WHAT TO DO

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When the antiepileptic drugs are not working

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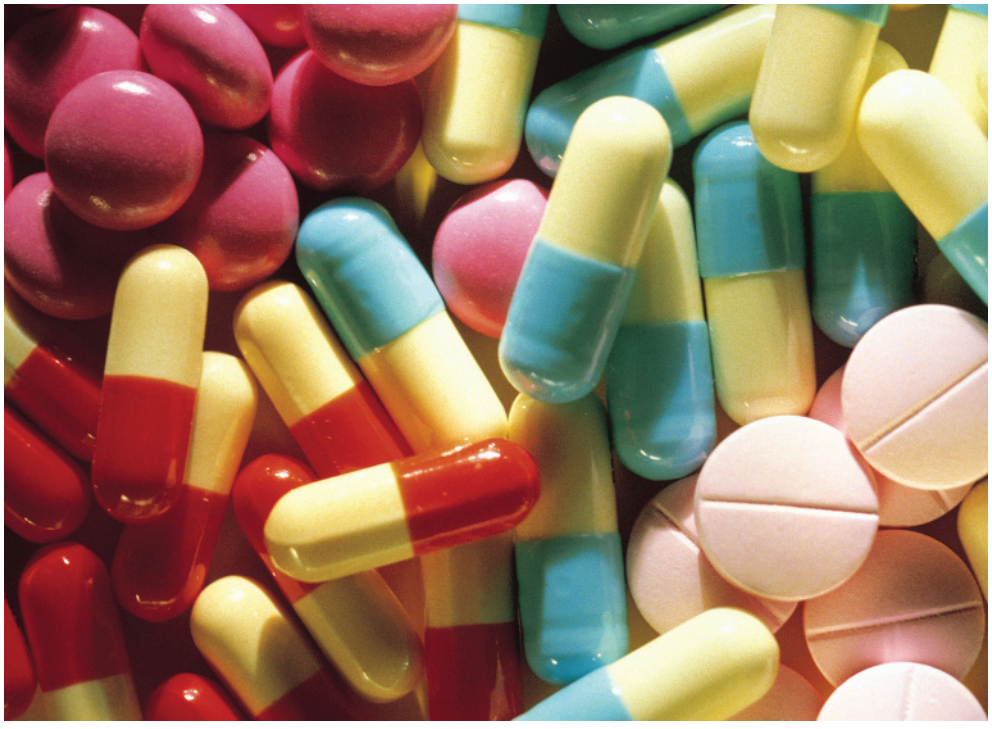

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Most patients with epilepsy respond to the initial antiepileptic drug (AED). But, as the responders are discharged, our clinics inevitably accumulate a number of "refractory" patients who require more manipulation of their treatment. This article looks at ways in which the identification and management of refractory epilepsy can be enhanced. The most important thing is to be able to assess if the initial diagnosis and classification are correct, and if the epilepsy is genuinely refractory, or if other medical or social issues are contributing to the deterioration in AED control. Once any treatment resistance is confirmed, specific attention should be paid to thorough investigation and, if appropriate, treatment manipulation. As all AEDs are equally efficacious, it is knowledge of the drug pharmacology and of expected adverse effects that is most helpful in determining drug choice. For those patients who do not fully respond to any medication, the challenges are to provide maximum benefit with minimum adverse effects, reducing risk to life, and risk to quality of life.

Most patients with epilepsy respond to the first or second antiepileptic drug (AED), indeed about two thirds on medication go into remission.[1] The SANAD studies of newly diagnosed epilepsy confirmed that remission is more likely with idiopathic generalised epilepsy than with focal epilepsy.[2, 3] Moreover, patients with an immediate good drug response are likely to remain seizure-free in the long term. Inevitably, because so many seizure-free patients will be discharged after a few outpatient visits, clinics accumulate the patients who do not respond to medication, giving most neurologists an unrepresentatively gloomy view of epilepsy outcome. Nonetheless, identifying drug-resistant patients at an early stage is important, because this will allow the early use of drug combinations, targeting of investigations, work-up for epilepsy surgery, and the provision of specific information.

For the purposes of this article, I will consider that the refractory patient has failed to achieve seizure freedom despite sustained use of at least one AED at adequate dose. Clarifying the reason for the initial failure is important; for example, patients who have had an adverse-effect-inspired withdrawal (especially following an idiosyncratic drug reaction) have a good long-term outlook, and may in fact have the same prognosis as they had when they were first treated. Patients failing due to lack of efficacy have a worse prognosis[1] and we can deal with these later.

