Antiepileptic Drug Withdrawal: Literature Review

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Of patients with epilepsy, 60% to 70% achieve control with antiepileptic medication. Antiepileptic drugs may be associated with unwanted adverse effects, inconvenience, and cost. Remission may occur in some patients, raising the issue of whether continued treatment is necessary. Identifying patients from whom treatment can be withdrawn successfully would be beneficial on many levels, but selecting patients may be difficult. Several published antiepileptic drug withdrawal studies show variable rates of success, with relapse rates ranging from 12% to 63%.

Several prognostic factors help identify patients who may be amenable to antiepileptic drug withdrawal. The results and limitations described in the antiepileptic drug withdrawal literature, prognostic factors, and general guidelines for antiepileptic drug withdrawal are presented in this article.


Epilepsy is a common condition with a cumulative incidence of 3.0% through age 74 years, according to data obtained from the Olmsted County, Minnesota, population.1 However, epilepsy is not a lifelong condition in all patients. A total of 60% to 70% of patients will experience a 5-year remission on medication.2,3 In a seizure-free patient, the issue may arise as to whether medication is still needed, given the adverse effects, cost, stigma, and inconvenience associated with antiepileptic drug therapy. In contrast, the decision to withdraw antiepileptic medication has implications for patient safety, driving privileges, employment, and liability. Indeed, the decision to stop treatment is in many ways more difficult than the decision to start it.4 This review presents the reasons prompting consideration of antiepileptic drug withdrawal, relapse rates found in the literature, predictive factors, risks, and guidelines for antiepileptic drug withdrawal. Several antiepileptic drug withdrawal studies were reviewed in preparation of this article (Table 1).5-33 Although the existing literature does not allow an algorithmic approach to antiepileptic drug withdrawal, it is hoped that this article will facilitate the counseling of patients who request advice regarding this issue.

REASONS TO CONSIDER ANTEPILEPTIC DRUG WITHDRAWAL

Adverse Effects

Adverse effects are common in the treatment of patients with epilepsy. In one survey, 31% of patients taking antiepileptic drugs reported adverse effects, of which 53% were deemed clinically important.34 In a meta-analysis of clinical studies evaluating the newer antiepileptic drugs, patients enrolled in treatment arms of the studies were 1.4 to 4.2 times as likely to drop out compared with those assigned to a placebo.35 Although the risk of life-threatening adverse drug reactions is low, adverse effects that negatively impact quality of life, such as dizziness, fatigue, and memory difficulties, are common. Adverse changes in behavior and personality have been attributed to antiepileptic medication, prompting some professional organizations to recommend the timely withdrawal of these drugs in patients in whom a reasonable chance of remission exists.36 Establishing the degree to which a medication contributes to a perceived change in behavior and cognition is often difficult because other factors, such as seizure burden and the presence of any associated central nervous system pathology, may also affect behavior and cognition.37 Indeed, many studies attempting to quantify the degree to which medications affect cognition have been inconclusive.38-41 However, several prospective studies have shown selective improvements in psychomotor speed and alertness after withdrawal of antiepileptic medication.42-46

Teratogenic Risk

For women taking antiepileptic medication, teratogenesis is a major concern. The mechanism of antiepileptic drug teratogenesis is unknown, and no proven preventive therapy exists. Although studies on this issue show variable rates of associated teratogenic effects, in general, the incidence of major anomalies associated with maternal antiepileptic drug use is 4% to 6%, in contrast to a 2% to 3% rate in the general population.47 In a recent study, 20.6% of offspring born to mothers who took antiepileptic medication during pregnancy showed abnormalities in interocular
distance, philtrum length, and distal phalanges length. However, 8.5% of controls showed similar abnormalities in this study, suggesting that these changes may have been subtle in some cases. Nonetheless, major anomalies such as neural tube defects, congenital heart defects, and cleft lip and palate occur at a disproportionate rate in offspring born to mothers taking antiepileptic medication. However, maternal generalized seizure activity also poses a risk to the unborn child. Fetal distress has been documented in association with maternal seizure activity. In the absence of prospective data comparing treatment and no treatment in this population, the physician must weigh the potential risk for relapse in an individual patient with the known risk of teratogenesis. The evidence supports considering antiepileptic drug withdrawal before conception in a woman with few risk factors for relapse, although the pros and cons of the possible consequences need to be clearly discussed with the patient.

**Cost**

The cost of antiepileptic drugs continues to increase, especially with the advent of newer patented medications. The estimated cost of medication for all patients who developed epilepsy in 1995 alone was projected to exceed $500 million over the lifetime of the patients. A patient with epilepsy can easily spend more than $200 to $300 per month for medication. If medication allows a patient to drive or work, then this cost may be offset. However, if suitable patents for medication withdrawal could be identified reliably, substantial health care savings could be achieved.

**Psychosocial Issues**

Daily medication is a constant reminder even to patients with well-controlled epilepsy that they harbor an unpredictable disorder that may recur at any time. Until patients are seizure-free without medication, they may believe that their condition is not controlled. Some patients perceive the need for medication as a vulnerability. Certain medications are associated with undesirable cosmetic effects, such as gum hypertrophy, hirsutism, and weight gain. Also, the responsibility of remembering to take medication on time, calling the pharmacy for refills, packing medication for trips, etc., is viewed by some as adding an unwanted level of complexity to daily life. Neuropsychological improvement may be expected after successful antiepileptic drug withdrawal, although measuring these improvements is logistically difficult from a research standpoint.

