



Recurrence, remission, and relapse of seizures

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- **BACKGROUND** Approximately 6% of the population will experience at least one afebrile seizure in their lifetime.
- **OBJECTIVE** To review the prognostic factors and clinical implications for recurrence, remission, and relapse of seizures.
- **SUMMARY** Antiepileptic drug treatment reduces the risk of recurrence after a first seizure by about half, but these drugs cause a variety of adverse effects. The risk of recurrence is higher in the presence of neurologic or electroencephalographic abnormalities or if the seizure is partial as opposed to generalized. Neurologic abnormalities and partial seizures also reduce the probability of remission. Gradual drug withdrawal can be considered if the patient has been in remission for 2 years in the absence of any negative prognostic indicators.
- **CONCLUSIONS** When deciding whether to begin or discontinue antiepileptic drug therapy, clinicians should consider the risks and possible benefits for the individual patient.

- INDEX TERMS: EPILEPSY; SEIZURES; RECURRENCE
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EPILEPSY is characterized by a spontaneous tendency to recurrent seizures, which are paroxysmal events resulting from excessive neuronal discharge in the central nervous system. The annual incidence (number of new cases) of epilepsy, defined as two or more afebrile, unprovoked seizures, is about 50 per 100 000 in the United States.¹ Sex-specific incidence rates show that more males get epilepsy than females do by a factor of between 1.1 and 1.5. The prevalence (number of cases present at one point in time) of epilepsy, defined as seizure activity or antiepileptic drug treatment in the past 5 years, was 6.8 per 1000 in the 1980 data from Rochester, Minnesota.²

Not all patients who suffer a seizure will develop epilepsy. The annual incidence of all afebrile seizures is 84 per 100 000.¹⁰ This rate exceeds that of epilepsy because up to one third of all seizures occur only once in the lifetime of the patient. If we assume a life expectancy of 70 years, the cumulative incidence of afebrile seizures predicts that some 6% of the population will experience at least one afebrile seizure in their lifetime.

TABLE 1
PROSPECTIVE STUDIES OF RECURRENCE AFTER A FIRST AFEBRILE SEIZURE

Investigator	Year	N	Age group	Interval to entry	Therapy	Recurrence (%)	
						1 year	4 to 5 years
Hopkins et al ⁴	1988	306	Adults	< 8 wk	14	37	52
Camfield et al ⁶	1989	31	Children	< 1 mo	No treatment 17 Carbamazepine 14	53 14	...
Hauser et al ³	1990	208	Mixed	< 24 h	80%	14	34
Shinnar et al ⁵	1990	283	Children	< 24 h	9%	26	42
FIRST Group ⁷	1993	397	Mixed	< 1 wk	No treatment 193 Treatment 204	41 17	...

TABLE 2
PROGNOSIS FOR SEIZURE REMISSION IN STUDIES FROM EPILEPSY CLINICS

Investigator	Year	Country	N	Age (y)	Seizure-free duration (y)	Follow-up (y)	Remission (%)
Turner ¹¹	1907	England	212	...	2	...	33
Alström ¹²	1950	Scandinavia	512	...	5	> 10	22
Strobo ¹³	1959	USA	228	...	1 to 2	2 to 15	38
Juul-Jensen ¹⁴	1963	Denmark	969	> 16	2	> 2	32
Kuhl et al ¹⁵	1967	Denmark	173	> 17	4	4 to 7	34
Rodin ¹⁶	1968	USA	90	32

RECURRENCE

From a clinical point of view, it is important to know the risk of recurrence after a first seizure and to identify patients at risk for recurrent seizures. Earlier retrospective studies reported a wide range of recurrence rates, from 27% to 71%. These differences were probably related to any of a number of methodological deficiencies in study design. Several prospective studies³⁻⁵ (Table 1) of seizure recurrence after a first unprovoked afebrile seizure were subsequently performed. The design of these studies had been improved in that patients were enrolled early, within a day to a few weeks of a first seizure; however, the decision whether to treat with antiepileptic drugs was still made nonrandomly based on clinical judgment. In these studies the probability of seizure recurrence at 1 year ranged from 14% to 37%, and at 4 to 5 years from 34% to 52%.

Two recent studies randomly assigned patients to receive either treatment or no treatment.^{6,7} Both studies showed that antiepileptic drug treatment reduced the risk of recurrence after a first unprovoked seizure. In the Italian First Seizure Trial Group study,⁷ the cumulative risk of recurrence at 1 year was 17% with treatment compared with 41% without treatment. At 2 years the risk was 25% with

treatment compared with 51% without treatment, and the calculated risk ratio was 2.8.

