

Practice Parameter:

A guideline for discontinuing antiepileptic drugs in seizure-free patients—Summary Statement

Report of the Quality Standards Subcommittee of the American Academy of Neurology

The Quality Standards Subcommittee of the American Academy of Neurology (AAN) develops practice parameters for neurologists pertaining to diagnostic procedures, treatment modalities, and clinical disorders. The selection of topics is based on prevalence or frequency of use; potential for improving health outcomes; and reducing variations in practice patterns, economic impact, and adequacy of scientific evidence. Whether and when to withdraw antiepileptic drugs (AEDs) is a common problem in the management of patients with epilepsy. This decision is often made in the absence of data. The following guideline is intended to help physicians in their decisions to withdraw AEDs.

Definition of the problem. When a patient with a history of epileptic seizures has remained seizure-free for a period of years, the question arises whether to continue or reduce AEDs. The decision to withdraw AEDs is often made in the absence of data; choice of patients and timing of the discontinuance are often not based on well-defined criteria.

This problem has been the subject of many retrospective and prospective investigations. Criteria for selecting patients to study and the procedures for ensuring continued follow-up vary greatly. Thus, results of these investigations are not uniform and are not easily compared. Even in prospective studies, it is not possible to control all factors relevant to discontinuance of medication. Nevertheless, the documented experiences presented in these studies are useful in constructing a guide to practice.

Description of the process. We conducted a MEDLINE search for the years 1967 to 1991 using the key words "discontinuance of antiepileptic drugs," "prognosis of epilepsy," "relapse/recurrence," and "remission." Studies of both children and adults were included and were considered separately. We reviewed all articles in their entirety, attempting to identify common factors relating to the probability that a patient no longer on medication would remain seizure-free. We identified 53 studies that discussed these factors.

Of the 53 studies, 52 were class II studies (see Definitions following this article) and 1 was a class I study. The nine factors or clinical characteristics we identified were sex, age of onset, seizure type, etiology, neurologic examination/I.Q., duration of seizure freedom on AEDs, treatment regimen, age at relapse, and normalization of the EEG. Only 17 studies discussed all nine factors. The negative health outcome is relapse, and the positive is the seizure-free patient without medication. Patients maintained on reduced dose of medication were not included.¹⁻³ The relapse rates reported in the 17 studies are summarized in the table. Relapse rates reported in each of the 17 studies were weighted according to the number of cases in that study.

Conclusions. An analysis of the studies yielded a weighted mean (by number of cases) relapse rate of 31.2% for children and 39.4% for adults. From the studies, certain clinical characteristics emerged that may predict successful remission. The longer the duration of seizure control with AEDs, the better the prognosis.⁴⁻⁶ The evidence presented in the 17 studies suggests that although their recurrence risk rates differ, both children and adult patients meeting the following profile have the greatest chance for successful drug withdrawal:

- Seizure-free 2 to 5 years on AEDs (mean 3.5 years);
- Single type of partial or generalized seizure;
- Normal neurologic examination and normal I.Q.;
- EEG normalized with treatment.

Recommendations. The data in studies demonstrate that children meeting the above profile can be expected to have at least a 69% chance and adults a 61% chance for successful withdrawal (weighted average of all studies including adults and children in the table). (The 31.2% relapse rate in children and 39% in adults refers to all patients studied. Data were not presented in sufficient detail to ascribe a probability rate to patients meeting the profile, but

Approved by the Quality Standards Subcommittee on July 17, 1994; the Practice Committee on July 29, 1994; and the Executive Board on September 24, 1994.

Received March 5, 1995. Accepted January 15, 1996.

Address correspondence and reprint requests to the American Academy of Neurology, 2221 University Ave, SE, Suite 335, Minneapolis, MN 55414.