**PATIENT AND FAMILY ATTITUDES TOWARD THE RISKS OF ANTEILEPTIC DRUG WITHDRAWAL**

In one survey, 20% of families indicated they would take up to a 75% risk of relapse to see whether antiepileptic medication could be withdrawn from their child. Although this same study also showed that 40% of families would be unwilling to accept a 25% risk, these data indicate that some patients and their families are willing to take what others would regard a considerable risk for the chance to discontinue medication. Of importance, this study did not assess the risk perception in adult patients facing these decisions.

Successful antiepileptic drug withdrawal has been associated with improvements in scales of general satisfaction and quality of life. In one study, which included more than 1000 patients, relapse increased distress. However, only 8% of those who relapsed regretted their decision to attempt withdrawal. Furthermore, those who did not relapse scored much more favorably on scales of satisfaction and self-perception of health than did those who remained seizure-free on medication. Also, patients who relapsed scored no worse on scales of worry and distress compared with patients who remained seizure-free yet never attempted withdrawal.

**OUTCOMES IN CLINICAL STUDIES EVALUATING ANTIEPILEPTIC DRUG WITHDRAWAL**

**Results and Limitations of Antiepileptic Drug Withdrawal Studies**

Many antiepileptic drug withdrawal studies have been published. These studies (summarized in Table 1) have provided valuable information regarding the feasibility of antiepileptic drug withdrawal and have elucidated important risk factors that may be used to identify patients in whom withdrawal is likely to succeed. However, some issues regarding methods need to be recognized when interpreting study results. Many of these studies enrolled a heterogeneous group of patients. For example, some studies contained a mixture of patients with favorable prognoses (such as those with benign childhood epilepsy with centrotemporal spikes or a history of a single seizure and unfavorable prognoses (such as Lennox-Gastaut syndrome and adult-onset partial epilepsy). In other studies, the types of epilepsy present in each cohort were not stated or were not classified in detail, in part because some of these studies were initiated before the development of the International League Against Epilepsy (ILAE) Classification of Epilepsies and Epileptic Syndromes, or at least before its widespread acceptance. Therefore, in some studies several epilepsy syndromes are represented in each cohort, which makes applying these results to particular groups of patients difficult. Berg and Shinnar performed a meta-analysis of the antiepileptic drug withdrawal literature for studies performed before 1994 that addressed many of these methodological differences and nicely summarized the literature up to that time.
<table>
<thead>
<tr>
<th>Published study</th>
<th>No. of patients</th>
<th>Study design</th>
<th>Age group</th>
<th>Relapse rate</th>
<th>Seizure-free duration before withdrawal</th>
<th>Follow-up</th>
<th>Unfavorable risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altunbasak et al.⁵ 1999</td>
<td>97</td>
<td>Retrospective†</td>
<td>Pediatric</td>
<td>21%</td>
<td>2-4 y</td>
<td>2-4 y</td>
<td>Age at onset &gt;2 y, &lt;6-mo taper</td>
</tr>
<tr>
<td>Gebremariam et al.⁶ 1999</td>
<td>80</td>
<td>Prospective</td>
<td>Pediatric</td>
<td>29% vs 36%</td>
<td>18 vs 24 mo</td>
<td>Mean, 24 mo</td>
<td>Abnormal EEG</td>
</tr>
<tr>
<td>Carvode &amp; Herranz⁷ 1998</td>
<td>226</td>
<td>Retrospective†</td>
<td>Pediatric</td>
<td>24%</td>
<td>2 y</td>
<td>Mean, 5.48 y</td>
<td>Neurologic abnormalities; interval between seizure(s) &lt;1 mo at onset; VPA at withdrawal; withdrawal started at age &gt;6 y; abnormal EEG; abnormal neonatal period; age at onset &gt;10 y; mean seizure duration &gt;1 mo; poor school progress; partial seizure</td>
</tr>
<tr>
<td>Peters et al.⁸ 1998</td>
<td>161</td>
<td>Prospective†</td>
<td>Pediatric</td>
<td>49%</td>
<td>6 vs 12 mo</td>
<td>Mean, 41.9 mo</td>
<td>Partial epilepsy; age at onset &gt;12 y; symptomatic etiology; \textit{epileptiform EEG}</td>
</tr>
<tr>
<td>Braathen &amp; Melander⁹ 1997</td>
<td>161</td>
<td>Prospective†</td>
<td>Pediatric</td>
<td>37%</td>
<td>1 vs 3 y</td>
<td>Mean, 5.8 y</td>
<td>Age at onset &gt;10 y; generalized \textit{epileptiform EEG} abnormalities; complex partial seizures</td>
</tr>
<tr>
<td>Dooley et al.¹⁰ 1996</td>
<td>97</td>
<td>Prospective†</td>
<td>Pediatric</td>
<td>22%</td>
<td>&gt;1 y</td>
<td>Mean, 32 mo</td>
<td>Age at onset &gt;10 y; female; partial seizures; neurologic abnormalities</td>
</tr>
<tr>
<td>Tinuper et al.¹¹ 1996</td>
<td>120</td>
<td>Prospective</td>
<td>Adult (partial seizure)</td>
<td>63%</td>
<td>&gt;2 y</td>
<td>3 y</td>
<td>Worsening of EEG during withdrawal</td>
</tr>
<tr>
<td>Donati et al.¹² 1995</td>
<td>82</td>
<td>Retrospective</td>
<td>Pediatric</td>
<td>29%</td>
<td>Mean, 4.7 y</td>
<td>4 y</td>
<td>Age at withdrawal &lt;9 y; complicated febrile convulsions; neurologic abnormalities; developmental delay; focal slowing or \textit{epileptiform discharges on EEG}</td>
</tr>
<tr>
<td>Marticardi et al.¹³ 1995</td>
<td>86</td>
<td>Retrospective†</td>
<td>Pediatric</td>
<td>27%</td>
<td>&gt;0.9 y (mean, 5.6 y)</td>
<td>Mean, 4.8 y</td>
<td>No. of seizures before remission &gt;30; history of febrile seizures</td>
</tr>
<tr>
<td>Murakami et al.¹⁴ 1995</td>
<td>304</td>
<td>Retrospective</td>
<td>Pediatric</td>
<td>13.5%</td>
<td>&gt;3 y</td>
<td>&gt;1 y</td>
<td>Symptomatic etiology; adolescent onset; juvenile myoclonic epilepsy; failure of EEG background to normalize during withdrawal</td>
</tr>
<tr>
<td>Nakazawa et al.¹⁵ 1995</td>
<td>55</td>
<td>Retrospective</td>
<td>All ages</td>
<td>22%</td>
<td>&gt;2 y</td>
<td>Mean, 4.8 y</td>
<td>No relapses; no risk factors; 12 of 55 patients lost to follow-up</td>
</tr>
<tr>
<td>Shunmar et al.¹⁶ 1994</td>
<td>264</td>
<td>Prospective†</td>
<td>Pediatric</td>
<td>36%</td>
<td>Mean, 2.9 y</td>
<td>Mean, 58 mo</td>
<td>Age at onset &gt;12 y; family history; EEG slowing; atypical febrile seizures; severe mental retardation</td>
</tr>
<tr>
<td>Tennyson et al.¹⁷ 1994</td>
<td>133</td>
<td>Prospective (6-wk vs 9-mo taper)</td>
<td>Pediatric</td>
<td>39% for each taper schedule</td>
<td>&gt;2 y</td>
<td>Mean, 39 mo</td>
<td>Mental retardation; \textit{epileptiform EEG} abnormalities</td>
</tr>
<tr>
<td>Gherpelli et al.¹⁸ 1992</td>
<td>70</td>
<td>Prospective</td>
<td>Pediatric</td>
<td>28.5%</td>
<td>&gt;2 y</td>
<td>Mean, 18.5 mo</td>
<td>No. of seizures before remission &gt;10; abnormal EEG, neurologic abnormalities; mental retardation; mixed seizure types</td>
</tr>
<tr>
<td>Mastropaoe et al.¹⁹ 1992</td>
<td>191</td>
<td>Prospective†</td>
<td>Pediatric</td>
<td>22.5%</td>
<td>Mean, 3.4 y</td>
<td>Mean, 3.5 y</td>
<td>Age at onset &gt;4 y; seizure free &lt;2 y; abnormal and \textit{epileptiform EEG}; “sudden” withdrawal</td>
</tr>
<tr>
<td>MRC.²⁰ 1991</td>
<td>1013</td>
<td>Prospective, randomized† (776 declined)</td>
<td>Adult</td>
<td>41%, AED withdrawal 22%, AED continued</td>
<td>Mean, 3.2-3.4 y</td>
<td>NA</td>
<td>Seizure free &lt;3 y before withdrawal; continued seizures despite treatment; &gt;1 AED before withdrawal; generalized tonic-clonic seizures</td>
</tr>
</tbody>
</table>
Table 1. Continued*

