

GUIDELINES

Diagnosis and management of the epilepsies in adults and children: summary of updated NICE guidance

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This is one of a series of *BMJ* summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Further information about the guidance, a list of members of the Guideline Development Group, the supporting evidence statements, and two tables summarising drug options are in the full version on bmj.com.

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Previous articles in this series

- Donor identification and consent for deceased organ donation (*BMJ* 2012;344:e341)
- Assessment and referral after emergency treatment of a suspected anaphylactic episode (*BMJ* 2011;343:d7595)
- Longer term management of self harm (*BMJ* 2011;343:d7073)
- Caesarean section: summary of updated NICE guidance (*BMJ* 2011;343:d7108)

Epilepsy is a common neurological disorder characterised by recurring epileptic seizures; it is not a single diagnosis but is a symptom with many underlying causes, more accurately termed the epilepsies. Antiepileptic drugs (AEDs) to prevent recurrence of seizures form the mainstay of treatment. Diagnosis can be challenging, making accurate prevalence estimates difficult. With a prevalence of active epilepsy of 5-10 cases per 1000,¹ epilepsy has been estimated to affect between 362 000 and 415 000 people in England, but with a further 5-30% (up to another 124 500 people) misdiagnosed with epilepsy.² Consequently, it is a physician or paediatrician with expertise in epilepsy who should diagnose and manage the condition. The 2004 guideline from the National Institute for Health and Clinical Excellence on the management of the epilepsies in adults and children was recently partially updated with regard to drug management. This article summarises the main recommendations of the updated version; new recommendations are indicated in parentheses.³

Recommendations

NICE recommendations are based on the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

After a first seizure

- Children, young people, and adults presenting to an emergency department after a suspected seizure should be screened initially for epilepsy. This should be done by an adult or paediatric physician with onward referral to a specialist when an epileptic seizure is suspected or there is diagnostic doubt. (A specialist is defined in the guidance as either a "medical practitioner with training and expertise in epilepsy" (for adults) or a "paediatrician with training and expertise in epilepsy" (for children and young people).)

Diagnosis

- All children, young people, and adults with a suspected seizure of recent onset should be seen urgently (within two weeks) by a specialist. This is to ensure precise and early diagnosis and start of therapy as appropriate to their needs.
- A definite diagnosis of epilepsy may not be possible. If the diagnosis cannot be clearly established, consider further investigations and/or referral to a tertiary epilepsy specialist. Always arrange follow-up.

Investigations

- Children, young people, and adults needing electroencephalography should have the test performed soon (within four weeks) after it has been requested.
- Do 12 lead electrocardiography in adults with suspected epilepsy.
- In children and young people, consider 12 lead electrocardiography in cases of diagnostic uncertainty.
- Magnetic resonance imaging should be the imaging investigation of choice in everyone with epilepsy.
- Magnetic resonance imaging is particularly important in those:
 - Who develop epilepsy before the age of 2 years or in adulthood
 - Who have any suggestion of a focal onset on history, examination, or electroencephalography (unless there is clear evidence of benign focal epilepsy)
 - In whom seizures continue despite first line medication.
- Children, young people, and adults needing magnetic resonance imaging should have it done soon.

General information about drug treatment

- Adopt a consulting style that enables the child, young person, or adult with epilepsy, and their family and/or carers as appropriate, to participate as partners in all decisions about their healthcare and take fully into account their race, culture, and any specific needs.
- Everyone with epilepsy should have a comprehensive care plan that is agreed between the person, their family and/or carers as appropriate, and primary and secondary care providers.
- Individualise the strategy for AED treatment according to the seizure type; epilepsy syndrome; comedication and comorbidity; the lifestyle of the child, young person, or adult; and the preferences of the person, their family, and/or carers as appropriate.
- If using carbamazepine, offer controlled release preparations. (New recommendation.)
For specific advice for women and girls of childbearing potential about AEDs, including sodium valproate, see later in this article.

Starting drug treatment

- When possible, offer an AED chosen on the basis of the presenting epilepsy syndrome. If the epilepsy syndrome is not clear at presentation, base the decision on the presenting seizure type(s). (New recommendation.) See the full version of this article on bmj.com for two tables summarising the different drug options according to seizure type and syndrome.