The longer the follow-up period, the higher the ultimate recurrence rate will be. However, most recurrences happen in the first year, if they happen at all, and more than 80% of recurrences happen within 2 years.⁸ Once a second seizure has occurred, the risk for further recurrences exceeds 90%.⁹

In childhood, the risk of recurrence after a first afebrile seizure provoked by an acute metabolic or neurologic illness is 23%, only one third of that for children with unprovoked seizures (69%).⁹

Prognostic factors for recurrence

Numerous risk factors for recurrent seizures have been identified. In an extensive meta-analysis, Berg and Shinnar⁸ concluded that three discriminant factors were the most important predictors of recurrence. First, evidence of a neurologic abnormality such as a known injury, a symptomatic etiology, a neurologic deficit, or mental retardation carries a risk ratio of 1.8. Second, epileptiform abnormalities on electroencephalography (EEG) carry a risk ratio of 1.3. Third, partial seizures (as opposed to generalized ones) carry a risk ratio of between 1.0 and 1.6. A history of neonatal seizures may also increase the risk of recurrence.

TABLE 3
PROGNOSIS FOR SEIZURE REMISSION IN POPULATION-BASED STUDIES

Investigator	Year	Population source	N	Age group	Seizure-free duration	Follow-up (y)	Remission (%)	Remission (y)
Annegers et al ¹⁷	1979	Community	457	All	5	10 to 20	61	10
Sofijanov ¹⁸	1981	Clinic	512	<14y	4	4 to 10	42	7
Okuma et al ¹⁹	1983	Clinic and hospital	1868	All	3	3 to 10	58	10
Goodridge and Shorvon ²⁰	1983	Family practice	122	All	2	...	56	5
Brorson and Wranne ²¹	1987	Community	194	< 20y	3	12	64	12
Shafer et al ²²	1988	Community	432	All	5	> 5	58	10

The probability of recurrence is higher when two or more risk factors are found. A patient with a neurologic abnormality (remote symptomatic etiology) and epileptiform EEG patterns has a 65% risk of recurrence, compared with 24% in a patient with an idiopathic seizure and normal EEG findings.

Clinical implications

In the investigation of a first seizure, EEG is the modality that has the highest yield: it will show some abnormality in 40% of such patients, and a specific epileptiform pattern in 25%.^{4,5} In contrast, computed tomography and magnetic resonance imaging studies of the brain detect structural abnormalities in only 5% of these patients.⁴ A previously unsuspected brain tumor is found in 4% to 5% on investigation of a first seizure.^{4,7} Laboratory studies of blood are usually uninformative, and cerebrospinal fluid analysis is not indicated unless specific indications exist.

When deciding whether to initiate antiepileptic drug therapy, one should weigh the risk of recurrence against the risk of adverse effects from antiepileptic drugs, and also consider personal factors unique to the patient. Although antiepileptic drug treatment, started early, effectively reduces the risk of seizure recurrence by about half, these drugs can cause a variety of allergic, systemic, neurological, and cognitive adverse effects. An acute symptomatic (provoked) seizure usually calls for correction of the underlying derangement instead of drug treatment, unless the patient's medical state is so critical that another seizure would be life-threatening. A brain lesion that is likely to persist, such as a tumor, clearly indicates treatment. If one or more risk factors are present, I recommend starting drug treatment after first discussing fully the risks and benefits of such treatment with the patient. Once treatment is agreed on, it should be continued for at least 1

year. If the patient is free of recurrence over this interval, treatment can then be withdrawn. If no risk factors can be found, it seems prudent to observe without treating.

REMISSION

A prolonged seizure-free interval constitutes a state of remission. Remission may occur "naturally" without treatment, but this is unusual. Practically no information is available on the prognosis of natural remission without treatment. Gowers¹⁰ wrote in 1881 that "the spontaneous cessation of the disease is an event too rare to be reasonably anticipated."

Just how many seizure-free years constitutes a remission has not been agreed upon. Most studies have specified a minimum of 2 years, but many have specified up to 5 years. A study with a longer follow-up is more likely to yield a higher remission rate. Studies based on patients from referral clinics (Table 2)¹¹⁻¹⁶ show a lower rate of remission than studies of patients identified from the community (Table 3),¹⁷⁻²² because the former have a higher proportion of patients with intractable epilepsy.