<table>
<thead>
<tr>
<th>Published study</th>
<th>No. of patients</th>
<th>Study design</th>
<th>Age group</th>
<th>Relapse rate</th>
<th>Seizure-free duration before withdrawal</th>
<th>Follow-up</th>
<th>Unfavorable risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ehrhardt &amp; Forsythe, 1989</td>
<td>18†</td>
<td>Prospective</td>
<td>Pediatric</td>
<td>12%</td>
<td>&gt;3 y</td>
<td>5 y</td>
<td>Age at onset &lt;3 y; No. of seizures before remission &gt;10</td>
</tr>
<tr>
<td>Gerstle de Pasquet et al, 1989</td>
<td>90</td>
<td>Prospective</td>
<td>Adolescent</td>
<td>31%</td>
<td>&gt;3 y</td>
<td>Mean, 1.3 y</td>
<td>No. of seizures before remission &gt;10; duration of epilepsy before remission &gt;5 y; age at onset &gt;11 y</td>
</tr>
<tr>
<td>Marzec et al, 1989</td>
<td>425</td>
<td>Prospective†</td>
<td>Pediatric</td>
<td>12%</td>
<td>&gt;2 y</td>
<td>8 y</td>
<td>Neurologic abnormalities: mental retardation; abnormal EEG; symptomatic etiology; seizure free &lt;4 y; &gt;1 AED before withdrawal</td>
</tr>
<tr>
<td>Arts et al, 1988</td>
<td>146</td>
<td>Prospective†</td>
<td>Pediatric</td>
<td>25.5%</td>
<td>&gt;2 y</td>
<td>Mean, 52 mo</td>
<td>Symptomatic etiology; female; neurologic abnormality; family history; &gt;1 AED before withdrawal</td>
</tr>
<tr>
<td>Brod et al, 1988</td>
<td>32</td>
<td>Retrospective</td>
<td>Neonatal</td>
<td>84%</td>
<td>3 mo</td>
<td>NA</td>
<td>Abnormal EEG</td>
</tr>
<tr>
<td>Callaghan et al, 1988</td>
<td>92</td>
<td>Prospective†</td>
<td>Mixed</td>
<td>33.7%</td>
<td>Mean, 26 mo</td>
<td>Mean, 26 mo</td>
<td>Abnormal EEG; partial seizures; VPA at withdrawal</td>
</tr>
<tr>
<td>Bouna et al, 1987</td>
<td>116</td>
<td>Prospective†</td>
<td>Pediatric</td>
<td>19.5%</td>
<td>&gt;2 y</td>
<td>Mean, 4.3 y</td>
<td>Age at onset &gt;7 y worse than at &lt;7 y</td>
</tr>
<tr>
<td>Overweg et al, 1987</td>
<td>62</td>
<td>Prospective†</td>
<td>Adult</td>
<td>66%</td>
<td>Mean, 6-8 mo</td>
<td>NA</td>
<td>Older age at last seizure, shorter seizure-free interval, and &gt;1 AED at time of withdrawal; lower AED levels</td>
</tr>
<tr>
<td>Pestre et al, 1987</td>
<td>272</td>
<td>Prospective†</td>
<td>Adolescent</td>
<td>49%</td>
<td>&gt;1 y</td>
<td>&gt;12 y</td>
<td>Abnormal EEG; generalized tonic-clonic seizure</td>
</tr>
<tr>
<td>Todt, 1984</td>
<td>433</td>
<td>Prospective†</td>
<td>Pediatric</td>
<td>36.3%</td>
<td>&gt;1 y</td>
<td>5-6 y</td>
<td>Abnormal EEG, worsening EEG; seizure-free interval &lt;3 y; &lt;6-mo taper period; seizure duration &gt;15 min; seizure frequency &gt;5/y; &gt;2 y before seizures controlled</td>
</tr>
<tr>
<td>Thurston et al, 1982</td>
<td>148</td>
<td>Prospective†</td>
<td>Pediatric</td>
<td>28%</td>
<td>&gt;4 y</td>
<td>Mean, 18.6 y</td>
<td>Long duration of epilepsy before control; partial seizures; mixed seizure types; neurologic abnormalities</td>
</tr>
<tr>
<td>Emerson et al, 1981</td>
<td>68</td>
<td>Retrospective†</td>
<td>Pediatric</td>
<td>31%</td>
<td>Mean, 4.9 y</td>
<td>Mean, 2.7 y</td>
<td>Abnormal EEG, No. of seizures before remission &gt;30</td>
</tr>
<tr>
<td>Jusl-Jensen, 1968</td>
<td>196</td>
<td>Retrospective</td>
<td>Mixed</td>
<td>40%</td>
<td>&gt;2 y</td>
<td>5 y</td>
<td>No firm risk factors established</td>
</tr>
</tbody>
</table>

