

# Treatment of resistant epilepsy

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## ABSTRACT

**Treatment resistance affects around 20% of people with epilepsy and carries a significant comorbidity. It is important to ensure that the diagnosis of epilepsy is secure and the underlying cause of the epilepsy is investigated thoroughly. Management involves early referral for epilepsy surgery when suitable, optimisation of pharmacological treatment, and consideration of comorbidities such as depression.**

**KEYWORDS:** Epilepsy, treatment resistance, management

## Introduction

Epilepsy is defined as an ongoing tendency to experience unprovoked epileptic seizures, with a prevalence in developed countries of around 1%. Although most people's epilepsy can be controlled successfully with one or two anti-epileptic drugs (AEDs), around 20% of people with epilepsy will have treatment-resistant or drug-resistant epilepsy.<sup>1</sup> Drug resistance can be defined as 'failure of adequate trials of two tolerated, appropriately chosen and used anti-epileptic drug schedules – whether as monotherapy or in combination – to achieve sustained seizure freedom'.<sup>2</sup>

Risk factors for developing drug-resistant epilepsy include a higher number of seizures at the time of diagnosis and symptomatic epilepsy (epilepsy with a known, often structural, cause).<sup>3,4</sup> It is still not clear why a significant minority of people with epilepsy develop drug-resistant epilepsy, although this probably relates to the heterogeneity of epilepsy and its underlying complex genetic aetiology. Plausible explanations include a genetic predisposition for reduced uptake of AEDs, reduced expression of AED targets, or differing mechanisms for epileptogenesis in people with drug-resistant epilepsy.<sup>5</sup>

Uncontrolled seizures are associated with significant comorbidity, including reduced quality of life, increased risk of anxiety and mood disorders,<sup>6</sup> impaired cognitive function,<sup>7</sup> and increased risk of premature death.<sup>8</sup> The prognosis for people with drug-resistant epilepsy has historically been poor: in a 40-year prospective study of 102 children with resistant epilepsy,

82% had 1 year of seizure freedom although only 51% had continuing seizure freedom.<sup>9</sup>

The clinician must consider many things when managing a patient with possible drug-resistant epilepsy, including alternative diagnoses, early referral for potentially curative surgical treatment and selection of the appropriate pharmacological management. This article outlines a pragmatic clinical approach to managing resistant epilepsy in adults, as outlined in Fig 1.

## Is the diagnosis correct?

There is no single 'test' for epilepsy and its diagnosis can sometimes be difficult, even in experienced hands. The misdiagnosis rate in people referred to specialist centres with a diagnosis of drug-resistant epilepsy may approach 30%.<sup>10,11</sup> The most common epilepsy 'mimics' are syncope (reflex and cardiogenic), and non-epileptic or dissociative seizures (previously called pseudo- or psychogenic seizures). Rarer epilepsy mimics include paroxysmal movement disorders, sleep disorders and metabolic disorders.<sup>12</sup>

