Assessing the benefits and risks of stopping antiepileptic drugs

Paul Gallagher MRCP and John Paul Leach MD, FRCP

Stopping drugs

Figure 1. Fear of teratogenicity may lead some pregnant women with epilepsy to stop treatment abruptly, without consideration of possible harm

Comencement of antiepileptic drug (AED) therapy in patients with a diagnosis of epilepsy will lead to seizure freedom in 60–70 per cent of patients.1 Many remain seizure free on monotherapy alone.

In most patients the risks of continuing treatment is markedly outweighed by the degree of seizure prevention, but in some the question should be asked as to whether the patient would benefit by trying to withdraw from AED treatment.

This article will consider when such trials may be warranted and how they may be attempted.

When to attempt drug withdrawal
In short, this discussion should take place when either the patient or the physician feels that the drugs are not helping to improve quality of life. All therapeutic choices involve taking into account the risks from the disease and risks and benefits from its treatment. In patients who have long-term seizure freedom, the risk of harm from continuing medication must be balanced against the risks and benefits of withdrawal of AEDs.

Patients may be attracted by the possibility of being freed from the need to take medication and the necessity of organising and maintaining a regular supply of treatment.

Most patients keen to consider drug withdrawal will have been
seizure free for some time, and it is for these cases that most quantitative evidence exists. Some patients (see Table 1), however, may wish to discuss drug withdrawal at an earlier stage.

Whatever the situation, patients should be made fully aware of the potential risks of changing treatment, allowing them to decide whether or not this is something they wish to pursue.

Assessing recurrence risk in individuals can be crudely attempted (see below) and each patient can weigh up whether this is of greater significance to them than the current and potential problems of continuing AEDs.

The first step in consideration of drug withdrawal is to ensure that the original diagnosis is correct. Even though many years may have passed, there can still be aspects of the diagnosis that may appear unsound. Ensuring that the patient on AEDs has a definite diagnosis of epilepsy is good practice.

Table 1. Patients who will be keen to consider drug withdrawal

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on risk of recurrence</th>
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<tbody>
<tr>
<td>seizure free for reasonable interval</td>
<td>longer duration reduces risk of recurrence, eg onset in childhood (&lt;10 years) offers lowest risk</td>
</tr>
<tr>
<td>perceived side-effects of treatment</td>
<td>causative lesion, ie symptomatic, increases risk of recurrence</td>
</tr>
<tr>
<td>past seizures infrequent or unintrusive</td>
<td>increased risk in patients with previous myoclonic jerks, generalised tonic-clonic seizures or partial seizures reduced risk in absence seizures</td>
</tr>
<tr>
<td>past seizures infrequent or unintrusive</td>
<td>effective monotherapy means reduced risk of recurrence polytherapy increases risk of recurrence</td>
</tr>
<tr>
<td>past seizures infrequent or unintrusive</td>
<td>no seizures after treatment commencement means lesser chance of seizure recurrence</td>
</tr>
<tr>
<td>past seizures infrequent or unintrusive</td>
<td>normal EEG has minimally predictive effect on reduced risk</td>
</tr>
<tr>
<td>past seizures infrequent or unintrusive</td>
<td>increases risk of recurrence</td>
</tr>
</tbody>
</table>

Subtle questioning may uncover some periods of DIY drug withdrawal. The success or otherwise of these phases can inform the likelihood of remaining seizure free on no medication.

Even where the diagnosis is unchallenged, the need for AEDs may not be clear. Some patients may benefit more from avoiding lifestyle provocations, eg alcohol, sleep deprivation, than from prescription of AEDs. The contribution of provocation to the presenting seizures should not be ignored.

Estimating adverse effects of current treatment

Patients and their families are often more concerned about side-effects than doctors realise, and they will be best placed to say whether the drugs are currently affecting quality of life. The physician should be careful not to overstate the chances of such side-effects regressing with withdrawal.

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The risk of seizure recurrence after drug withdrawal

Much work has gone into estimating risk of seizure recurrence across trial populations. The ability to individualise this recurrence risk has been of much more help.

Once seizure freedom has lasted for two or more years, some rough estimates can be obtained by consulting the tables provided in the Scottish Intercollegiate Guidelines Network guidelines on epilepsy (SIGN 70). The tables of recurrence risk take into account a number of factors, most importantly duration of seizure freedom, number of AEDs used and seizure type.

Using these tables it may be possible for the clinician to give the patient an idea of the two-year recurrence risk on and off treatment. In interpreting these data it should be remembered that other factors (see Table 2) may indicate an increased risk of seizure recurrence and the figures for treatment continuation and withdrawal may need to be interpreted accordingly.

Of course the impact of any seizure recurrence will be partly determined by their social effects (occupation, driving eligibility) as well as the clinical severity of the seizures themselves. This should be considered by the patient (see Table 3) as part of any advanced discussion.

Other risks of drug withdrawal

Removal of AEDs should reduce any drug-related adverse effects, but there is also a risk of adverse outcomes from other concomitant drugs. One particularly important
example is in oral anticoagulation, where withdrawal of enzyme-inducing AEDs may lead to marked increases in international normalised ratio (INR) and possibility of harm from haemorrhage.