*AED = antiepileptic drug; EEG = electroencephalogram; MRC = Medical Research Council Antiepileptic Drug Withdrawal Study Group; NA = not available; VPA = valproate sodium.  
†Risk factors that are statistically significant on multivariate analysis.

Case ascertainment could have been a source of error in some studies. Since many studies were performed at well-known epilepsy centers, the overall rate of case ascertainment error would be expected to be low. Nonetheless, the diagnosis of epilepsy is not always straightforward. Syncope and psychogenic disorders can be mistaken easily for epilepsy. It is conceivable that nonepileptic disorders may have been included in the cohort in some of these studies, although the number is likely to be small.

Of note, the antiepileptic drug withdrawal literature is heavily weighted toward the pediatric population. Although the reasons for this are understandable, it makes counseling the adult patient with epilepsy difficult. The etiology, prognosis, and consequences of relapse for adults and children are considerably different. Extrapolation of results from one group to the other is not valid.

Many of the antiepileptic drug withdrawal studies unfortunately were performed before the era of magnetic resonance imaging. Certain lesions, such as neuronal migrational abnormalities and mesial temporal sclerosis, affect overall prognosis for seizure control.60,61 These same lesions also might be expected to affect the chances for remission, although this was not included in the literature. The presence of such lesions may prevent consideration of drug withdrawal in the first place, given the worse prognosis for seizure control in this group. Future studies may help
Table 2. Unfavorable Prognostic Factors for Antiepileptic Drug Withdrawal*

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset &gt;10-12 y</td>
<td>7-10, 14, 16, 20, 22, 27</td>
</tr>
<tr>
<td>Symptomatic vs idiopathic etiology</td>
<td>8-10, 14, 16, 24, 30, 62</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>9, 12, 16-18, 23, 24, 30, 32</td>
</tr>
<tr>
<td>Abnormal neurologic examination</td>
<td>7, 10, 12, 18, 20, 23, 24, 31, 62</td>
</tr>
<tr>
<td>Family history of epilepsy</td>
<td>10, 16, 20, 24</td>
</tr>
<tr>
<td>Poor initial response to treatment</td>
<td>9, 18, 20, 22, 23, 26, 29-32</td>
</tr>
<tr>
<td>More than 1 drug being used at time of withdrawal</td>
<td>20, 23, 24, 26</td>
</tr>
<tr>
<td>Epileptiform EEG changes</td>
<td>8, 9, 14, 17-19, 23, 30, 32</td>
</tr>
<tr>
<td>Slowing on EEG</td>
<td>6, 7, 12, 16, 20, 25, 26, 32</td>
</tr>
<tr>
<td>Emergence of EEG abnormalities during drug withdrawal</td>
<td>11, 27, 63-66</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>67</td>
</tr>
</tbody>
</table>

