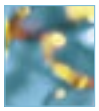

Withdrawal of antiepileptic drugs in seizure-free adults

Christine J. Kilpatrick, Associate Professor, Departments of Neurology and Medicine, Royal Melbourne Hospital, University of Melbourne, Melbourne

Summary

Whether or not antiepileptic drugs should be withdrawn after a patient has been seizure-free for several years is a complex issue. Some studies suggest the overall risk of seizure recurrence is approximately 30% if treatment is withdrawn. Clinical factors associated with a greater chance of successful withdrawal include childhood onset epilepsy, a normal electroencephalogram prior to drug withdrawal, being seizure-free for more than two years, monotherapy, normal neuroimaging and normal intellect. If antiepileptic drugs are withdrawn, they should be withdrawn slowly, ideally over several months.

Key word: epilepsy.

(Aust Prescr 2004;27:114–7)

Introduction

Longitudinal and community-based studies suggest that antiepileptic drugs will result in approximately 70% of adults diagnosed with epilepsy becoming seizure-free.[1] Whether or not antiepileptic drugs should be withdrawn after a patient has been seizure-free for several years is a complex issue. Discontinuing antiepileptic drugs implies the seizure tendency is no longer present. A number of clinical factors can help to predict the risk of seizure recurrence. This can assist when making a decision as to whether or not to discontinue antiepileptic drug treatment. The decision must include weighing up the harms and benefits of continuing and discontinuing therapy, and the risk and consequences of seizure recurrence.

Importance of remaining seizure-free

For many adults a recurrence of their seizures would have significant implications. Seizures impact on the ability to drive, possibly the ability to work. For many patients there is a significant negative impact on their psychological state and well-being. Seizures may also be associated with injury, and sudden unexpected death may occur as a direct result of seizures, particularly tonic-clonic seizures. Although the risk of seizure recurrence may be low, some patients choose to remain on treatment as they feel more secure taking an antiepileptic drug.

Reasons for discontinuing antiepileptic drugs

Patients may want to stop their treatment because antiepileptic drugs are commonly associated with mild adverse effects and have the potential for serious adverse effects. The risk of teratogenicity in women of childbearing years may prompt drug withdrawal earlier than might otherwise occur, but the risk of seizures recurring in pregnancy needs to be balanced against the possible harm of continuing treatment. Other problems include interactions with other drugs, for example the interaction between carbamazepine (liver enzyme inducer) and the oral contraceptive pill. For some patients, taking daily medication is a constant reminder of their chronic condition and has a negative impact on their well-being.

Relapse following withdrawal of antiepileptic drugs

A meta-analysis of 25 studies estimated the overall rate of seizure relapse following the withdrawal of antiepileptic drugs.[2] After discontinuing therapy 25% of patients relapsed within one year and 29% by two years. A randomised study of continued treatment versus slow withdrawal in 1013 patients who had been seizure-free for at least two years, reported that 78% of patients who continued treatment and 59% of those who stopped treatment were still seizure-free two years later.[3] These figures are overall estimates only and several factors need to be considered in individual patients when determining risk of relapse.

Factors influencing relapse

A number of studies have assessed clinical factors which might predict seizure recurrence following antiepileptic drug withdrawal (see Table 1).

Age of onset of epilepsy

The risk of seizure recurrence following drug withdrawal is higher in adolescents than children.[2,3] This probably reflects the prognosis of age-related syndromes. Childhood absence epilepsy and benign rolandic epilepsy have a good prognosis for antiepileptic drug withdrawal while juvenile myoclonic epilepsy is more likely to recur.

Seizure type and epilepsy syndrome

Epilepsy is not one disease, but comprises a number of syndromes each with a different prognosis (see Box 1). Juvenile myoclonic epilepsy, probably the commonest type of primary

Table 1

Factors predicting seizure recurrence following antiepileptic drug withdrawal

Associated with increased risk	Associated with reduced risk
Juvenile myoclonic epilepsy	Childhood absence epilepsy
Partial seizures with secondary generalisation	Benign rolandic epilepsy
Abnormal electroencephalogram	Normal electroencephalogram
Epileptogenic lesion on neuroimaging	Normal neuroimaging
	Onset in childhood
	No seizures for more than two years prior to antiepileptic drug withdrawal
	Monotherapy
	No seizures following introduction of antiepileptic drug
	Normal intellect

Box 1

Features of common epilepsy syndromes

Childhood absence epilepsy

This is a form of primary generalised epilepsy which has a genetic predisposition and begins in childhood. It is characterised by frequent absence seizures, however it is estimated that 50% of patients will have a generalised tonic-clonic seizure. Seizures usually respond well to treatment and the condition often remits in adult life.