TABLE 1 Questions to ask when things are not going well: the eight Cs

Correct diagnosis?
Correct classification?
Correct drug?
Covert lesion?
Compliance?
Comorbidity?
Clarifying triggers?
Consistent with the truth?

QUESTIONS TO ASK WHEN THINGS ARE NOT GOING WELL

If seizures are not completely controlled by medication, there are a number of questions—all beginning with C as it happens—that should be asked to identify if the epilepsy is genuinely refractory (table 1). As listed below, these questions may highlight any quick solutions to the continuing episodes.

Correct diagnosis?

Misdiagnosis of epilepsy in around 20–25% of patients has been reported in series based in both hospital and the community.[4, 5] Neurologists are not immune to this; revision of diagnosis in one study was made in 44/1721 (3%) patients after enrolment.[2] However, increasing availability of specialist services has led to a decrease in the likelihood of misdiagnosis. Lack of response to AEDs may suggest the origin of these initial episodes as being syncopal or psychological. Further descriptions in follow-up clinics may be required to uncover the original error. Even where the diagnosis of epilepsy is correct, it

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should not be taken for granted that all "events" are seizures, and a full description should be obtained for each one to ensure that continuing episodes really are epileptic in origin. Common examples of "impostors" in patients with genuine epilepsy are panic symptoms or syncope—a hasty misdiagnosis of these can lead to inappropriate use of increasing numbers of AEDs and a false impression of refractoriness.

Correct classification?

Even where the diagnosis of epilepsy is secure, the classification may be wrong, or may not have been considered at all.[4] In practice, the classification is often not apparent on presentation, and may need to be reconsidered in the light of an EEG (if under 35 years old at onset), imaging, and any other emergent seizure types.[6] Patients with an idiopathic generalised epilepsy are less likely to respond to sodium channel blockers such as carbamazepine or phenytoin and may in fact find their epilepsy exacerbated. Use of broad spectrum AEDs (that is, drugs useful in generalised *and* focal onset epilepsies) such as lamotrigine, topiramate and valproate will be necessary. Carbamazepine remains licensed for patients with primary generalised tonic clonic seizures, but for some this will provoke myoclonus or, less commonly, absences. Most would agree that the broad spectrum AEDs should be used where the epilepsy is unclassified.

Covert lesion?

Most patients will have undergone brain imaging early in diagnosis, but where epilepsy is proving refractory, consideration and exclusion (with MRI) of a covert lesion is vital. This is particularly so where seizures are either unclassified or have a clinical focal onset. Most clinicians have experienced patients where a previously normal MRI has been repeated, only to show an abnormality as the lesion (or the magnet!) has increased in size some years later. Where refractory epilepsy emerges after a period of good control, imaging requirements should be identical to those of the newly diagnosed patient.

Compliance?

There is an expanding range of descriptors for the fact that some patients do not take their prescribed medication. Terms range from the old-fashioned (but well understood) "compliance", the 1990s favourite "adherence", through to the uber-politically correct "concordance" (never mind *new* terms, wouldn't you just long for a touch of "obedience" from your patients!) Whichever word you use, it comes down to asking if patients are or are not (for what may in their minds be good reason) taking the expected medication at the expected time in the expected dose. Accurate assessment of the extent of this problem varies, but most people would acknowledge that it occurs in a significant minority of cases. No diagnostic method is absolute, but a few key questions can be useful when used sequentially (table 2). If the patient describes difficulty sticking to the drug schedules, offering different regimens, different timings or different formulations may help inspire his or her confidence in both you and the medication. Counselling about the negative effects of poor seizure control may be appropriate, including a discussion about sudden unexpected death in epilepsy (SUDEP). For some, reassurance about the lack of addictive or negative long-term effects will suffice. Exploration of latent concerns (for example, about teratogenicity) can prove fruitful, and addressing misguided fears may allow successful use of a previously "ineffective" drug.

TABLE 2 The compliance discussion

Do the drugs agree with you?
Do you feel differently after you take them?
Do you ever miss a dose to avoid these feelings?

Identifying drug-resistant patients at an early stage is important

Comorbidity?

This currently fashionable term refers to the psychological and psychiatric problems that often accompany the diagnosis of epilepsy, usually in the form of depression and anxiety.[7] Whether these are another marker of brain disease, a result of the psychological effects of seizures, or an adverse effect of AEDs is uncertain. Whatever the case, patients with epilepsy and psychological and psychiatric comorbidity are less likely to go into remission, but the processes leading to resistance are poorly understood.