*EEG = electroencephalogram.

elucidate the predictive value of magnetic resonance imaging in selecting patients for antiepileptic drug withdrawal. Finally, data pertaining to quality of life, morbidity, and socioeconomic and medicolegal issues are insufficient as related to the success or failure of antiepileptic drug withdrawal. The main reason to withdraw medication is the assumption that doing so will lead to a net improvement in such factors, as long as the risk for recurrence is sufficiently low. A few prospective studies evaluating quality of life were performed as part of antiepileptic drug withdrawal studies.77 Nonetheless, more data pertaining to these issues are needed so that a clearer determination of the risks and benefits can be made.

Risk of Relapse

The relapse rates quoted in antiepileptic drug withdrawal literature range from 12% to 63% (Table 1). In the only randomized trial on this subject, the relapse rate in patients assigned to drug withdrawal was 41%.20 It should be noted parenthetically that in the control arm of this study, a 22% recurrence rate was observed despite the continuation of therapy.20 A total of 70% to 80% of relapses occurred within the first year of drug withdrawal. In the largest trial, 48% of relapses occurred during the drug taper, which in this study extended at least 6 months.20 After the taper was completed, the relapse rate steadily decreased. In one study, the relapse rate decreased from 5.9% per month for the first 3 months, to 2.7% per month for months 3 through 6, and 0.5% per month for months 6 through 9.26 Relapse may continue to occur after the first year but at a lower incremental rate. In a study of antiepileptic drug withdrawal in children, the percentage of patients remaining seizure-free after withdrawal decreased from 79% at 1 year, to 72% after 2 years, and 69% after 3 years.20 If a patient remains seizure-free throughout the withdrawal phase, the chances for success are encouraging but not ensured. If a patient does not relapse during the first year, the prognosis is more optimistic.

FACTORs THAT PREDICT THE SUCCESS OR FAILURE OF ANTI EPIL EPTIC DRUG WITHDRAWAL

Several useful prognostic signs were identified in previous antiepileptic drug withdrawal studies that can be used to assess risk in an individual patient. Numerous risk factors have been identified through univariate and multivariate analyses. Table 1 indicates risk factors found to be statistically significant on multivariate analysis in a given study. Unfavorable risk factors for withdrawal are summarized in Table 2.6-12,14,16,20,22-27,29-32,62-67 No one risk factor is singularly predictive of outcome, with few exceptions. Until a clearer understanding of the specific etiology, pathophysiology, and natural history of the different forms of epilepsy is developed, the clinician must rely on a rendering of the different risk factors and special circumstances present in a given case to make a final risk assessment.

Etiology

Improvements in neuroimaging and genetics have helped elucidate the etiology of several forms of epilepsy during the past 20 years. However, the etiology remains unclear in many cases despite these advances. The ILAE Classification of Epilepsies and Epileptic Syndromes provides a general categorization scheme for the etiology of epilepsy.58 In this system, etiology is classified into 3 broad categories—symptomatic, idiopathic, and cryptogenic—on the basis of the presence or absence of an associated central nervous system lesion.58,68 Symptomatic refers to epilepsy related to a known brain lesion, such as a tumor or previous hypoxic-ischemic insult. Abnormalities of intelligence or neurologic examination are more common in patients with symptomatic epilepsy. Idiopathic refers to epilepsy in which no associated underlying neuropathologic lesions are present and in which abnormalities in intelligence or neurologic status are largely absent. The idiopathic epilepsies are presumed to be genetic in origin in most cases. The term idiopathic in the field of epilepsy is generally reserved for specific syndromes as defined in the ILAE classification system. Cryptogenic refers to epilepsy in which underlying central nervous system pathology is postulated to be present, but the nature remains unclear. This classification system, although imprecise, was of prognostic use in some antiepileptic drug withdrawal studies.8,10,14,16,24,30,62 Etiologic classification of most epilepsies is possible when the ILAE classification system is used by physicians familiar with it.69 Patients with symptomatic or cryptogenic epilepsy generally fare less well than patients with idiopathic epilepsy as far as the prognosis for seizure control is concerned.20 Therefore, withdrawal of
antiepileptic drugs in patients with symptomatic or cryptogenic epilepsy is less likely to be successful.\textsuperscript{4,14,16,79,24} In one study, the relapse rate in patients with symptomatic epilepsy was 45%, compared with 25% in those with idiopathic epilepsy.\textsuperscript{16} However, etiology may be misleading in some cases. For example, in juvenile myoclonic epilepsy, a relatively common idiopathic epilepsy syndrome, the relapse rate associated with withdrawal is prohibitively high, and antiepileptic drug discontinuation is generally discouraged.\textsuperscript{67} Nonetheless, etiology is a useful starting point when evaluating the prospects for withdrawal.

