

Starting antiepileptic drug treatment

MARGARET J. JACKSON

Department of Neurology, Royal Victoria Infirmary, Newcastle upon Tyne

Antiepileptic medication should not be prescribed without 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 treatment¹. The decision to start medication is a major one and will depend upon factors such as the risk of recurrence, seizure type, fear of further seizures, desire to regain a driving licence and, for women, the risks of antiepileptic drugs (AEDs) and seizures in pregnancy. Antiepileptic medication is normally taken for years, and good adherence is essential to avoid withdrawal seizures. Before starting medication it is important to give information about side effects, drug interactions, teratogenicity and driving. 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, requiring another period without driving in the future.

When to start antiepileptic medication – the single seizure

This is the source of much debate. People who have had an isolated seizure or who have long gaps between seizures may be treated differently to those with frequent seizures. 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)² 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.

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; and learning difficulties and spike-wave on EEG^{3,4}. The DVLA now recognise this evidence and allow individuals who have had a single seizure and in whom investigations are normal to drive after six rather than 12 months. But it is important to make sure that the patient has just had a single seizure by asking carefully about subtle seizures, e.g. myoclonic, focal with retained awareness, and seizure-markers from sleep. Patients choosing not to start medication need to be warned of the risks of seizures including, if appropriate, SUDEP (sudden unexplained death in epilepsy).

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 ineffective⁵. Seizures exclusively provoked by external factors, e.g. strobe lights or alcohol withdrawal, should be treated by avoiding the provocation.

Early epilepsy

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 by the seizure type(s) (see Table I). A single AED should be started in a low dose and escalated to a reasonable dose (see Table II). Rapid escalation is more likely to be associated with acute idiosyncratic side effects such as rash and drowsiness that can dishearten the individual. 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 outcome⁶. About 50% will enter a remission quickly, of the remainder 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

Trials of AEDs tend to be designed for regulatory purposes; their subjects are individuals with refractory epilepsy (usually focal), new medications are added into existing therapy and their duration is usually four months or less. 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 addressed this. This large pragmatic study comprised two arms: arm A compared carbamazepine with lamotrigine, topiramate, gabapentin and latterly oxcarbazepine⁷; arm B compared valproate with lamotrigine and topiramate⁸. 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 has led to downgrading of it as evidence; but it 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 is now needed to establish the place of levetiracetam and other newer AEDs 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 to avoid AEDs that exacerbate seizures, e.g. carbamazepine in absence or myoclonic seizures.

Table I shows the first-line AEDs for focal seizures and Table II their starting and usual maintenance doses with common side effects. Cost is a factor we cannot ignore and, if standard cheaper medication is acceptable it should be prescribed. Generic prescribing can be problematic because minor changes in AED levels can result in breakthrough seizures and it is not always possible to obtain the same preparation on a continuous basis.

Table I. 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 II. Starting and maintenance doses and common side effects for first-line AEDs.

Drug	Starting dose	Maintenance dose	Dosing interval	Commonest side effects
Carbamazepine MR	200 mg	400–1800 mg	Bd	Rash Diplopia Dizziness Headache Nausea Hyponatraemia
Ethosuximide	250 mg	500–2000 mg	Bd	Nausea Drowsiness Headache
Lamotrigine	25 mg	100–400 mg	Bd	Rash Nausea Dizziness Headache Insomnia
Levetiracetam	250 mg	750–3000 mg	Bd	Lethargy Irritability Behavioural problems Insomnia Drowsiness Unsteadiness
Oxcarbazepine	300 mg	600–2400 mg	Bd	Rash Diplopia Dizziness Headache Nausea Hyponatraemia
Sodium valproate	300 mg	600–2500 mg	Bd	Weight gain Tremor Hair loss Teratogenesis

Carbamazepine should be prescribed in the modified-release preparation as this reduces side effects⁹. Individuals who cannot tolerate carbamazepine in whom it is effective may tolerate oxcarbazepine, 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 to be false; it is now known that lamotrigine levels can fall unpredictably when oestrogen-containing contraceptives are used concomitantly¹⁰. Similarly lamotrigine levels can fall unpredictably in pregnancy, making management of epilepsy in women taking lamotrigine problematic¹¹. 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^{12,13}; 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 seizures¹⁴ and can be very effective for myoclonic seizures¹⁵ but there are no data for its use as first-line therapy and it can occasionally exacerbate seizures. Lamotrigine is recognised to exacerbate myoclonic seizures in some individuals. 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 effective¹⁶. If there is doubt about the seizure type a broad spectrum AED should be used.