Estimating future negative impact of AED continuation

Modern drugs would appear to be better tolerated than their older counterparts and the long-term side-effects evident with use of phenytoin and phenobarbital have not become apparent with the newer drugs, even 20 years after their introduction.

The effects of seizure recurrence after AED withdrawal should also be considered. This was associated with increased distress on several psychological measures in a follow-up questionnaire study from the MRC withdrawal study patients two years after randomisation. However, this work suggested that the psychosocial benefits of discontinuation may be considerable.

Estimating future potential effects is most pertinent in women contemplating pregnancy. Fear of teratogenicity may lead many pregnant women with epilepsy to stop treatment abruptly, without consideration of possible harm.

The rate of teratogenicity varies markedly with the AED used, and to a lesser extent on the dose. Across all prospective studies sodium valproate has the highest attributable risk of teratogenicity (see Table 4), and also has a documented risk of effect on the child’s cognitive function, which should motivate careful consideration before continuing treatment throughout pregnancy.

In any event, it is important that full discussion of pregnancy-related AED effects occurs in advance so that hasty unplanned treatment changes do not place the patient in danger.

Patients on more than one AED should have drugs withdrawn sequentially, one at a time.

Conclusions

Even with the best available evidence it is difficult to give a highly individualised and accurate assessment of the potential harm and benefit of drug withdrawal. In such circumstances the doctor’s views are

<table>
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<th>If I withdraw treatment:</th>
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<tr>
<td>• what are my chances of seizure recurrence?</td>
</tr>
<tr>
<td>• will it reduce any symptoms I am currently experiencing?</td>
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<tr>
<td>• what harm may arise from seizures returning</td>
</tr>
<tr>
<td>– physical?</td>
</tr>
<tr>
<td>– occupational (direct or secondary to driving)?</td>
</tr>
<tr>
<td>– psychological?</td>
</tr>
<tr>
<td>– recreational (impact on leisure/hobbies)?</td>
</tr>
<tr>
<td>• how will withdrawal affect my concurrent drug treatment (especially anticoagulants, oral contraceptives)?</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>If I remain on treatment:</th>
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<tbody>
<tr>
<td>• what are my chances of seizure recurrence?</td>
</tr>
<tr>
<td>• what are the potential effects on my health?</td>
</tr>
<tr>
<td>• how will it affect any future pregnancy?</td>
</tr>
<tr>
<td>• will it have any effect on any future treatments (anticoagulation, hormones, chemotherapy, etc)?</td>
</tr>
</tbody>
</table>

Table 3. Questions patients should ask themselves when considering stopping AEDs

Stopping drugs

Once the discussion about AED withdrawal has taken place (and been documented) and the patient has considered all aspects of treatment change (see Table 3), the patient can go away to consider whether or not to proceed with treatment withdrawal.

They should be advised, where appropriate, that the DVLA advises cessation of driving for a period of up to six months after drug treatment is stopped.

If the patient decides to withdraw, any changes should be gradual. As a rule gradual reduction is preferable to sudden dramatic changes in dosage.

Research in this area has followed different strategies. The most recent major study, which was double blinded and included newer AEDs (monotherapy only), reduced the initial AED dose by 20 per cent in the first six weeks and 20 per cent of the initial dose every second week until discontinuation. The largest but oldest study had a set dose reduction every four weeks, but advised withdrawal over six months.

One study compared a six-week taper with a nine-month taper in children and found no difference in final relapse rate. In adults the recurrence rate has been similar whether drugs are withdrawn over two to three months or six. Thus tapering and withdrawal over two to six months is a reasonable approach.

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How to withdraw drugs

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not of paramount importance: only patients and their families can determine the intrusion from seizures and side-effects, and only they can tell how inconvenient they find the monthly grind of maintaining supplies of their drug treatments. While we can give numerical estimates, patients are in the best position to give ‘global’ assessments to help direct treatment changes.

References

2. Wheless JW. Epilepsy & Behavior 2006; 8:566–64.

<table>
<thead>
<tr>
<th></th>
<th>Valproate</th>
<th>Carbamazepine</th>
<th>Lamotrigine</th>
<th>Phenytoin</th>
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<tbody>
<tr>
<td><strong>UK Epilepsy and Pregnancy Register</strong></td>
<td>6% (44/715)</td>
<td>2% (20/900)</td>
<td>3% (21/647)</td>
<td>4% (3/82)</td>
</tr>
<tr>
<td><strong>North American AED Pregnancy Registry</strong></td>
<td>9% (30/323)</td>
<td>3% (31/1033)</td>
<td>2% (31/1562)</td>
<td>3% (12/416)</td>
</tr>
<tr>
<td><strong>International Registry of Antiepileptic Drugs and Pregnancy (EURAP)</strong></td>
<td>10% (98/1010)</td>
<td>6% (79/1402)</td>
<td>3% (37/1280)</td>
<td>6% (6/103)</td>
</tr>
</tbody>
</table>

Table 4. Teratogenicity risk of AEDs in prospective studies; after reference 7


Declaration of interests

None to declare.

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