**Epilepsy Syndrome**

Identifying the epilepsy syndrome, as defined in the ILAE Classification of Epilepsies and Epileptic Syndromes, is also useful in determining relapse risk. An epilepsy syndrome refers to a seizure disorder defined by age at onset, electroencephalographic (EEG) findings, seizure type, and etiology. Although many patients with epilepsy can be classified by using this system,\textsuperscript{71} assignment to a particular epilepsy syndrome may be difficult in patients presenting after having had only a few seizures in their lifetime.\textsuperscript{69} Consultation with an epileptologist is recommended before providing counseling on the basis of an epilepsy diagnosis.

Examples of epilepsy syndromes associated with a favorable outcome for antiepileptic drug withdrawal include benign childhood epilepsy with centrotemporal spikes, childhood absence epilepsy, and benign neonatal convulsions.\textsuperscript{72-74} Benign childhood epilepsy with centrotemporal spikes is a common partial seizure disorder characterized by the presence of centrotemporal spikes on EEG. This syndrome of nocturnally predominant seizures, which accounts for 5.4% of all childhood epilepsy in the general population,\textsuperscript{75} usually begins between 4 and 7 years of age and remits by mid adolescence, at which time drug withdrawal can be achieved successfully in more than 90% of patients.\textsuperscript{15,76} Childhood absence epilepsy is a disorder manifested by recurrent, brief (10-20 seconds) absence, or petit mal, seizures with onset at early childhood; this disorder is characterized by 3-per-second generalized spike-and-slow wave abnormalities on EEG. Absence seizures were shown to be a good prognostic factor for withdrawal in some studies,\textsuperscript{16,20} although the prognosis is not as favorable as in benign childhood epilepsy with centrotemporal spikes. In one study, medication was successfully withdrawn from 57% of patients with childhood absence epilepsy, in contrast to more than 90% of patients with benign childhood epilepsy with centrotemporal spikes\textsuperscript{76} from whom medication was successfully withdrawn. Another disorder in which withdrawal should be considered is benign neonatal convulsions, in which remission typically occurs within the first few months of life.\textsuperscript{74}

For certain epilepsy syndromes, antiepileptic drug withdrawal is not advised. The primary example is juvenile myoclonic epilepsy, which affects 3% to 11% of the epilepsy population.\textsuperscript{77,78} In this condition, seizures begin in early adolescence and consist of a variable combination of myoclonic, generalized tonic-clonic, and absence seizures. Up to 86% of patients with juvenile myoclonic epilepsy will have an excellent initial response to valproic acid therapy and therefore may be considered for eventual antiepileptic drug discontinuation.\textsuperscript{79} However, relapse occurs in more than 90% of these patients at antiepileptic drug withdrawal, according to the available literature.\textsuperscript{57}

**Seizure Type**

Seizure type is an important prognostic factor in some studies. Generalized absence seizures are associated with a relatively favorable prognosis, as discussed earlier.\textsuperscript{5,9} However, patients with both absence seizures and generalized tonic-clonic seizures have a less favorable prognosis. In one study, medication could be successfully withdrawn from only 35% of patients with both absence seizures and generalized tonic-clonic seizures.\textsuperscript{79} Almost all other seizure types, including generalized tonic-clonic,\textsuperscript{9,20,26} myoclonic,\textsuperscript{20} partial,\textsuperscript{4,10,20,31} and complex febrile seizures,\textsuperscript{16} have been associated with an increased relapse risk in one study or another. The context in which a particular seizure type arises, such as the associated epilepsy syndrome and etiology, is more important than seizure type alone when considering antiepileptic drug withdrawal. For example, the prospects for a patient with partial seizures related to benign childhood epilepsy with centrotemporal spikes are far better than for the patient with partial seizures related to a structural brain lesion.

**Previous Response to Antiepileptic Drug Treatment**

Two unfavorable signs for eventual antiepileptic drug withdrawal are the continuation of seizure activity after treatment is initiated and multiple seizures that occurred before seizure control.\textsuperscript{20,32} Similarly, taking more than one medication at the time of withdrawal is a poor prognostic risk factor.\textsuperscript{20,28} Related to this is the observation that the rate for success is proportional to the duration of seizure freedom before withdrawal.\textsuperscript{19,20,30} Patients with juvenile myoclonic epilepsy, again, are an exception, since the initial response to medication is typically favorable in these patients, and a prolonged seizure-free duration may belie the high rate of relapse associated with antiepileptic drug withdrawal.

**Age at Onset**

Age at onset was identified as an important risk factor in several studies. Seizure onset before age 10 to 12 years
portends a favorable prognosis, whereas onset after this age range indicates a higher rate of relapse. Age at onset is probably a surrogate marker for certain etiologies and epilepsy syndromes. For example, the peak age at onset of benign childhood epilepsy with centrotemporal spikes is younger than 10 years, whereas the mean age at onset of juvenile myoclonic epilepsy, a condition with a poor prognosis for withdrawal as discussed earlier, is 14.2 years.

Neurologic Deficits and Mental Retardation
The presence of mental retardation and other neurologic deficits was shown to be an unfavorable risk factor in some studies. These factors tend to correlate with the presence of an underlying pathology in the brain and thus may serve as a surrogate marker for symptomatic epilepsy, which also is associated with a relatively poor prognosis. The type of neurologic abnormality, however, may be more important than the mere presence of one. For example, in a study in which antiepileptic drug withdrawal was evaluated in patients with cerebral palsy, the relapse rate was higher in patients with hemiplegia (62%) compared with patients with spastic diplegia (14%). Of note, mental retardation is not a contraindication to antiepileptic drug withdrawal because some studies have shown success in patients with mental retardation. In fact, such patients may particularly benefit from the elimination of unnecessary sedating medications if other risk factors for relapse are absent.