In patients who cannot tolerate the first AED prescribed 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 seizures increase, the cause can be identified. 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 if the first has failed. Theories of 'rational polytherapy' are not supported by extensive evidence¹⁷, 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 outcomes¹⁸. 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)¹⁹ suggest that the underlying nature of the epilepsy is more important and AEDs prevent seizures but do not alter outcome.

References

1. CHADWICK, D., REYNOLDS, E.H. When do epileptic patients need treatment? Starting and stopping medication. *Br Med J (Clin Res Ed)* 1985; 290(6485): 1885–8.
2. MARSON, A., JACOBY, A., JOHNSON, A., KIM, L. GAMBLE, C., CHADWICK, D. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet* 2005; 365(9476): 2007–13.
3. HART, Y.M., SANDER, J.W., JOHNSON, A.L., SHORVON, S.D. National General Practice Study of Epilepsy: recurrence after a first seizure. *Lancet* 1990; 336(8726): 1271–4.
4. KIM, L.G., JOHNSON, T.L., MARSON, A.G., CHADWICK, D.W. Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial. *Lancet Neurol* 2006; 5(4): 317–22.
5. SCHIERHOUT, G., ROBERTS, I. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. *Cochrane Database Syst Rev* 2000(2): CD000173.
6. KWAN, P., BRODIE, M.J. Early identification of refractory epilepsy. *N Engl J Med* 2000; 342(5): 314–9.
7. MARSON, A.G., AL-KHARUS, A.M., ALWAIDH, M. et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; 369(9566): 1000–15.
8. MARSON, A.G., AL-KHARUS, A.M., ALWAIDH, M. et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; 369(9566): 1016–26.
9. PERSSON, L.I., BEN-MENACHEM, E., BENGTTSSON, E., HEINONEN, E. Differences in side effects between a conventional carbamazepine preparation and a slow-release preparation of carbamazepine. *Epilepsy Res* 1990; 6(2): 134–40.

10. SABERS, A., BUCHHOLT, J.M., ULDALL, P., HANSEN, E.L. Lamotrigine plasma levels reduced by oral contraceptives. *Epilepsy Res* 2001; 47(1-2): 151–4.
11. PENNELL, P.B., NEWPORT, D.J., STOWE, Z.N., HELMERS, S.L., MONTGOMERY, J.Q., HENRY, T.R. The impact of pregnancy and childbirth on the metabolism of lamotrigine. *Neurology* 2004; 62(2): 292–5.
12. MORROW, J.I., RUSSELL, A., GUTHRIE, E. et al. Malformation risks of anti-epileptic drugs in pregnancy: A prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006; 77(2): 193–8.
13. VAJDA, F.J., O'BRIEN, T.J., HITCHCOCK, A. et al. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. *J Clin Neurosci* 2004; 11(8): 854–8.
14. BERKOVIC, S.F., KNOWLTON, R.C., LEROY, R.F., SCHIEMANN, J., FALTER, U. Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy. *Neurology* 2007; 69(18): 1751–60.
15. NOAHTAR, S., ANDERMANN, E., MEYVISCH, P., ANDERMANN, F., GOUGH, W.B., SCHIEMANN-DELGADO, J. Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. *Neurology* 2008; 70(8): 607–16.
16. GLAUSER, T.A., CNAAN, A., SHINNAR, S. et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med* 2010; 362(9): 790–9.
17. BRODIE, M.J., YUEN, A.W. Lamotrigine substitution study: evidence for synergism with sodium valproate? 105 Study Group. *Epilepsy Res* 1997; 26(3): 423–32.
18. MACDONALD, B.K., JOHNSON, A.L., GOODRIDGE, D.M., COCKERELL, O.C., SANDER, J.W., SHORVON, S.D. Factors predicting prognosis of epilepsy after presentation with seizures. *Ann Neurol* 2000; 48(6): 833–41.
19. TUAN, N.A., TOMSON, T., ALLEBECK, P., CHUC, N.T., CUONG-LE Q. The treatment gap of epilepsy in a rural district of Vietnam: a study from the EPIBAVI project. *Epilepsia* 2009; 50(10): 2320–3.