Chapter 26

Starting antiepileptic drug treatment

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The single most important consideration before starting antiepileptic medication is to be secure of the diagnosis of epilepsy based on the clinical history and, where needed, supporting investigations. Antiepileptic drug (AED) treatment should never be started as a trial to 'test' the diagnosis; this will only cause problems for you and the patient, and is generally unhelpful in resolving diagnostic uncertainty.

Given a likely clinical diagnosis the next questions are when to start treatment, followed by what choice of AED. AEDs should prescribed after a careful evaluation of the risks and benefits of treatment and a discussion with the individual patient about the merits and potential side effects of treatment[1]. The decision to start medication is a major one – treatment will be for many years, even lifelong, and future withdrawal will bring its own issues around recurrence risk and driving, for instance. The decision to start will depend upon factors such as the risk of recurrence, seizure type, the risk around implication of further seizures, desire to regain a driving licence and, for women, the risks of AEDs and seizures in pregnancy.

Antiepileptic medication is normally taken for years, and good adherence is essential to avoid withdrawal seizures. Before starting any medication it is important to give information about side effects, drug interactions, teratogenicity and driving. It is helpful to have to hand one or two of the commonest possible side effects for each AED, to caution the patient about these for any new drug started and to document this clearly in notes and letters. Individuals need to appreciate that starting medication does not hasten the return of their driving licence, and that the DVLA recommend not driving during withdrawal and for six months after stopping AEDs. Patients choosing not to start medication need to be warned of the risks of seizures including, if appropriate, SUDEP (sudden unexplained death in epilepsy).

When to start antiepileptic medication – the single seizure

When dealing with a single generalised tonic-clonic seizure (GTCS) it is important to make sure that the patient has just had a single seizure by asking carefully about events or symptoms that the patient would not necessarily recognise as seizures or volunteer in the history, e.g. myoclonic jerks, stereotyped focal symptoms with retained awareness, symptoms like epigastric rising, déjà vu, periods with loss of awareness, and seizure-markers from sleep.

In 2014 the ILAE task force presented a new category for epilepsy diagnosis, and in addition to the established 'at least two unprovoked seizures occurring more than 24 hours apart' was added 'one unprovoked seizure and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (at least 60%)'[2]. Examples are a single seizure occurring one month after a stroke, or a single seizure with a structural abnormality, for instance focal cortical dysplasia on MRI. While the ILAE task force publication does not concern itself with when to start AEDs, this new definition does have implications for the treating clinician and should be discussed with the patient and documented. It is left to the treating clinician to apply the >60% risk of recurrence in these situations; this is very difficult to estimate in clinic, and most clinicians would currently agree that starting AEDs after a single seizure is not appropriate in the majority of circumstances.

When to start antiepileptic medication – rare seizures

People who have who have long gaps between seizures may be treated differently to those with frequent seizures, depending on the type of seizure. For instance a patient with GTCS at, say, five-year intervals should in most circumstances be recommended AED treatment because of the risk of injury or SUDEP; a patient with **only** rare complex partial seizures, or even more frequent simple partial seizures may take a different view. A risk of a GTCS and attendant SUDEP risk should still be discussed in these cases. In the past, fear that having a seizure might make another more likely (similar to kindling in the rat) led some to recommend early treatment. But the multicentre study of early epilepsy and single seizures (MESS)[3] showed that the likelihood of remission is the same if treatment is immediate or deferred. AEDs do not appear to alter the prognosis of the underlying condition.

When to start antiepileptic medication – recurrence risk

The decision to start medication is a balance between the risk of recurrent seizures and the requirement for regular medication with all this entails. The risk is greatest close to the first seizure; individuals seen months after a seizure are already low risk. Factors associated with higher risks of recurrence include: an underlying structural abnormality, learning difficulties and spike-wave on EEG[4,5]. The DVLA now recognise this evidence and allow individuals who have had a single seizure in whom investigations are normal and the risk of recurrence is deemed to be low (<20% per annum) to drive using a Class 1 (not HGV) licence after six rather than 12 months.

Acute symptomatic and provoked seizures

Seizures associated with acute insults to the brain, e.g. infection or trauma, need to be treated but AED treatment should not be given to prevent the development of epilepsy because this is ineffective[6] and AEDs should be discontinued within or at most six months after the insult. Seizures exclusively provoked by external factors, e.g. alcohol withdrawal, should be treated by avoiding the provocation.