THE ROLE OF EEG IN SELECTING PATIENTS FOR ANTIEPILEPTIC DRUG WITHDRAWAL
The role of EEG in antiepileptic drug withdrawal is controversial. Although an abnormal EEG before drug withdrawal was a negative prognostic factor in many studies, the predictive value of EEG has not been confirmed universally. In one study, patients with an abnormal EEG before drug withdrawal were twice as likely to relapse than were patients with a normal EEG. However, these results have not been replicated in other studies. For example, the relapse rate in patients with an abnormal EEG before drug withdrawal in one study was 47%, compared with a 33% relapse rate in patients with a normal EEG. Although this difference was statistically significant, the clinical significance is questionable, given the inconclusive absolute difference in relapse rates in these 2 groups. Clearly, factors other than the EEG need to be considered when deciding whether to withdraw antiepileptic medication.

Several factors account for the limited predictive value of the EEG before drug withdrawal. Epileptiform EEG activity may be suppressed by medication in some patients, which may lead to a false-negative result. The “normalizing” effect of the different antiepileptic medications varies. Phenytoin, carbamazepine, and phenobarbital may marginally affect the presence of abnormalities on the EEG, whereas valproic acid is believed to have a more substantial effect, at least in patients with idiopathic generalized epilepsy syndromes. In some patients, EEG abnormalities may not occur until medication is reduced, which may have prognostic value in patients during withdrawal. In one study, relapse occurred in 83% of patients whose EEG worsened during dose reduction, compared with a relapse occurrence of 54% in patients whose EEG remained unchanged. Other studies have corroborated these observations. Thus, the normalizing effect of medication seen in some patients may limit the usefulness of the EEG before drug withdrawal as an a priori tool in patient selection.

Another factor affecting the predictive value of the EEG relates to the limited sensitivity of EEG in the epilepsy population in general. In one study involving a large population of US veterans with predominantly partial seizures, diagnostic EEG abnormalities were present in only 29% of patients on the initial recording. The yield increased to 59% after 3 or more EEGs. The yield of EEG in the general epilepsy population has been reported to be higher in other studies. For example, in one study based at a tertiary center, the sensitivity of the EEG was found to be 82%. This inherent limitation in the sensitivity of EEG affects its predictive value in selecting patients for antiepileptic drug withdrawal.

RISKS TO THE PATIENT WHO RELAPSES
Status Epilepticus and Seizure-Related Morbidity and Mortality
Most seizures are self-limited events without sequela. Nonetheless, the potential for status epilepticus needs to be considered when counseling patients for antiepileptic drug withdrawal. Antiepileptic drug self-discontinuation and noncompliance are the etiology in about 20% of cases of status epilepticus. In the antiepileptic drug withdrawal literature, the number and severity of seizures at relapse are reported rarely, and the presence or absence of status epilepticus is usually not stated specifically. Status epilepticus was reported in 6 of 161 participants (4%) in one of the few studies in which a rate was specified. In the largest antiepileptic drug withdrawal study (N=1013), in which seizure-free patients were randomized to antiepileptic drug withdrawal or continuation, 15 deaths were reported. Thirteen of the deaths were not related to seizure activity. Two of the deaths were related to seizures but occurred in patients who were randomized to the drug continuation arm. A review of this literature therefore implies that the mortality, morbidity, and status epilepticus
incidence rates are low in the setting of prescribed anti-epileptic drug withdrawal in selected patients.

**Patient Response to Reinstitution of Treatment if Relapse Occurs**

Some practitioners hesitate to recommend drug withdrawal because control may not be achievable again if a relapse occurs. The literature suggests that this is an extremely unlikely outcome. In one large series, 90% of patients who relapsed during withdrawal again achieved a 2-year remission after reinstitution of therapy.

**Medicolegal Risks Associated With Antiepileptic Drug Withdrawal**

The medicolegal consequences of antiepileptic drug withdrawal have received little attention in the medical literature. Data are lacking on the incidence of automobile crashes, civil litigation, and personal injury related specifically to relapse during physician-supervised antiepileptic drug withdrawal. These issues are of great importance to physicians and patients when they need to make decisions about antiepileptic drug withdrawal. The increased driving risk in the epilepsy population is well established in the literature. In one study comparing the incidence of motor vehicle crashes in patients with and without a history of epilepsy, serious crashes increased 40% and nondriver fatalities increased 2-fold in the cohort with a history of epilepsy. The possession of a driver's license is an important determinant in a patient's willingness to attempt antiepileptic drug withdrawal. In the largest antiepileptic drug withdrawal trial (N=1013), 776 additional patients, who were otherwise eligible, declined to participate; the proportion of patients who had a driver's license was significantly higher in the group of patients who declined to participate compared with patients who consented.

**GUIDELINES FOR STOPPING ANTIPELLEPTIC MEDICATION**

Several useful review articles, guidelines, and meta-analyses have been published on the subject of antiepileptic drug withdrawal. Any evidence-based guideline is limited by certain methodological issues in the antiepileptic drug withdrawal literature, as discussed previously, and by our incomplete understanding of the etiology, pathogenesis, and natural history of many of the epilepsies. In general, the greater the number of risk factors for relapse that the patient has, the greater the chance for recurrence. Scales have been developed to help quantify the risk for an individual patient on the basis of the number and type of risk factors present. However, none of these scales have been applied prospectively; therefore, their accuracy has not been validated for clinical use.