Juvenile myoclonic epilepsy

This is a common form of primary generalised epilepsy which usually begins in adolescence. It is characterised by tonic-clonic seizures and myoclonic jerks. Seizures may be precipitated by sleep deprivation and excess alcohol. The condition responds well to valproate, but there is a high chance of recurrence after drug withdrawal.

Benign rolandic epilepsy

This is a common form of idiopathic partial epilepsy which occurs in otherwise normal children and usually remits in adolescence. The seizures are often sleep-related and characterised by orofacial or oropharyngeal involvement which frequently evolve into secondarily generalised tonic-clonic seizures. The interictal EEG demonstrates a spike focus in the centrotemporal region. Seizures usually respond to carbamazepine.

Partial epilepsy (focal epilepsy)

The most common form is temporal lobe epilepsy characterised by frequent complex partial seizures and occasional secondarily generalised tonic-clonic seizures. Partial epilepsy is often resistant to antiepileptic drug treatment.

generalised epilepsy in adults, has a high risk of seizure recurrence on drug withdrawal.

Studies assessing seizure type report myoclonic seizures, tonic-clonic seizures and partial seizures as associated with an increased risk of seizure recurrence following antiepileptic drug withdrawal.[3] One study reported 63% of patients with partial seizures relapsed on drug withdrawal.[4] Remote symptomatic seizures (defined as seizures occurring in patients with a prior neurologic insult such as head injury, stroke or history of intellectual disability) are associated with a high risk of seizure relapse following discontinuation of therapy.[2]

Seizure frequency, timing and antiepileptic drug usage

The UK Medical Research Council (MRC) trial found that an increased risk of seizure recurrence was associated with:

- a shorter duration of seizure-free period prior to study entry
- seizures after starting antiepileptic drug treatment
- patients taking multiple antiepileptic drugs at the time of study entry.[3]

Electroencephalogram

There is limited evidence to support the assumption that an interictal electroencephalogram (EEG) is predictive of seizure recurrence following antiepileptic drug withdrawal. The MRC study found that patients with only tonic-clonic seizures and generalised spike wave on EEG had a higher recurrence rate. Patients with tonic-clonic seizures and focal features or normal EEG had no increased risk of recurrence.[3]

The meta-analysis of 25 studies noted that an abnormal EEG was associated with an increased risk of recurrence, but there was considerable variability in the results and in most studies the epileptiform activity was not differentiated.[2] In some studies patients with an abnormal EEG, particularly the presence of epileptiform activity, were excluded, biasing the results.

Another study assessed the role of the EEG in predicting seizure recurrence in partial epilepsies. It found that although the interictal EEG at time of antiepileptic drug withdrawal did not predict recurrence, a worsening of the EEG after withdrawal was predictive of seizure recurrence.[4]

Role of video-EEG monitoring

The value of video-EEG monitoring in assessing the chance of remaining seizure-free following antiepileptic drug withdrawal has not been systematically studied. However, it is not uncommon for patients with generalised epilepsy to report no seizures and yet continuous monitoring reveals frequent sub-clinical seizure activity.

Neuroimaging

Although studies are lacking, it seems likely that patients with an epileptogenic lesion on computed tomography or magnetic resonance imaging of the brain are more likely to have recurrences on drug withdrawal. This is consistent with the data on recurrences in a population of patients presenting with their first seizure – patients with an epileptogenic lesion on neuroimaging have a higher risk of seizure recurrence.[5]

Patients need to be advised there is no guarantee they will remain seizure-free

Provoked seizure

It is likely that provoked seizures (such as seizures occurring with excess alcohol, sleep deprivation or induced by drugs) are less likely to recur if these factors are avoided.

Certainty of diagnosis

Occasionally patients are commenced on an antiepileptic drug and in retrospect there is some doubt about the diagnosis of epilepsy. In these patients drug withdrawal is a reasonable option.