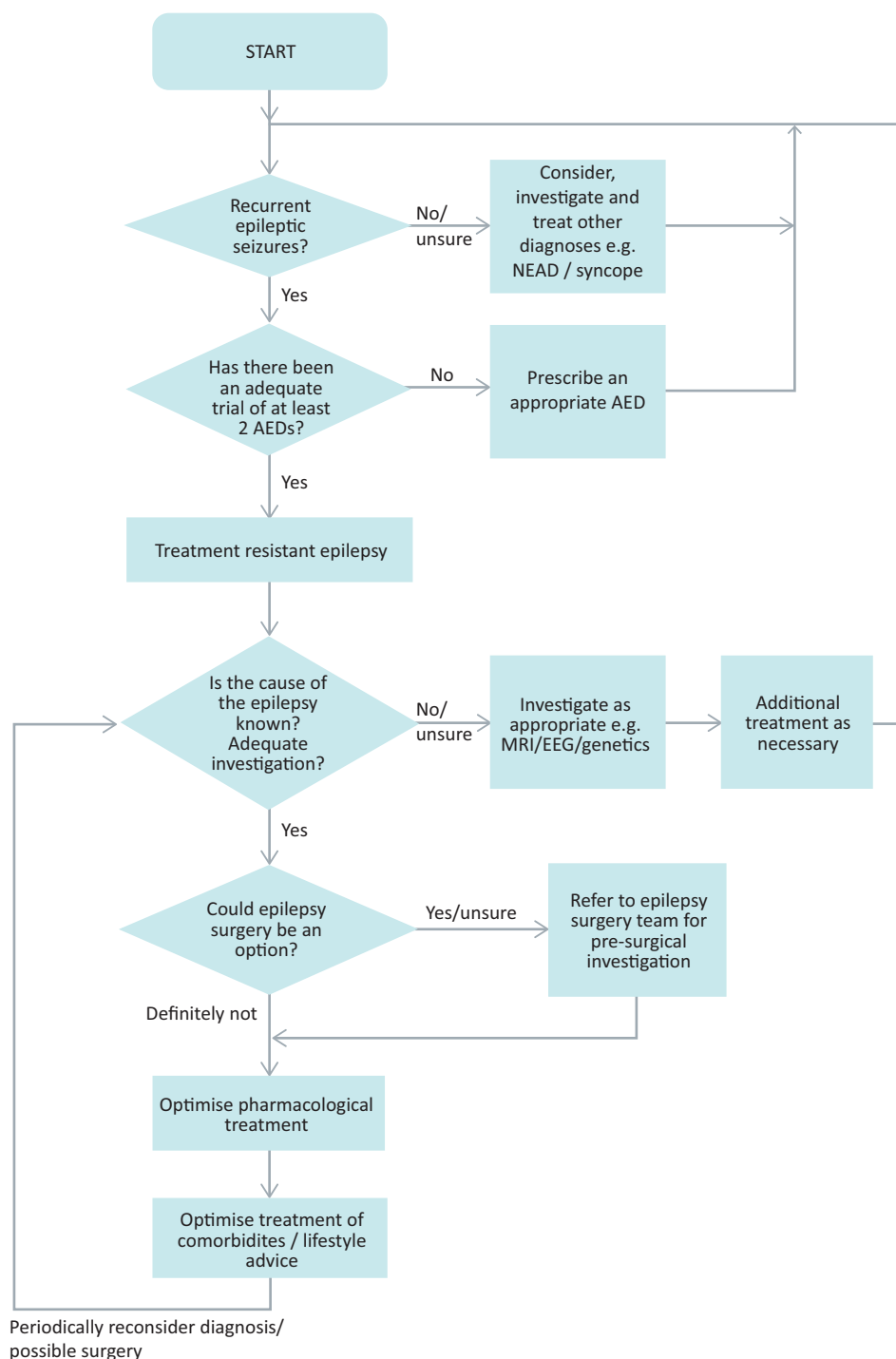
Non-epileptic seizures are typically caused by a psychogenic dissociative process, rather than by the abnormal electrical activity of epileptic seizures. Non-epileptic seizures may account for up to 25% of cases of drug-resistant epilepsy<sup>10</sup> and perhaps pose the greatest diagnostic dilemma, even to specialist epileptologists. The diagnosis is often even harder in the 10% of those with non-epileptic seizures who also have epileptic seizures.<sup>13</sup> Table 1 summarises some key clinical features that can help to differentiate epileptic from non-epileptic seizures.<sup>13</sup> Paying particular attention to the consultation conversation may also help. For example, people with epileptic seizures tend to volunteer information about their seizures and make attempts to describe them in as much detail as possible. People with non-epileptic seizures find it harder to describe details involving the seizures, tending instead to focus on the circumstances surrounding the seizure, rather than the seizure itself.<sup>14</sup>

## Investigating the cause of the epilepsy

Epilepsy is not a single disease but may be caused by a variety of underlying brain disorders or injuries, each increasing the tendency to experience epileptic seizures. The clinician must make every effort to uncover the underlying cause of the epilepsy to guide treatment strategies and to inform prognosis.