**Duration of Seizure Freedom Before Antiepileptic Drug Withdrawal**

Most experts recommend a 2-year seizure-free period before considering antiepileptic drug withdrawal. In a meta-analysis comparing the relapse rate in patients with seizure-free intervals greater than and less than 2 years before withdrawal, the greater risk of relapse was with earlier withdrawal, with an odds ratio of 1.32 (95% confidence interval, 1.02-1.70). This corroborates findings in earlier studies in which an association was found between the duration of seizure freedom and the chance for successful drug withdrawal. Proponents of early withdrawal might argue that the increased risk associated with early withdrawal is slight and is offset by the benefits of minimizing the duration of medication exposure. Indeed, the integration of objective quality-of-life measures in future studies should allow an objective evaluation of such assertions. At this time, however, the literature supports requiring 2 years of seizure freedom before drug withdrawal to reduce the chance for relapse.

**Groups for Which Antiepileptic Drug Withdrawal Should Be Considered**

Antiepileptic drug withdrawal should be considered for children after a reasonable seizure-free period if favorable prognostic factors are present. Drug withdrawal should be considered in children with a favorable epilepsy syndrome, such as benign childhood epilepsy with centrotemporal spikes, childhood absence epilepsy, and benign neonatal convulsions. Evaluation by an epileptologist is advised if the epilepsy diagnosis is uncertain. Also, drug withdrawal should be considered in children whose condition does not fit into these defined epilepsy syndromes if important risk factors for relapse are absent.

In the adult population, the decision to withdraw treatment is more complicated. Unlike with children, adult syndromes with a high likelihood of remission have not been defined. Nonetheless, it is clear that medications can be successfully withdrawn from some adults. In the few clinical studies concentrating on the adult population, success rates from 34% to 77% have been reported. In adult patients, risk is weighed on the basis of the number and type of risk factors present and the potential consequences of a seizure, given the patient's life circumstances. In all patients, a careful assessment of all risk factors, the likely benefit to be achieved from drug withdrawal, and the possible effects of seizure recurrence on employment and quality of life must be carefully weighed when making a final recommendation.
The Role of Diagnostic Testing

A normal EEG before drug withdrawal does not guarantee a seizure-free outcome, especially in the presence of other unfavorable prognostic factors. However, an abnormal EEG can serve as compelling evidence against drug withdrawal in a patient who remains unconvincing despite the presence of other negative risk factors. As indicated previously, serial EEG recordings may be useful for monitoring patients after drug withdrawal.63

The Taper Rate During Antiepileptic Drug Withdrawal

Whether the tapering rate influences the success or failure of antiepileptic drug withdrawal has been debated. A taper period of less than 6 months was found to be an unfavorable prognostic factor in 2 studies.520 However, in the only randomized trial in which a 6-week and 9-month taper schedule were compared, no difference in final relapse rate was seen.17 However, the rapid taper cohort experienced relapse earlier than the cohort assigned to the slower taper rate. We generally taper patients over a 6-month period, once the decision to withdraw an antiepileptic drug has been made. In patients taking more than one medication, one drug should be withdrawn at a time.

Speculation has long existed that certain medications, namely phenobarbital and benzodiazepines, may be associated with a higher relapse rate. However, little supportive evidence has been published in the literature. Several studies have shown that the relapse rate for phenobarbital withdrawal is no different than for other medications.55,95-97 Some experts recommend a slower taper rate when withdrawing barbiturates and benzodiazepines compared with other drugs, but no data prove this to be necessary. Nonetheless, medication rarely needs to be withdrawn rapidly in this setting. A 6-month taper period should suffice for phenobarbital, as with other antiepileptic medications.

PATIENT COUNSELING FOR ANTEIEPILEPTIC DRUG WITHDRAWAL

Physicians counseling patients and their families on the prospects for antiepileptic drug withdrawal should discuss the relapse rates published in clinical studies and reviewed in this article. A thorough review of the medical record and history is necessary to identify all risk factors present for a given patient (Table 2). The patient and family should then be informed regarding the patient’s individual risk and informed that no test or risk factor analysis available allows flawless prognostication. Patients should be informed that a low but potential risk exists for status epilepticus, and they should be advised to seek prompt medical attention if seizure activity recurs. Also, they should be advised that the period of greatest risk of relapse is during the first year after initiation of drug withdrawal, particularly during the taper. Serial EEGs can be considered to help monitor the effects of antiepileptic drug withdrawal in selected patients.

Finally, one must determine the patient’s motivations and goals for antiepileptic drug withdrawal to ensure that the patient’s objectives are realistic and justify the risk. Patients wishing to stop medication because of unsubstantiated fears about the consequences of long-term medication should be counseled about the limited evidence for such effects and reminded of the real health risks associated with untreated seizure activity.78 For women who cite concerns regarding the teratogenic potential of antiepileptic drugs, physicians should provide education about the true risks as substantiated in the literature.77 Parents who attribute a child’s neurocognitive deficits to medication must be cautioned that these problems may not improve after drug withdrawal and that ultimately the problems may be found to be due to other factors. The physician is in the best position to provide perspective and risk assessment in these situations and to offer counseling regarding the best course of action for the individual and family.

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