

TO STOP OR NOT TO STOP THE AED?

Consequences of Antiepileptic Drug Withdrawal: A Randomized, Double-Blind Study (Akershus Study). Lossius MI, Hessen E, Mowinckel P, Stavem K, Erikssen J, Gulbrandsen P, Gjerstad L. *Epilepsia* 2008;49:455–463. **OBJECTIVE:** Despite side effects associated with the use of antiepileptic drugs (AEDs), withdrawal of AEDs remains controversial, even after prolonged seizure freedom. The main objective of this study was to assess the effects of AED withdrawal on cognitive functions, seizure relapse, health-related quality of life (HRQOL), and EEG results. Additionally, potential predictors for freedom from seizures after AED withdrawal were studied. **METHODS:** Patients, seizure-free for more than 2 years on AED monotherapy, were recruited for a controlled, prospective, randomized, double-blinded withdrawal study lasting for 12 months, or until seizure relapse. Patients were randomized to AED withdrawal ($n = 79$) and nonwithdrawal ($n = 81$) groups. The examination program included clinical neurological examinations, neuropsychological testing, EEG-recordings, cerebral MRI, and assessments of HRQOL. Follow-up data on seizure relapse were also collected beyond the 12-month study period (median 47 months). **RESULTS:** Seizure relapse at 12 months occurred in 15% of the withdrawal group and 7% of the nonwithdrawal group (RR 2.46; 95% CI: 0.85–7.08; $p = 0.095$). After withdrawal, seizure relapse rates were 27% after a median of 41 months off medication. A normal result to all 15 neuropsychological tests increased significantly from 11% to 28% postwithdrawal. We found no significant effects of withdrawal on quality of life and EEG. Predictors for remaining seizure-free after AED-withdrawal over 1 year were normal neurological examination and use of carbamazepine prior to withdrawal. **CONCLUSION:** Seizure-free epilepsy patients on AED monotherapy who taper their medication may improve neuropsychological performance with a relative risk of seizure relapse of 2.46, compared to those continuing therapy.

COMMENTARY

Approximately two-thirds of patients with new-onset epilepsy become seizure-free when treated with antiepileptic drugs (AEDs) (1). In a portion of these patients who maintain prolonged remission, it is possible to withdraw AED therapy. The study by Lossius et al. adds additional information to help clinicians inform patients of the risks and benefits, when trying to make the decision as to whether to withdraw AEDs. Even when prior studies have been prospective and randomized, they have been open label. Lossius et al. conducted a well-controlled prospective, randomized, double-blind investigation assessing not only the effects of AED withdrawal on the risk of seizure relapse but also on possible changes in cognitive functions.

A critical review of 28 studies encompassing 4,571 patients noted that the risk of seizure relapsed after AED withdrawal ranged from 4 to 34% at 1 year and 9 to 39% at 2 years (2). The findings of Lossius et al. are similar to the largest single study of AED withdrawal, which was conducted by the Medical Research Council (MRC) from 1984 to 1988 (3). Lossius and colleagues found that the risk of seizure relapse in patients who withdrew AEDs was about double the risk of patients who continued AEDs at the end of 1 year (i.e., 15% vs 7% at the end

of the double-blind period). In comparison, the MRC study, which included 1,031 patients, found that the risk of seizure recurrence was doubled at the end of 2 years (i.e., 41% vs 22%) (3). Since patients who were not in the AED withdrawal group in the first year of the Lossius et al. study were offered withdrawal after the 1 year double-blind period, data on recurrence with continued AED therapy are not available from their report after the first year; however, the AED withdrawal group can be compared to the MRC study. In fact, seizure recurrence at the end of 2 years in the AED withdrawal groups is remarkably similar (i.e., 19% in the present study vs 22% in MRC study). Further, a meta-analysis published in 1994 found that the risk of seizure relapse after AED withdrawal was 29 percent at 2 years (95% confidence intervals [CI], 24%, 34%) (4). In both studies and both reviews cited above, the large majority of seizure relapses occurred in the first 12 months, with the risk of seizure relapse thereafter being very similar, especially after 2 years, for the withdrawal and continued AED treatment groups.

Various factors may affect the risk of seizure relapse, although there is some controversy as to the importance of specific issues. Average risks may not be relevant to an individual patient, as epilepsy is a heterogeneous disorder (5). Thus, some patients will require AEDs for continued control of seizures, whereas prolonged AED treatment for others may be unnecessary. For example, up to 90% of patients with juvenile myoclonic epilepsy will relapse if AEDs are withdrawn, but children with