When managing drug-resistant epilepsy, it is worth taking or retaking a detailed 'epilepsy history', looking for clues to the cause of the epilepsy (Table 2 highlights some of these). All patients with resistant epilepsy should have had

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**Fig 1. Suggested algorithm for managing drug-resistant epilepsy.**

AED = antiepileptic drug; NEAD = non-epileptic attack disorder; MRI = magnetic resonance imaging; EEG = electroencephalogram.

a magnetic resonance imaging (MRI) scan of their brain to look for potential structural causes of the epilepsy, unless the diagnosis of genetic generalised epilepsy is certain.<sup>15</sup> If possible, a neuroradiologist should report the scan to maximise the chances of identifying a subtle epileptogenic lesion.

An electroencephalogram (EEG) is generally not as useful as brain imaging, but can still provide useful information. EEGs can support the diagnosis of a generalised epilepsy or photosensitivity,

help to localise focal epilepsies and occasionally may help confirm the diagnosis of non-epileptic seizures if a typical seizure is captured without corresponding epileptiform changes. Repeat EEGs or sleep-deprived EEGs can sometimes yield useful diagnostic information.<sup>15</sup> Video recordings taken by patients' family members or carers can sometimes help. Video telemetry EEG monitoring is perhaps the gold standard investigation and, if available, is worth requesting in difficult cases.

**Table 1. Some key clinical features that may help to differentiate epileptic seizures from non-epileptic seizures.<sup>13</sup>**

Feature	Epileptic seizures	Non-epileptic/dissociative seizures
Nature	Predominately stereotypical	Typically lack consistency
Occurrence during sleep	Can occur from sleep	Rarely occur from sleep
Eyes	Rarely closed	Can be closed
Duration	Rarely longer than seconds to minutes	Can be several to tens of minutes in duration
Breathing	Typically apnoeic in expiration	May have rapid breathing or breath hold in inspiration
Colour	May be cyanosed, pale or flushed	Rarely cyanosed
Amplitude of movements	Tend to reach maximum then decrease	Can 'wax and wane'
Seizure frequency	Typically unpredictable and can 'cluster'	Frequency can be regular
Injuries	Can sustain injuries and lateral tongue bites during seizures	Rarely sustain injuries or lateral tongue bites

Table 3 gives examples of rare conditions requiring more specialist investigations, for example genetic tests. Although rare, these diagnoses are worth considering as sometimes there are condition-specific treatment options available.

### Surgical treatment

Clinicians should consider surgery as soon as possible for patients with drug-resistant focal epilepsy, as earlier surgery can improve outcomes.<sup>16</sup> The chance of obtaining seizure freedom with surgery is significantly higher than with medical therapy. In one long-term study of 615 patients undergoing epilepsy surgery, 50% remained seizure free after 10 years.<sup>17</sup>

Traditionally, curative epilepsy surgery has been considered the most suitable option for a patient with drug-resistant epilepsy who has a definitive epileptogenic lesion on an MRI scan, most commonly hippocampal sclerosis or mesial temporal sclerosis (Fig 2). Although there needs to be conclusive evidence

