve after AEDs are withdrawn.⁷⁰⁻⁷³ Successful withdrawal of AEDs may eliminate other problems as well. Some epilepsy patients have a poor self-image and an increased sense of distress⁷⁴; many are glad to lose the epilepsy "label." Other potential advantages may include removing the limits on driving, employment, and health insurance.

The risks of discontinuing AED therapy primarily involve seizure recurrence and seizure-related sequelae. Significant injury from a brief, recurrent seizure is relatively rare.² The risk of status epilepticus is very low after gradual AED withdrawal.

In children, the main impact of seizure recurrence is psychological.⁴ Older adolescents may lose their driving privileges temporarily. Economic aspects, such as job dismissal (which might be illegal), may need to be considered.

If seizures recur, restarting medication works well. Todt⁷⁵ found that 86% of children who relapsed became seizure-free again with the original medication. Seizure control is regained promptly in virtually all patients who relapse.^{71,72}

Risk factors for seizure recurrence after AED withdrawal

The Medical Research Council randomized 1013 patients to continue to receive medication or to have it withdrawn.⁷⁶ By 4 years, 25% of patients whose medication was maintained had recurrent seizures, as opposed to 45% of previously seizure-free patients who underwent AED withdrawal. Possible risk factors for recurrence are shown in *Table 4*.

Guidelines for stopping AED therapy

Owing to the known side effects of AEDs, the relatively low risks involved, and the likelihood of success in AED withdrawal, it appears advisable to “aggressively pursue withdrawal of medication in children who are seizure-free for 2 or more years,” and one should consider an attempt at AED withdrawal at least once in most children and adolescents “regardless of risk factors.”⁷⁴ The concerns of the patient and the parents should be addressed. In light of prognostic uncertainty, the clinician should arrive at a withdrawal plan jointly with the patient and family.

There are a few possible exceptions to prompt AED withdrawal. An adolescent engaged in driving or other activities in which seizure recurrence would be dangerous may have to continue taking medication. Children and adolescents with high-risk medical conditions or neurodegenerative processes may have to continue AED therapy beyond 2 years. Age-specific forms of epilepsy, such as generalized absence seizures, may merit treatment until adolescence. Steroids and adrenocorticotrophic hormone, prescribed for infantile spasms, may need to be tapered slowly. Occasionally, the patient or family will strongly favor early discontinuation. In such cases, a slow tapering of the AED, coordinated by the physician, is preferable to a sudden discontinuation by the patient.

A patient who has a recurrence of unprovoked seizures soon after AED discontinuation should restart the AED previously felt to be most effective in his or her case. There are no current guidelines as to whether or when to consider a second attempt at AED withdrawal after recurrence.

Epilepsy will remain intractable to medication in approximately 5% to 10% of all patients.¹⁴ Identifying these patients early can allow early referral to physicians and centers specializing in intractable epilepsy,⁷⁷ and prompt consideration of alternatives such as newer medications,^{78,79} experimental AED protocols,⁸⁰⁻⁸⁴ and surgery for suitable candidates.^{66,85} When to withdraw AEDs after epilepsy surgery in seizure-free patients is controversial.⁸⁶

CONCLUSION

In the past, epilepsy “has been complicated by years of ignorance, injustice, intolerance, and gross misinformation.”⁸⁷ More rigorous studies and ra-

TABLE 4
RISKS FACTORS FOR RECURRENCE AFTER ANTIEPILEPTIC DRUG WITHDRAWAL IN CHILDREN AND ADOLESCENTS

Definite risk factors
Identifiable cause, neurologic abnormality
Abnormal electroencephalographic findings
At onset
At discontinuation (idiopathic cases)
Multiple seizure types
Age at onset ≥ 12 years
Possible risk factors
Duration of antiepileptic drug therapy
Duration of active epilepsy
Duration of seizure-free period
Number of seizures
Seizure type
Partial
Myoclonic
Any generalized
Polypharmacy
Rapid medication withdrawal
Minimal or no effect
Age at discontinuation
Sex
Race
Socioeconomic status
Family history of seizures
Serum drug level at discontinuation
Type of medication

tional approaches to the initiation and cessation of AED therapy could benefit millions of people. The “decade of the brain” has witnessed further extraordinary advances in neuroscience and areas of clinical concern. Technology and cost-effectiveness must be coupled both with a strong desire to benefit the individual with epilepsy, and with persistent diligence. As epilepsy research enters the 21st century, it would be worthwhile to remember the words of Gowers⁸⁸ in 1881:

“The management of many of these cases of chronic convulsive disease is a task of difficulty, requiring the utmost patience and perseverance on the part of both the patient and the physician. The old power of casting them out has gone from the earth, and it is only by the study of their origin and history, and careful experiment in their treatment, that we can hope to regain over them such power as may still be possible to man.”

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