Two studies (Table 4)^{23,24} of patients with newly diagnosed and previously untreated epilepsy who began treatment with single-drug antiepileptic regimens revealed the highest rate for remission of any published studies to date: between 80% and 90% of patients had attained a 2-year remission at 5 years.

Prognostic factors of remission

Two important factors for seizure recurrence also influence the probability of remission: the presence of a neurological abnormality reduces the chance of remission,^{17,19,23} and the outcome for patients with partial seizures is less favorable than for those with generalized seizures.^{14,16,17,19,23}

The role of EEG in predicting the chances for

TABLE 4
SEIZURE REMISSION IN NEWLY DIAGNOSED
AND PREVIOUSLY UNTREATED EPILEPSY: PROSPECTIVE STUDIES OF MONOTHERAPY

Investigator	Year	N	Age group	Seizure-free period (y)	Remission at 5 y (%)
Elwes et al ²²	1984	106	All	2	79
Beghi et al ²⁴	1992	280*	All	2	92

remission is inconclusive. Well-preserved background rhythms and the absence of epileptiform abnormalities were associated with better outcome in some studies.^{14,19,22} However, improvement or deterioration in serial EEG studies neither guarantees nor precludes long-term remission.^{23,24}

An age younger than 16 years at onset of epilepsy may improve the chance of remission.^{17,19} However, very early onset (before 1 year of age) may be an unfavorable factor.^{13,19} The severity of seizures (as reflected in frequency, occurrence of generalized convulsions, and multiple seizure types) affects remission adversely.^{14,16,19,23,24}

The early course of the response to treatment predicts the later probability of remission. The probability of remission is halved if seizures continue for 2 years after starting treatment.²³ Similarly, a relapse in the first year of treatment reduces the likelihood of eventually attaining remission.²⁴

Clinical implications

Recent studies show that single-drug treatment is appropriate and effective in the vast majority of patients with newly diagnosed epilepsy. Once treatment is decided upon, it should be monitored rigorously because the early course of treatment may determine later outcome. An alternative explanation for this trend is that seizures that are more difficult to bring under control simply reflect more severe underlying brain dysfunction, irrespective of the intensity of treatment.

Patients who have persistent seizures for more than 5 years despite adequate treatment with available antiepileptic drugs are not likely to enter prolonged remission later. These patients may benefit from investigational antiepileptic drugs, and from evaluation for possible surgical treatment.

RELAPSE

A relapse of seizures can occur either with continued treatment or after discontinuation of antiepileptic drugs. Twenty-two percent of patients who had

been in remission for 2 years suffered relapse over the next 2 years despite continued treatment in the Medical Research Council antiepileptic drug withdrawal study.²⁵ Undoubtedly, a sizeable proportion

of relapses during treatment is the result of noncompliance with medication regimens, estimated at approximately 60% in one study.²³

After patients have been seizure-free for a number of years, there are good reasons why they and their physicians may question the need for continued drug treatment. Discontinuation of medication is still the only method to ascertain if active epilepsy is present. Furthermore, chronic antiepileptic medications have side effects, are costly, and carry a social stigma.

In most studies, antiepileptic medications were withdrawn after a minimum remission period of 2 to 5 years. The relapse rate has been approximately 40% for adults (Table 5),²⁵⁻³⁰ and 30% in children (Table 6).³¹⁻³⁶ The 1991 Medical Research Council trial²⁵ randomly assigned 1013 patients to continue treatment or withdraw from drugs over 6 months. By 2 years, 22% of patients continuing treatment and 41% of patients withdrawing from treatment suffered relapses.

Prognostic factors for relapse after drug withdrawal

The presence of a neurologic abnormality increases the risk of relapse.^{31,32,35} The length of remission is inversely correlated with the risk of relapse.^{25,33} The risk of relapse for someone who has been seizure-free for 5 years before discontinuing drug treatment is half that of someone who has been free of seizures for only 2 years. Other indices of seizure activity, such as the duration of treatment, the number of antiepileptic drugs, and the frequency of seizures before control is achieved, also increase the risk of relapse.^{25,30-33} The value of EEG in predicting the risk of relapse is not clear-cut. Epileptiform EEG abnormalities increased the relapse rate in some^{30,33,34,36} but not all studies.^{25,29,32} In other studies, patients were selected for drug withdrawal only if their EEG studies were normal.