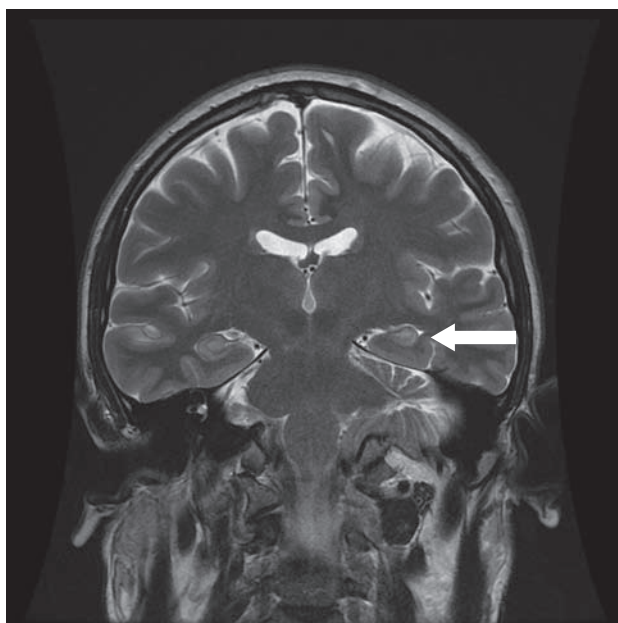
of a resectable epileptogenic zone before proceeding to surgery, advances in imaging technology and the development of techniques such as intracranial EEG monitoring mean that surgery is possible for some patients with focal epilepsy and a normal MRI scan. A recent retrospective study found that 28% of patients referred with drug-resistant MR scan-negative extra-temporal lobe epilepsy underwent surgery: 33% were seizure free and 75% had a worthwhile seizure improvement a mean of 9 years after surgery.<sup>18</sup>

Vagus nerve stimulators are surgically implanted battery-powered devices that repeatedly stimulate the vagus nerve. The devices are similar in size to cardiac pacemakers and are implanted in the upper chest with connecting wires attached to the left vagus nerve in the carotid sheath. Vagus nerve stimulation can be considered as an adjunctive therapy in patients with drug-resistant epilepsy with focal or generalised epilepsy who are not suitable for resective surgery.<sup>15</sup> Around 50% of patients experience a reduction in seizure frequency

**Table 2. Important topics to cover when taking an 'epilepsy history'**

Topic	Areas to cover	Relevance
Remote history	Birth history Significant CNS infections Significant head trauma Febrile seizures	Potential causes of symptomatic structural epilepsy  Increased risk of adult epilepsy Genetic epilepsy with febrile seizures plus (GEFS+)
Seizure history	Age at onset of different seizure types Frequency of seizure types Description of typical seizures Provoking/alleviating factors	Identification of a defined epilepsy syndrome (eg juvenile myoclonic epilepsy) Classification of seizure type (eg temporal lobe epilepsy) Reflex epilepsies (eg photosensitive epilepsy)
Medical/drug history	Comorbidities Medication history	Potential causes of symptomatic epilepsy (eg stroke) Some drugs can lower seizure threshold (eg tramadol)
Family history	Epilepsy Other comorbidities Sudden/unexplained deaths	Familial epilepsy syndromes Other genetic syndromes Genetic cardiac conditions as epilepsy mimics
Social history	Concomitant alcohol/recreational drug use Occupation/shift work	Potential seizure triggers

CNS = central nervous system.



**Fig 2. MRI scan of left hippocampal sclerosis (note the asymmetry in size when compared with the right [arrowed]).** MRI = magnetic resonance imaging.

after vagus nerve stimulator insertion however, around 25% have no change in seizures at all and complete seizure remission is rare (<5%).<sup>19</sup> It is also important to remember the potential side effects of vagus nerve stimulation, including voice change and cough; the finite battery life necessitating device change every 10 years or so; and the inability to have an MRI scan with a vagus nerve stimulator *in situ* – an important consideration if the option of surgery is to be reconsidered in future.

## Medical treatment

Medical treatment is currently the mainstay for patients who are not suitable for surgery, have refused surgery, or have developed seizure recurrence following surgery. Patients with resistant epilepsy understandably often become wary of repeated medication changes if they have tried several in the past, only to accumulate new side effects with little change in seizure frequency or (more importantly) quality in life. There is, however, a small but significant chance of benefit when trying medication changes. Around 5% of patients with drug-resistant epilepsy will become seizure free each year with medication changes (compared to 0.4% without).<sup>20</sup> Among one group of patients with chronic epilepsy, 16% of drug introductions made by an experienced epileptologist resulted in seizure freedom.<sup>21</sup>