Deciding to start

The diagnosis of epilepsy can be straightforward, but may be problematic. Unwitnessed attacks and subjective symptoms such as fear or panic can cause difficulties. In almost all cases it is sensible to wait until the diagnosis is beyond reasonable doubt before starting medication. And it should be noted that some people choose not to take medication, e.g. a young woman with focal seizures and little if any loss of awareness who does not want to drive and is about to start a family. Relevant factors such as lifestyle, work, personal safety, driving and responsibilities for others should be discussed with the individual when deciding whether to start medication or not. This is not a consultation that should be hurried.

The aim of antiepileptic medication is to prevent seizures with minimal discomfort to the individual. All AEDs have the potential for side effects and some have significant interactions with other medication. Choice of AED will depend on these and the efficacy of the drug. Choice of AED is determined to an extent by the seizure type(s) and epilepsy syndrome (see Tables 1 and 2). A single AED should be started in a low dose and escalated – slowly – to a maintenance dose (see Table 3). Rapid escalation is more likely to be associated with acute idiosyncratic and dose-related side effects such drowsiness or rash that can dishearten the individual or put them at risk of iatrogenic harm. Many individuals will respond to a low dose of an appropriate AED. Indeed the response to the first well-tolerated AED helps to predict the outcome[7]. About 50% will enter a remission quickly, of the rest 20–30% will enter

remission with active management including alternative monotherapy or polytherapy, while the remainder have refractory epilepsy and continue to have seizures. It is helpful to talk to patients about these figures in general terms at the outset, particularly if they have factors that suggest poor prognosis. Over-optimism can lead to disillusionment and poor adherence.

Choice of AED

Industry-sponsored phase 3 clinical trials of AEDs are designed to satisfy regulatory requirements for drug licensing. For ethical reasons (one cannot randomise a patient to no treatment) new AEDs can only be initially tested as add-on therapy, however this does not mean they are necessarily unsuitable for monotherapy, just untested and unlicensed for such. As experience is gained as add-on therapy and in further open studies, applications for the monotherapy licence are made. Research participants in phase 3 trials are generally individuals with highly refractory epilepsy (usually focal) and frequent seizures. New medications are added into existing therapy and the randomised phase of the trial usually lasts 3–4 months, with relatively rapid dose escalations. This is far removed from the typical clinical scenario of an individual with newly diagnosed epilepsy starting their first AED in monotherapy. The SANAD (Standard and New Antiepileptic Drug) study coordinated from Liverpool aimed to address this[8,9].

This large pragmatic study comprised two arms: arm A compared carbamazepine with lamotrigine, topiramate, gabapentin and latterly oxcarbazepine[8]; arm B compared valproate with lamotrigine and topiramate[9]. Arm A contained individuals with predominantly focal epilepsy and arm B mostly generalised epilepsy (though unclassified epilepsies were also entered into arm B). The study was randomised but not blinded, which gives a lower evidence grade; however SANAD is by far the largest and best-conducted study of treatment in newly diagnosed epilepsy available. And it confirmed what clinical experience suspected, i.e. no new AED in the study was more effective than carbamazepine for focal epilepsy but lamotrigine and oxcarbazepine were better tolerated. In arm B valproate was the most effective drug. The SANAD study did not include the newest AEDs because they were not widely available at the time. Another study (SANAD II) is now under way to establish the place of levetiracetam and zonisamide compared to the established lamotrigine and sodium valproate in the treatment new onset focal and generalised epilepsy.

AED therapy should be chosen according to the type of seizure and tailored to the individual. It is important to characterise the seizure type and epilepsy syndrome and to avoid AEDs that might exacerbate seizures, e.g. carbamazepine in absence or myoclonic seizures in the idiopathic generalised epilepsies.

Cost is a factor that cannot be ignored and if standard cheaper medication is acceptable it should be prescribed. Generic prescribing can be problematic, more so for those already established on an AED, because minor changes in AED levels can result in breakthrough seizures, and changes in brand should be avoided if at all possible.

Carbamazepine should be prescribed in the modified-release preparation as this reduces side effects[10]. Individuals who cannot tolerate carbamazepine in whom it is effective may tolerate oxcarbazepine, or possibly eslicarbazepine (this is not currently licensed for monotherapy in the UK) though the long-term side effect of hyponatraemia and the risk of rash are seen with both. Lamotrigine was originally promoted as ‘the AED for women’ and was said to have no interactions with hormonal contraceptives. This has been shown not to be the case; it is now known that lamotrigine levels can fall unpredictably when oestrogen-containing contraceptives are used concomitantly[11]. Similarly lamotrigine levels can fall unpredictably in pregnancy[12].

Table 1. Choice of AED by seizure type.