First line treatment for newly diagnosed focal seizures

- Offer carbamazepine or lamotrigine as first line treatment. (New recommendation.)
- Levetiracetam is not cost effective at June 2011 unit costs (the estimated cost of a 1500 mg daily dose was £2.74 (€3.30; \$4.20) in June 2011⁴). Offer levetiracetam, oxcarbazepine, or sodium valproate (provided the acquisition cost of levetiracetam falls to at least 50% of the June 2011 value documented in the National Health Service Drug Tariff for England and Wales) if carbamazepine and lamotrigine are unsuitable or not tolerated. If the first AED tried is ineffective, offer an alternative from these five AEDs. (New recommendation.)
- Consider adjunctive treatment if a second, well tolerated AED is ineffective. (New recommendation.)

Adjunctive treatment for refractory focal seizures

- If first line treatments are ineffective or not tolerated, offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate as adjunctive treatment. (New recommendation.)
- If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist, who may consider other AEDs: eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin, and zonisamide. Carefully balance the risks and benefits when using vigabatrin because of the risk of an irreversible effect on visual fields. (New recommendation.)

First line treatment for newly diagnosed generalised tonic-clonic seizures

- Offer sodium valproate as first line treatment. (New recommendation.)
- If sodium valproate is unsuitable, offer lamotrigine. If the person has myoclonic seizures or is suspected of having juvenile myoclonic epilepsy, be aware that lamotrigine may exacerbate myoclonic seizures. (New recommendation.)
- Consider carbamazepine and oxcarbazepine, but be aware of the risk of exacerbating myoclonic or absence seizures. (New recommendation.)

Adjunctive treatment for generalised tonic-clonic seizures

- If first line treatments are ineffective or not tolerated, offer clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment. (New recommendation.)
- If myoclonic seizures are absent or if juvenile myoclonic epilepsy is suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin. (New recommendation.)

Continuation of drug treatment

- Maintain a high level of vigilance for the emergence of adverse effects associated with the drug treatment (such as reduced bone density) and neuropsychiatric problems (as there is a small risk of suicidal thoughts

and behaviour; available data suggest that this risk applies to all AEDs and may occur as early as a week after starting treatment⁵). (New recommendation.)

Ketogenic diet

- Refer children and young people with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary paediatric epilepsy specialist for consideration of introducing a ketogenic diet. (New recommendation.)

Prolonged or repeated seizures and convulsive status epilepticus

- Only prescribe buccal midazolam or rectal diazepam for use in the community for those who have had a previous episode of prolonged or serial convulsive seizures. (New recommendation.)
- Administer buccal midazolam as first line treatment in the community. Administer rectal diazepam if preferred or if buccal midazolam is not available. If intravenous access is already established and resuscitation facilities are available, administer intravenous lorazepam. (New recommendation.)

Advice for women and girls with epilepsy

- Discuss with women and girls of childbearing potential (including young girls who are likely to need to continue treatment into their childbearing years)—and their parents and/or carers if appropriate—the risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child. Assess the risks and benefits of treatment with individual drugs. Data are limited on the risks to the unborn child that are associated with newer drugs. Specifically discuss the risk to the unborn child of continued use of sodium valproate, being aware that higher doses of sodium valproate (>800 mg a day) and multidrug treatment, particularly with sodium valproate, are associated with greater risk. (New recommendation.)
- Discuss with women and girls taking lamotrigine the evidence that the simultaneous use of any oestrogen based contraceptive can result in a significant reduction in lamotrigine levels and loss of seizure control. When starting or stopping these contraceptives, the dose of lamotrigine may need adjustment. (New recommendation.)

People with learning disabilities

- Ensure adequate time for consultation to achieve effective management of epilepsy. (New recommendation.)
- Do not discriminate against people with learning disabilities; offer the same services, investigations, and treatments to them as to the general population. (New recommendation.)

Older people with epilepsy

- Do not discriminate against older people; offer the same services, investigations, and treatments to them as to the general population. (New recommendation.)