There are over 20 AEDs currently licensed for use in the UK.<sup>22</sup> There are many things to consider when choosing an AED, including epilepsy type or syndrome, side effect profile, comorbidities, drug interactions, potentially teratogenic effects, and patient preference. Table 2 lists (in approximate order of efficiency and tolerability) some of the more commonly used AEDs. Given the results of the SANAD trial in 2007 (a landmark large pragmatic multicentre open-label trial),<sup>23,24</sup> lamotrigine is generally considered the AED of choice for focal epilepsy and sodium valproate for generalised or unclassified epilepsy. For patients with drug-resistant epilepsy, it is therefore worth trying lamotrigine for focal epilepsy or valproate for generalised epilepsy if they are suitable and have not been tried before. Sodium valproate should be avoided where possible in women of childbearing age, given the evidence for increased teratogenicity and neurodevelopmental problems in children born to mothers taking the drug.<sup>25,26</sup> Levetiracetam is usually used as an alternative in this case.

There is little good quality evidence to guide choice of AED after the first drug and it is often a matter of trial and error, taking into account individual circumstances. Despite this,

**Table 3. Examples of underlying causes of apparent drug-resistant epilepsy in adults.**

Condition	Clinical clues	Test	Management
Autoimmune voltage-gated potassium channel encephalitis	Usually late onset drug resistant temporal lobe epilepsy Facio-brachial dystonic seizures	Voltage-gated potassium channel complex antibodies	Immunosuppression
Autoimmune NMDA receptor encephalitis	Usually prominent psychiatric features Fairly rapid decrease in mental state	NMDA receptor antibodies	Immunosuppression
Glucose transporter deficiency	Typically presents in childhood but can present in adults; learning difficulties; movement disorders (ataxia, dystonia, chorea)	Decreased CSF to plasma glucose ratio <i>SLC2A1</i> gene mutation	Ketogenic diet
Dravet's syndrome	Progressive severe myoclonic epilepsy, first seizure usually around the age of six months	80% have <i>de novo</i> mutations in the <i>SCN1A</i> gene	Avoidance of AEDs acting on the voltage-gated sodium channel eg lamotrigine
<i>POLG</i> -associated mitochondrial disease	Episodes of status epilepticus early in disease course, multifocal seizures (occipital lobe common) neurological signs eg ataxia, raised CSF lactate, MRI changes	Mutations in the <i>POLG</i> gene (encodes mitochondrial DNA polymerase)	Avoidance of sodium valproate (can precipitate liver failure)

AEDs = anti-epileptic drugs; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; NMDA = N-methyl-D-aspartate receptor; SLC2A1 = solute carrier family 2, facilitated glucose transporter member 1.

**Table 4. Some of the more commonly used anti-epileptic drugs (AEDs).**

	<b>Focal epilepsy</b>	<b>Generalised/unclassified</b>
First line	Lamotrigine, <sup>a</sup> levetiracetam, <sup>a</sup> carbamazepine <sup>a</sup>	Sodium valproate, levetiracetam, <sup>a</sup> lamotrigine <sup>ab</sup>
Second line	Sodium valproate, zonisamide, oxcarbazepine, lacosamide, topiramate, clobazam	Zonisamide, clobazam, topiramate
Other AEDs to consider	Perampanel, eslicarbazepine acetate, gabapentin, phenytoin, retigabine	

<sup>a</sup>Generally considered safer in pregnancy than other AEDs. <sup>b</sup>May exacerbate absences and myoclonus. AEDs = anti-epileptic drugs.

certain AEDs are more effective than others; Table 2 suggests an order for trying different AEDs, based on the available evidence and the authors' experience.

It is useful to consider the mode of action of the drug when trying a new AED. Table 3 lists the main targets of some of the more commonly used AEDs. If a particular AED has been tolerated but has not been successful in terms of seizure control, it is probably better to then try an AED with a different mode of action. For example, if carbamazepine has been tolerated but has not been successful in a patient with focal epilepsy, it is preferable to try levetiracetam rather than lamotrigine.

Current guidelines recommend that patients normally take the first and second AED as monotherapy.<sup>15</sup> After this, it is probably worth switching to polytherapy, choosing AEDs with different modes of action. There is some evidence for this approach, with lamotrigine and sodium valproate, for example, having a probable synergistic action when prescribed as polytherapy.<sup>27</sup> Avoiding the co-prescription of AEDs with the same mode of action also helps reduce the incidence of side effects.