Withdrawal after surgery for temporal lobe epilepsy

A reduction in antiepileptic drug therapy following successful surgery on the temporal lobe should be considered. However, the timing of withdrawal and whether or not all medications should be withdrawn is controversial. Many experts would agree that treatment should continue for two years. If the patient is then seizure-free and on several drugs, a reduction in medication could be commenced, but at least one antiepileptic drug should be continued for the long term.[6]

When to start antiepileptic drug withdrawal

No randomised-controlled trials have studied how long patients should be seizure-free before withdrawing their treatment can be considered. Studies in children suggest two years, but the MRC study of adults suggests a longer period of at least three years is desirable.[3]

Precautions during and after antiepileptic drug withdrawal

Patients need to be advised there is no guarantee they will remain seizure-free. The risk of relapse is greatest during the first 12 months.

'Assessing fitness to drive', produced by Austroads and the National Road Transport Commission, advises that the patient 'should not drive for the full period of withdrawal and for three months thereafter' unless withdrawal is advised by an experienced consultant on the basis that the risk of seizure recurrence is low.[7] Safety advice such as not swimming alone, avoiding heights and having a shower rather than a bath, should be reinforced.

How to withdraw antiepileptic drugs

Withdrawal should be gradual and take place over approximately six months. Rapid withdrawal, particularly of barbiturates and benzodiazepines, can precipitate seizures. The withdrawal protocol for adults in the MRC study decreased doses every four weeks (see Box 2).[3] This approach may need to be modified in patients on low doses of antiepileptic drugs. For patients taking multiple drugs, the withdrawal should be sequential.[3]

Box 2

Suggested protocol for antiepileptic drug withdrawal

The following decrements are recommended every four weeks:

phenobarbitone	30 mg
phenytoin	50 mg
carbamazepine	100 mg
valproate	200 mg
primidone	125 mg

Management of seizure recurrence

If seizures recur the previous medication that controlled seizures should be restarted.

Conclusion

For adults who are seizure-free, there are limited data to help them make an informed decision regarding drug withdrawal. The decision is an individual one and in general should be patient driven, as it is very important that the patient supports the decision, is aware that seizures may recur and understands the associated risks.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 133)

1. Seizures which began after a head injury rarely recur after antiepileptic drugs are stopped.
2. Patients with epilepsy who stop their medication should not drive for three months after their treatment is withdrawn.

Book review

Medicines out of control? Antidepressants and the conspiracy of goodwill. Medawar C, Hardon A.

Amsterdam: Aksant Academic Press; 2004.

258 pages. Price approx $64*

Professor Robert Moulds, Professor of Medicine, Fiji School of Medicine, Suva, Fiji, and Chairman, Australian Prescriber Editorial Executive Committee

This book is not for the faint-hearted. It is in small type, heavily referenced (30 pages of references), and has extensive footnotes (on some pages the footnotes occupy more space than the text). However, as a chronicle of the complexity of the development and use of drugs in modern medicine it makes fascinating reading.

The authors use the example of the selective serotonin reuptake inhibitors (SSRIs) and the slow percolation of knowledge about their adverse effects to develop the overall thesis that we are all part of a 'conspiracy of goodwill' regarding new drugs. They contend that this conspiracy is fostered by the pharmaceutical industry for its own financial purposes. The book also contends that the industry is aided by academia and the medical profession, not only by their endless pursuit of panaceas and naïve faith that new drugs must be better than old ones, but also by their reluctance to tackle the conflicts of interest that arise in acting as intermediaries between the industry and patients.

Despite its focus on the SSRIs, the book is wide ranging in its scope – and criticism. It puts the SSRIs into a historical perspective, arguing that it was naïve to think that the SSRIs would prove fundamentally different from their antecedents – alcohol, opioids, bromides, barbiturates and benzodiazepines. Along the way, the book strays into discussion of other aspects of modern drug use. These include the disease creation and awareness industry, the dangers of direct-to-consumer advertising and the power of changing terminology (for example, withdrawal syndromes becoming discontinuation syndromes).

The book is particularly critical of the reliance of regulatory systems on voluntary reporting of adverse drug reactions. It contends that for years it was clear in the voluntary reports that there were extensive problems of withdrawal reactions to SSRIs. These reactions went unrecognised because of the rigid classification system used by the regulators and their reluctance to revisit their initial evaluation that the drugs had few adverse effects. They (and others, including academia) fell for the 'NERO' argument – no evidence of risk equals evidence of no risk.

There are some strong streaks of 'wisdom of hindsight', and even paranoia, in this book, but it is powerful and well argued. It should be read by everyone interested in the sociology of the use of pharmaceuticals in modern medicine.

* ISBN 9052601348. Available from DA Information Services (03) 9210 7717 or e-mail service@dadirect.com