Table Studies on withdrawal of antiepileptic drugs in children and adults

Study	Study type	N	Seizure-free with Rx	Follow-up after withdrawal (yr)	Relapse rates (yr)
Children					
Emerson et al. ⁷	Ret	68	4.9	0.5–6	18 (26%)
Holowach-Thurston and O'Leary ⁵	Ret	148	4.0	15–23	41 (28%)
Foerster and Schmidtberger ⁸	Ret	114	4–5	0.5	35 (31%)
Todt ⁶	Pros	433	4.0	5–6	157 (36%)
Shinnar et al. ⁹	Pros	88	2–4	0.5–6	22 (25%)
Shinnar et al. ¹⁰	Pros	264	1.4	2.5	95 (36%)
			(2.9 mean)		
Bouma et al. ¹⁴	Pros	116	2.0	5.0	26 (22%)
Arts et al. ¹¹	Pros	146	2.0	1–10	37 (25%)
Pooled relapse rate for children		1377			
431 (31.2%)					
Adults					
Juul-Jensen ¹⁵	Ret	196	2–4	5–6	79 (40%)
Janz and Sommer-Burkhardt ¹⁶	Ret	253	2	5	124 (49%)
Oller-Daurella et al. ¹	Ret	138	5	5–27	29 (21%)
Oller-Daurella et al. ²	Ret	228	5	10–30	69 (30%)
Overweg et al. ³	Ret	46	3	0.75–1.6	29 (63%)
Overweg et al. ³	Pros	62	3	0.5–0.75	41 (66%)
Callaghan et al. ⁴	Pros	92	2	0.5–5	31 (24%)
Chadwick ¹²	Rand	503	2–4	5	206 (41%)
Dean and Penry ¹³	Pros	62	4	5	15 (24%)
Pooled relapse rate for adults		1580			
623 (39.4%)					
Pooled relapse rates for adults and children		2957			
					1054 (39.4%) weighted mean

Ret = retrospective study; Pros = prospective study; LT = long-term follow-up; Rand = randomized controlled study.

we can assume that when the factors most likely to be associated with successful withdrawal are present, the relapse rate would be less than 31.2% for children and 39% for adults.)

Drug withdrawal should be offered to patients who meet this profile and who have complied with treatment. The adult patient, a child's family, and the physician should make the decision together, taking into account not only the medical factors, including the statistical probability for relapse but also the social, emotional, or other consequences should relapse occur. Evidence reported in the literature, expert opinion, and the results described in a 1991 consensus conference at Bowman Gray School of Medicine support the following recommendation that we present as a **guideline** (see Definitions), based on the strength of evidence:

After assessing the risks and benefits to both patient and society from a recurrent seizure, the discontinuance of antiepileptic drugs may be considered by the physician and informed patient or parent/guardian if the patient meets the following profile:

- **Seizure-free 2 to 5 years on AEDs (mean 3.5 years);**
- **Single type of partial seizure (simple partial or complex partial or secondary generalized tonic clonic seizure) or single type of primary generalized tonic clonic seizures;**
- **Normal neurologic examination/normal I.Q.;**
- **EEG normalized with treatment.**

Although the likelihood and consequences of seizure recurrence may differ, this recommendation to consider AED withdrawal applies to both children and adults. Discontinuance of AEDs may be appropriate in patients *not* meeting this profile even though the risk of recurrence may be higher than 31.2% for children and 39% for adults.

Recommendations for future research

1. Multicenter randomized double-blind controlled prospective trials are needed to better define the

risk of relapse for individual patients (adults and children).

2. The effects of the number of AEDs used, duration of treatment producing freedom from seizure, and measurement of serum levels need to be studied in patients considered candidates for withdrawal.

Acknowledgments

The Quality Standards Subcommittee wishes to express its gratitude to Jay H. Rosenberg, MD, who facilitated this project and wrote the practice parameter.

Quality Standards Subcommittee: Michael K. Greenberg, MD, Chair; Milton Alter, MD, PhD; Thomas N. Byrne, MD; Jasper R. Daube, MD; Gary Franklin, MD, MPH; Michael L. Goldstein, MD; Michael K. Greenberg, MD; Douglas J. Lanska, MD; Shrikant Mishra, MD, MBA; Germaine L. Odenheimer, MD; George Paulson, MD; Richard A. Pearl, MD; Jay H. Rosenberg, MD, Past Chair; and James Stevens, MD.

Note. This statement is provided as an educational service of the AAN. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

Definitions

Classification of evidence

Class I: Evidence provided by one or more well-designed randomized controlled clinical trials.

Class II: Evidence provided by one or more well-designed clinical studies such as case-control studies, cohort studies, and so forth.

Class III: Evidence provided by expert opinion, non-randomized historical control subjects, or one or more case reports.