### Ketogenic diet

The ketogenic diet, conceived in the 1920s, is a high fat, low carbohydrate and low protein diet designed to induce ketosis. A landmark randomised control trial in children showed >50%

reduction in seizures in half of the children treated with the diet.<sup>28</sup> Current UK guidelines recommend consideration of the diet for children and young people with resistant epilepsy.<sup>15</sup> There is less evidence for its use in adults although the success rates seem to be broadly similar.<sup>29</sup> It is of particular relevance as a therapeutic option for people with glucose transporter 1 (GLUT-1) related epilepsy or Dravet syndrome.

The ketogenic diet however is restrictive and not particularly palatable, making adherence to its strict requirements difficult for most people and impossible for some. It is recommended that specialist dietetic support and advice is sought if it is used. Alternative (more palatable) diets such as the modified Atkins diet or medium chain triglyceride diets might become options when better evidence is available.<sup>29</sup>

### Other things to consider

Potentially avoidable factors that can increase the likelihood of seizures include sleep deprivation, consumption of large volumes of alcohol (due mainly to its affect on sleep), and certain drugs (eg tramadol, aminophylline, cocaine and amphetamines). A significant minority of women with epilepsy experience seizure clustering at certain times of their menstrual cycle (catamenial epilepsy). In this instance, it may be useful to consider the co-prescription of an oral contraceptive pill, if appropriate, or an AED such as clobazam to be taken for a few days at the relevant stage of the menstrual cycle. Reflex epilepsies, where certain factors (eg light patterns) will induce seizures, are relatively rare.

Clinicians frequently concentrate on trying to improve seizure frequency in patients with drug-resistant epilepsy. Yet other factors often have more of an effect on the quality of life of a patient with drug-resistant epilepsy. Psychiatric comorbidity (especially depression and anxiety) is common, affecting up to 60% of patients with resistant epilepsy.<sup>30</sup> Side effects of AEDs, in particular somnolence, cognitive impairment and dizziness, can be important and difficult to predict, especially when using polytherapy. A compromise between seizure control and side effects in patients with drug-resistant epilepsy is frequently a better approach than trying to achieve complete seizure freedom.

Unfortunately, drug-resistant epilepsy increases the risk of sudden unexpected death in epilepsy, which may be as high as 1% per year in patients with resistant epilepsy awaiting surgery.<sup>31</sup> Although it is sometimes a difficult topic to broach within a consultation, it is important that patients and their families and carers are aware of the risk; there are several useful patient information leaflets available.<sup>32</sup>

**Table 5. Main targets of some commonly used AEDs.**

<b>Main target</b>	<b>AED</b>
Voltage-gated sodium channel	Carbamazepine, lamotrigine, oxcarbazepine, lacosamide, phenytoin, eslicarbazepine acetate
GABA receptor	Clobazam, phenobarbital
SV2A	Levetiracetam
AMPA glutamate receptor	Perampanel
Voltage-gated potassium channel	Retigabine
Voltage-gated calcium channel	Pregabalin, gabapentin
Multiple mechanisms	Sodium valproate, topiramate, zonisamide

AEDs = anti-epileptic drugs; AMPA =  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA =  $\gamma$ -aminobutyric acid; SV2A = synaptic vesicle protein 2A.



## Summary points

- > Drug-resistant epilepsy affects around 20% of people with epilepsy and carries a significant comorbidity.
- > It is important to consider epilepsy mimics and to identify the underlying cause of the epilepsy wherever possible.
- > Refer early for epilepsy surgery if appropriate.
- > Optimise medical treatment, paying particular attention to the patient's concerns, side effects, comorbidities, previous treatment successes and failures, and the mode of action of anti-epileptic drugs.
- > Comorbidities and social stigma in drug-resistant epilepsy frequently have more of an effect on the patient's quality of life than do the seizures themselves. ■

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