TABLE 3 Factors influencing choice of add-on treatment

Epilepsy classification
Drug interactions (AEDs, oral contraceptive, etc)
Adverse effects
Side benefits

Clarifying triggers?

Both sleep deprivation and alcohol play an important role in increasing the frequency of epileptiform discharges, especially in patients with idiopathic generalised epilepsy. Identification of such triggers is helpful, and again may lead to helpful discussion and counselling about the importance of avoidance. Recreational drug use is, among some age groups, another consideration; cocaine, amphetamines, LSD and ecstasy all lower seizure threshold. Cannabis and opiates (including methadone) have less clearly defined proconvulsant effects, but their secondary effects on mood and compliance with "proper" medicines may be important.

Consistent with the truth?

Some patients may have reasons to exaggerate or inflate the number and/or severity of their seizures. These patients are (probably) rare, and the motivation may be financial (for disability benefit, medicolegal reasons, etc) or social (effects on family). Definitive diagnosis is difficult, but it is important to suspect this because discovery of "inconsistency" may avoid exposing the patient to iatrogenic harm and wastage of resources.

TABLE 4 Targeting drugs on the type of epilepsy

Focal onset epilepsy	Generalised epilepsy
Carbamazepine	Benzodiazinies
Gabapentin	Lamotrigine
Lacosamide	Levetiracetam
Lamotrigine	Topiramate
Levetiracetam	Valproate
Phenobarbital	Zonisamide
Phenytoin	
Pregabalin	
Topiramate	
Vigabatrin	
Zonisamide	

MANAGEMENT OF POOR DRUG RESPONSE

If, after addressing all the eight Cs, it becomes apparent that the epilepsy is genuinely refractory to the initial AED, then a full discussion must ensue. A revision of prognosis is important, and I usually tell patients that the chances of seizure freedom are now approximately 10%.[1] However, the patient should be reminded that full control, if not likely, is at least a possibility.

The rest of the patient discussion will focus on how the drugs should be altered—either substitution or adding on (table 3). Aside from studies using older AEDs with enzyme inducing pharmocokinetics, there is little randomised trial evidence comparing these two approaches. There are reasons for preferring drug substitution, because patients will be on fewer treatments at any one time, with less expense, improved compliance, and less risk of pharmacodynamic or pharmacokinetic interactions. On the other hand, patients not responding to the first one or two drugs may benefit from a period of relative stability where you are changing only one thing at a time; phased substitution—that is, adding on a drug with future expectation of withdrawal of the baseline medication—is reasonable (with care taken to avoid mixing drugs with a tendency to interact). Any patient finding themselves free of seizures with add-on medication may be keen not to upset their new-found control, and may dictate either the status quo or a slower pace of withdrawal of the first AED than the clinician would usually make.

The choice of second drug depends on a number of factors, the most important being the classification of the epilepsy (table 4) Clinical trials have failed to demonstrate superiority of any particular agent, either in direct comparison or meta-analysis. The possibility of pharmacokinetic drug–drug interactions, patient gender, adverse effects and possible "side benefits" will therefore help decide between treatments.

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Drug–drug interactions

We routinely accept that previous treatment with enzyme-inducing AEDs will mean that higher doses of any add-on treatments are required. The most troublesome interaction of recent times has been the use of lamotrigine alongside valproate, where inhibition of lamotrigine metabolism leads to a marked increase in adverse effects. It is also vital to remember the possibility of oral contraceptive failure with traditional enzyme inducing drugs, or with lamotrigine and topiramate. Efforts at proving synergy between AEDs have been unproductive, and knowledge of basic mechanisms of action is of no help in choosing add-on therapy.

Gender

Drug combinations in pregnancy should be avoided if at all possible. The safety of AEDs has received a great deal of attention in recent years, those least likely to cause major malformations being carbamazepine and lamotrigine. While information on newer AEDs remains sketchy, valproate should probably be regarded as a last resort where pregnancy is possible or likely. In some patients with idiopathic generalised epilepsy, however, valproate may be inescapable, and in these circumstances the drug should be used at the lowest dose possible, acknowledging that the risk to the fetus of uncontrolled seizures may shift the balance of risks and benefits towards valproate.