benign rolandic epilepsy usually remit permanently. A multivariate analysis of the MRC study found that the risk of seizures with AED withdrawal increased with specific factors including: age > 16 years, seizures only on awakening, myoclonic seizures, more than one AED, seizures after the start of AED therapy, and shorter seizure-free periods on AEDs (5). Other factors that have been found to increase the risk of seizure relapse include syndrome (e.g., juvenile myoclonic epilepsy), mental retardation, and abnormal neurological exam (2). Lossius et al. found that risk was reduced in patients with a normal neurological exam and in those withdrawing from carbamazepine. Interestingly, a similar finding for carbamazepine was seen in the MRC study, although the reason for the finding remains obscure (6). The lack of AED dose and blood level data in these studies may create variance in the results. Investigations have yielded mixed results on the risks related to age of onset and to duration of epilepsy. The role of EEG also has been inconclusive; however, many studies have lumped abnormal EEG findings, so distinct factors cannot be identified. One might expect that well-formed spike wave complexes, especially occurring in runs, would suggest a higher risk than poorly formed sharps or slowing. Unfortunately, EEG in the present study was only assessed for change and was not included in the analysis of possible predictors of seizure relapse. Hippocampal atrophy and sclerosis on MRI have been shown to increase the risk of relapse (7), but other types of MRI abnormalities have not been adequately studied. In addition, the certainty of the original diagnosis is another factor that might impact the risk of seizure relapse. Lossius et al. found that the presence of an MRI abnormality did not predict seizure relapse, but they did not analyze types of MRI abnormalities separately.

How long should a patient be seizure free before considering AED withdrawal? A Cochrane review concluded that there is evidence to support waiting ≥ 2 years with children; however, the optimal time period remains uncertain in adults (8). Note that most adult studies have been conducted in patients who are ≥ 2 years seizure free. The MRC study did find that a shorter duration of the seizure-free period increased risk of seizure relapse after AED withdrawal (3).

Does the rate at which the AED is tapered affect risk of relapse? A recent Cochrane review did not come to any reliable conclusion on the optimal taper rate (9). Of course, some AEDs (e.g., phenobarbital) require slow taper to avoid withdrawal seizures. Further, many physicians choose to taper slowly, based on the concept that if relapse occurs during the taper, the seizure may be less severe than after full withdrawal.

The risks associated with AED withdrawal (e.g., injury or loss of driving privileges) need to be balanced against the risks and cost of long-term AED therapy. Risks associated with long-term AED use include cognitive and behavioral side effects, osteopenia/osteoporosis, connective tissue abnormalities, weight

gain, drug interactions (e.g., altered effectiveness of other drugs affected by AEDs), anatomical and behavioral teratogenesis in the children of women with epilepsy, and other untoward side effects. The study by Lossius et al. investigation found that AED withdrawal resulted in a modest improvement in cognitive functions. The magnitude of the cognitive effect was similar to prior studies (10) that examined the older AEDs employed in the Lossius et al. study. Although modest, these effects can be clinically significant (10). Given that several of the newer AEDs possess fewer cognitive effects (10), the benefit may not exist on withdrawal.

The decision to withdraw an AED in a patient who is seizure-free is ultimately one that has to be individualized and undertaken with the patient fully informed of the risks and benefits. The decision needs to take into account the known risk factors, the possible benefits of withdrawal, the certainty/uncertainty of our present data, and the individual patient's psychosocial factors. Additional blinded, randomized, controlled trials are needed to identify the optimal timing of AED withdrawal, further delineate the risk factors, and determine the risk/benefit ratios for the newer AEDs.

by Kimford J. Meador, MD

References

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314–319.
2. Specchio LM, Beghi E. Should antiepileptic drugs be withdrawn in seizure-free patients? *CNS Drugs* 2004;18:201–212.
3. Medical Research Council Antiepileptic Drug Withdrawal Group. Randomized study of antiepileptic drug withdrawal in patients in remission. *Lancet* 1991;337:1175–1180.
4. Berg AT, Sinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. *Neurology* 1994;44:601–608.
5. MRC Antiepileptic Drug Withdrawal Study Group. Prognostic index for recurrence of seizure after remission of epilepsy. *BMJ* 1993;306:1374–1378.
6. Chadwick D, MRC Antiepileptic Drug Withdrawal Study Group. Does withdrawal of different antiepileptic drugs have different effects on seizure recurrence? *Brain* 1999;122:441–448.
7. Cardoso TAM, Coan AC, Kobayashi E, Guerreiro, Li LM, Cendes F. Hippocampal abnormalities and seizure recurrence after antiepileptic drug withdrawal. *Neurology* 2006;67:134–136.
8. Sirven JI, Sperling M, Wingerchuk DM. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *Cochrane Database Syst Rev* 2001(3):CD001902.
9. Ranganathan LN, Ramaratnam S. Rapid versus slow withdrawal of antiepileptic drugs. *Cochrane Database Syst Rev* 2006;(2):CD005003.
10. Meador KJ. Cognitive effects of epilepsy and of antiepileptic medications. In: Wyllie E., ed. *The Treatment of Epilepsy. Principles and Practices, 4th Edition*. Philadelphia: Lippincott Williams & Wilkins, 2005:1185–1195.