Seizure type	First-line drugs	Adjunctive drugs	Drugs to be avoided (may worsen seizures)
Focal with/without secondary generalisation	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	
Generalised tonic-clonic	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate	Clobazam Lamotrigine Levetiracetam Topiramate	(if there are absence or myoclonic seizures, or if JME suspected) Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Tonic or atonic	Sodium valproate	Lamotrigine	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin
Absence	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Myoclonic	Levetiracetam Sodium valproate	Levetiracetam Topiramate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin

Table 2. Choice of AED for common epilepsy syndromes.

Epilepsy syndrome	**First-line AEDs**	**Adjunctive AEDs**	**AEDs to avoid (may worsen seizures)**
Childhood absence epilepsy or other absence syndromes	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Juvenile absence epilepsy or other absence syndromes	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Juvenile myoclonic epilepsy	Lamotrigine Levetiracetam Sodium valproate Topiramate	Lamotrigine Levetiracetam Sodium valproate Topiramate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Epilepsy with generalised tonic-clonic seizures only	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate	Clobazam Lamotrigine Levetiracetam Sodium valproate Topiramate	
Idiopathic generalised epilepsy	Lamotrigine Sodium valproate Topiramate	Lamotrigine Levetiracetam Sodium valproate Topiramate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Benign epilepsy with centrotemporal spikes	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	

Table 3. Starting, maintenance doses and common side effects for first-line AEDs.

Drug	Starting dose/day	Typical maintenance dose/day	Dosing interval	Commonest side effects
Carbamazepine MR (modified release)	200 mg	400–1800 mg	b.d.	Rash Diplopia Dizziness Headache Nausea Hyponatraemia
Ethosuximide	250 mg	500–2000 mg	b.d.	Nausea Drowsiness Headache
Lamotrigine	25 mg	100–400 mg	b.d.	Rash (always caution patients and document this, as persisting with the drug in the face of rash can lead to severe Stephens Johnson Syndrome) Nausea Dizziness Headache Insomnia
Levetiracetam	250 mg	1000–3000 mg	b.d.	Lethargy Irritability Mood disturbance Insomnia Drowsiness Unsteadiness
Sodium valproate	300 mg	600–2500 mg	b.d.	Weight gain Tremor Hair loss Teratogenesis

Lamotrigine is recognised to exacerbate myoclonic seizures in some individuals with JME. Valproate, the most effective drug in generalised epilepsy is best avoided as first-line therapy in women of childbearing potential because of the higher risk of teratogenicity[13,14]; it can also be associated with significant weight gain and extrapyramidal side effects. But in some individuals valproate is the only drug that is effective. Levetiracetam is effective as add-on for generalised seizures[15] and can be very effective for myoclonic seizures[16] but there are no data for its use as first-line therapy in generalised epilepsy Ethosuximide is the most effective AED for absence seizures, but if the individual also has generalised tonic-clonic seizures lamotrigine or valproate should be used, the latter being more effective[17].

In patients who cannot tolerate the first prescribed AED then an alternative first-line AED for their seizure type should be introduced to replace the first. If the first AED is tolerated but fails to be effective several questions need to be answered before moving on to an alternative. These are:

1. Is the diagnosis of epilepsy correct?
2. Is the individual taking his or her medication?

3. Is the wrong AED for the seizure type being prescribed?
4. Has a progressive underlying condition, e.g. glioma, been missed?
5. Is there undeclared use of alcohol or drugs?

If these can be excluded the dose of the first AED needs to be increased to the level that individual can tolerate and, if the seizures continue, the dose is then usually reduced a little before a second AED is introduced and the dose titrated up. If the second AED is effective then the original AED can gradually be withdrawn. It is good practice to change only one AED at a time so that, if for example seizures increase or worsen, the cause is clearer. Which AED should be added if the first fails is difficult to proscribe, but it would seem reasonable to choose an AED with a different mechanism of action from the first. Theories of 'rational polytherapy' are not supported by extensive evidence[18], but it is recognised that the use of drugs with similar mechanisms of action, e.g. sodium channel blockers, can be associated with more side effects if used in high dose together.

Prognosis

The outcome for many patients starting AEDs is good, with 70% entering a prolonged remission. Structural abnormalities, frequency of seizures and learning difficulties are associated with poorer outcomes[19]. Whether treatment alters the long-term outcome is uncertain, but studies from developing countries where the treatment gap is very wide (up to 85% not receiving medication)[20] suggest that the underlying nature of the epilepsy is more important and AEDs prevent seizures but do not alter outcome.

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