Strength of recommendations

Standards: Generally accepted principles for patient management that reflect a high degree of clinical certainty (i.e., based on class I evidence or, when circumstances preclude randomized clinical trials, overwhelming evidence from class II studies that directly addresses the question at hand or from decision analysis that directly addresses all the issues).

Guidelines: Recommendations for patient management that may identify a particular strategy or range of management strategies and that reflect moderate clinical certainty (i.e., based on class II evidence that directly addresses the issue, decision

analysis that directly addresses the issue, or strong consensus of class III evidence).

Practice options/advisories: Other strategies for patient management for which there is unclear clinical certainty (i.e., based on inconclusive or conflicting evidence or opinion).

Practice parameters: Results, in the form of one or more specific recommendations, from a scientifically based analysis of a specific clinical problem.

Medical societies and others invited to review and provide comment on this practice parameter:

Epilepsy Foundation of America; American Epilepsy Society of America; American Academy of Family Physicians; American Society of Internal Medicine (IMCARE); Ten members of the American Academy of Neurology Member Reviewer Network.

References

1. Oller-Daurella L, Pamies R, Oller FV. Reduction of discontinuance of antiepileptic drugs in patients seizure-free for more than 5 years. In: Janz D, ed. *Epileptology*. Stuttgart: Thieme, 1975:218-277.
2. Oller-Daurella L, Oller FV, Pamies R. Clinical, therapeutic and social status of epileptic patients without seizures for more than five years. In: Penry JK, ed. *Epilepsy, Eighth International Symposium*. New York: Raven Press, 1977:69-75.
3. Overweg J, Rowan AJ, Binnie CD, Oosting J, Nagelkerke NJD. Prediction of seizure recurrence after withdrawal of antiepileptic drugs. In: Dam M, Gram L, Penry JK, eds. *Advances in epileptology: XIIth Epilepsy International Symposium*. New York: Raven Press, 1981:503-508.
4. Callaghan N, Garrett A, Goggin T. Withdrawal of anticonvulsant drugs in patients free of seizure for two years. *N Engl J Med* 1988;318:942-946.
5. Holowach-Thurston DL, O'Leary J. Prognosis in childhood epilepsy. *N Engl J Med* 1972;286:69-74.
6. Todd H. The late prognosis of epilepsy in childhood: results of a prospective follow-up study. *Epilepsia* 1984;25:137-144.
7. Emerson R, D'Souza BJ, Vining EP, et al. Stopping medication in children with epilepsy. *N Engl J Med* 1981;304:1125-1129.
8. Foerster C, Schmidtberger G. Prognosis in childhood epilepsy after discontinuation of therapy. *Monatschr Kinderheilk* 1982; 130:225-228.
9. Shinnar S, Vining EPG, Millits ED, et al. Discontinuing antiepileptic medication in children with epilepsy after two years without seizures. *N Engl J Med* 1985;313:976-980.
10. Shinnar S, Berg AT, Moshe SL, et al. Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. *Ann Neurol* 1994;35:534.
11. Arts WFM, Visser LH, Loonen MCB, et al. Follow-up of 146 children with epilepsy after withdrawal of antiepileptic therapy. *Epilepsia* 1988;29:244-250.
12. Chadwick D. Randomized study of AED withdrawal in patients in remission. Medical Research Council, AED Withdrawal Study Group. *Lancet* 1991;337:1175-1180.
13. Dean JC, Penry PK. Remission and relapse in chronic epilepsy [abstract]. *Epilepsia* 1990;31:648.
14. Bouma PAD, Peters ACB, Arts RJHM, et al. Discontinuation of antiepileptic therapy: a prospective study in children. *J Neurol Neurosurg Psychiatry* 1987;50:1579-1583.
15. Juul-Jensen P. Frequency of recurrence after discontinuance of anticonvulsant therapy in patients with epileptic seizures. A new follow-up after 5 years. *Epilepsia* 1968;9:11-16.
16. Janz D, Sommer-Burkhardt EM. Discontinuation of antiepileptic drugs in patients with epilepsy who have been seizure-free for more than two years. In: Janz D, ed. *Epileptology: Proceedings of the Seventh International Symposium on Epilepsy*, Berlin (West). Stuttgart: Thieme, 1976:228-234.