Drug adverse effects (and "side benefits")

The adverse effect profile of some drugs (most notably vigabatrin) has relegated them to a few specialist centres with expertise. The mainstream new drugs have their contraindications, but are largely safe in a general setting. For some patients with pre-existing medical conditions, certain adverse effects are to be avoided. Specific conditions may militate against particular drugs (for example, nephrocalcinosis and topiramate), while others may make you keen to avoid specific adverse effects; for example, patients with hypertension, asthma, diabetes or coronary heart disease may be made worse if they gain weight. Conversely, some non-epilepsy medical conditions may respond to treatment with individual AEDs (table 5) or may benefit from the "adverse effects" of individual AEDs—"side benefits" as it were.

TABLE 5 Adverse effects and unexpected benefits of antiepileptic drugs

	Aggravates	No effect	Helpful
Weight gain (hypertension, diabetes mellitus, etc)	Carbamazepine Pregabalin Valproate Gabapentin	Lamotrigine Levetiracetam Oxcarbazepine	Topiramate Zonisamide
Anxiety	Levitiracetam	Oxcarbazepine Valproate	Pregabalin ?Carbamazepine ?Lamotrigine
Depression	Topiramate ?Levitiracetam	Oxcarbazepine	Pregabalin ?Carbamazepine ?Lamotrigine
Migraine		Lamotrigine Oxcarbazepine	Gabapentin Pregabalin Topiramate Valproate

MANAGEMENT OF CONTINUING POOR RESPONSE

In a significant minority of patients, it becomes apparent that even careful addition and manipulation of drugs is not enough. In such cases, the neurologist is left trying to balance the best control possible for the individual patient with the fewest adverse effects. It is important not to forget that surgical options may still be available, and an increasing number of patients with focal epilepsy may merit video telemetry to try and localise seizure origin, perhaps opening the way to surgical intervention. The role of vagal nerve stimulation remains uncertain—for patients with refractory symptomatic generalised epilepsies the devices may provide some benefit, but the experience in other patient groups is less convincing, with little evidence to suggest that a wider use is appropriate.

WHEN TO STOP FIDDLING WITH THE DRUGS

In patients with incomplete drug response, it is sometimes difficult to know how long one should keep striving to change medication and optimise control. In short, this stage has come when the patient is unwilling to countenance further drug changes. A frank discussion with the patient along these lines

Valproate should probably be regarded as a last resort where pregnancy is possible or likely

TABLE 6 Should I keep trying doctor?

What are the chances of getting rid of the seizures?
Are the current seizures a risk to life?
Are the current seizures a risk to quality of life? (eg, driving, independence)
Given the (un)realistic estimate of the chance of remission, do you want to keep trying?

is vital and in the end the decision lies with the patient. We now have a large range of medications available (with perhaps more on the way), and if a patient is keen to keep pursuing seizure freedom, it would be disempowering to force our helplessness on them. Conversely, a relentless trawl through unhelpful treatments can be a dispiriting experience, with the clinician's lack of enthusiasm signalling a high chance of failure. I find it helpful to consider a series of questions to assess how the ongoing seizures are likely to threaten life or quality of life (table 6). The answers to these questions will help gauge enthusiasm for further changes from the clinician's and the patient's perspective.

CONCLUSIONS

In some ways, the profusion of new AEDs has complicated an already difficult situation. There is no evidence to suggest that the numbers of patients seizure-free has increased with increasing AED choice. While failing to enhance efficacy, however, these newer drugs can offer improved tolerability. As with other branches of medicine, the field of epileptology has progressed by degrees. With time, we may have better drugs offering universal seizure freedom, but even the greatest optimist would think this unlikely. Until then we should learn to use the drugs we have already at our disposal, and guide our patients through the opportunities and limitations. Ultimately, there will be a significant number of patients for whom seizure freedom is unattainable. In time, managing these patients can be as rewarding as successfully treating "immediate responders". For these "long-timers" you will become an ally, at worst a familiar face, at best the person to whom they will turn if things get even worse. Managing unresponsive epilepsy has few ground rules, but should be guided by realistic expectations. Where you have something to offer—do it. Where you have nothing to offer just listen, react to any calls for help, and be alert to any future developments that may help the patient with troublesome or dangerous seizures.

PRACTICE POINTS

When seeing the refractory patient

- Don't assume the patient has epilepsy.
- Don't assume the ongoing episodes are epileptic.
- Make sure the previous drug treatment was given a fair chance to work.
- Make sure there are no triggers or medical causes for worsening seizures.
- Choose add-on drugs by virtue of their adverse effects and possible side-benefits—they all probably work equally well at preventing seizures.
- Know when progress is unlikely.

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