Relapses can occur both during and after drug withdrawal, and there is little reason to analyze these conditions separately in this review. Indeed, about 50% of relapses can be expected to occur

TABLE 5
RELAPSE AFTER ANTIEPILEPTIC DRUG DISCONTINUATION IN ADULTS OR MIXED POPULATIONS

Investigator	Year	N	Remission period (y)	Withdrawal interval	Follow-up/endpoint (y)	Relapse (%)
Juul-Jensen ²⁶	1968	196	> 2	2 to 3 mo	5	40
Janz and Sommer-Burkhardt ²⁷	1976	85	> 2	Years	0.5 to 21	37
Oller-Daurella et al ²⁸	1976	138	> 5	Years	0.5 to 27	21
Overweg et al ²⁹	1987	62	> 3	Months	> 2	66
Callaghan et al ³⁰	1988	92	> 2	6 to 12 mo	0.5 to 5	34
MRC ²⁵	1991	510	> 2	> 6 mo	2	41*

*Actuarial probability at stated endpoint

TABLE 6
RELAPSE AFTER ANTIEPILEPTIC DRUG DISCONTINUATION IN CHILDREN

Investigator	Year	N	Remission period (y)	Withdrawal interval (mo)	Follow-up/endpoint (y)	Relapse (%)
Emerson et al ³¹	1981	68	4	2 to 3	4	31*
Thurston et al ³²	1982	148	> 4	3	15 to 23	28
Todt ³³	1984	433	> 2	1 to 12	> 3	36
Shinnar et al ³⁴	1985	88	> 2	2 to 3	2	23*
Arts et al ³⁵	1988	146	> 2	4 to 6	2	17*
Matricardi et al ³⁶	1989	425	> 2	...	2	14*

*Actuarial probability at stated endpoint

during drug withdrawal.^{25,29} The risk is highest in the first year, when 80% of all relapses take place.³¹⁻³³ After 3 years, further relapses become unlikely.

Whether the rapidity of drug withdrawal affects the risk of relapse remains unsettled.^{33,37} In most studies, drugs were withdrawn over periods ranging from 4 weeks to 6 months or more. Possibly, more rapid drug withdrawal simply brings on seizures sooner in patients who are destined to relapse in any case. Medications should not be withdrawn abruptly. Abruptly stopping barbiturates and benzodiazepines can cause a withdrawal syndrome complicated by generalized seizures, even in patients without prior epilepsy.

Clinical implications

The decision to discontinue antiepileptic drugs must take into account personal factors specific to the individual concerned. The specifics of the epilepsy syndrome should also be considered. A youngster who has benign epilepsy of childhood with Rolandic spikes can be expected to enter spontaneous and long-term remission by the age of 16 to 17 years.^{38,39} Withdrawing medication at that time is clearly to be encouraged. On the other hand, a patient with a cerebral arteriovenous malformation should probably continue treatment even if seizures

have stopped for some time. Likewise, a patient with juvenile myoclonic epilepsy is likely to require long-term treatment because of the high rate of relapse after discontinuing medication.⁴⁰

In general, withdrawing medication can be reasonably considered after a 2-year seizure-free period in the absence of any negative prognostic indicator. If adverse indicators are identified, a 5-year seizure-free period may be preferred. Drugs can be withdrawn over 2 to 6 months. If the patient is taking more than one drug, it would seem sensible to withdraw one drug at a time, although no specific guidelines are available. Patients will require follow-up for at least 1 year. If seizure relapse takes place, there is every reason to expect prompt response to the same medication that had previously controlled the seizures, without jeopardy to the long-term course of the disease.

SUMMARY

The clinician should weigh the risks and possible benefits to the individual patient when deciding to initiate or discontinue antiepileptic drug treatment. Treatment with drugs reduces the risk of recurrence after a first seizure by about half. However, the drugs can cause adverse effects that many pa-

tients find intolerable, and many patients do not comply with their medication regimen. If no risk factors for seizure recurrence are present, it seems prudent to continue to observe the patient without treating. If risk factors are present, the clinician should discuss the situation with the patient at length before proceeding with treatment.

Single-drug treatment is effective in the majority of patients with newly diagnosed epilepsy, as 80% to 90% can be expected to achieve 2-year remission. If the patient has remained seizure-free for at least 2 years, it is reasonable to consider gradually withdrawing medications while continuing to closely observe the patient for relapses.

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