- Pay particular attention to pharmacokinetic and pharmacodynamic problems with multidrug treatment and comorbidity. Consider using lower doses of AEDs, and, if using carbamazepine, offer controlled release carbamazepine preparations. (New recommendation.)

Review and referral

- Provide a regular structured review to everyone with epilepsy. In children and young people, conduct the review at least yearly (but this may be reduced to between 3 and 12 months by arrangement) by a specialist. In adults, conduct the review at least yearly by a generalist or a specialist, depending on how well the epilepsy is controlled and/or the presence of specific lifestyle problems (such as sleep pattern, alcohol consumption).

Overcoming barriers

The Guideline Development Group was aware of concerns about prescribing sodium valproate to girls and women of childbearing age. The updated recommendations offer alternative prescribing options for this group and also provide additional relevant information when considering prescribing antiepileptic drugs to women of childbearing age. The group also wished to ensure that people with learning disabilities and older people had optimal treatment and had the same opportunities as other adults

to access treatments and specialist epilepsy services; the group expressed concern that this is not necessarily current practice.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: all authors were funded by NICE for the submitted work. In the previous three years JHC has been an expert witness in a proposed action on the possible effects of sodium valproate on the unborn child. She also led the first randomised controlled trial of use of the ketogenic diet in drug resistant epilepsy in children, published in 2008. She currently receives an educational grant to her department from the drug companies UCB and Eisai for a clinical training fellowship in epilepsy, and in 2011 she undertook advisory work for Eisai and Viropharma, with the fees given to her department.

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THERAPEUTICS

Newer drugs for focal epilepsy in adults

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A 28 year old woman sees her general practitioner after experiencing what sounds like a convulsion without any apparent provoking factor. Over the past month she has also had “blank spells” during which her husband noticed her to be unresponsive. Her general practitioner suspects she may have developed focal epilepsy and refers her to an epilepsy specialist. The specialist elicits from the patient and her husband additional features in the history that are highly compatible with seizures arising from the temporal lobe (lip smacking, ipsilateral motor automatism, and contralateral dystonia) and confirms the diagnosis by finding focal epileptiform discharges on electroencephalography and cortical dysplasia in the left temporal lobe on brain imaging. To prevent further seizures the specialist advises treatment with antiepileptic drugs (AEDs). The patient is reluctant to start treatment because she has read that AEDs have many adverse effects, could interact with her oral contraception, and are harmful for babies. She wonders if there are newer AEDs that for her might be better than the traditional ones.

What are the newer antiepileptic drugs?

Epilepsy is resistant to drug treatment in a third of patients.¹ Driven by this high prevalence of drug resistance,

12 agents have been developed to treat adult epilepsy since the late 1980s. These are often referred to collectively as the “newer” antiepileptic drugs—that is, newer than the established drugs, such as phenobarbital, phenytoin, carbamazepine, sodium valproate, and several benzodiazepines, with phenobarbital having been around for 100 years.² In this article we will review the clinical use of (in chronological order of approval in the United Kingdom) lamotrigine, gabapentin, topiramate, oxcarbazepine, levetiracetam, pregabalin, zonisamide, and lacosamide (table 1). We will not discuss the other newer AEDs tiagabine and vigabatrin because they are rarely used for focal epilepsy in adults (owing to efficacy and safety concerns respectively) or eslicarbazepine acetate and retigabine, which have only recently been approved and for which clinical experience is therefore limited.

How well do the newer antiepileptic drugs work?

Add-on therapy

To obtain licensing approval as add-on therapy, all AEDs have to show superior efficacy compared with placebo in double blind randomised controlled trials. In regulatory studies for AEDs, the primary efficacy measure is statistical significance against placebo for responder rate in

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Philip Routledge, professor of clinical pharmacology, Cardiff University. To suggest a topic for this series, please email us at practice@bmj.com.

Table 1 | Mechanisms of action, year first licensed, and approved indications for newer antiepileptic drugs discussed in this review for use in adults in the United Kingdom

Antiepileptic drug (year first licensed)	Mechanism of action	Indications		
		Seizure type*	Add-on therapy	Monotherapy
Lamotrigine (1991)	Blocks fast-inactivated state of sodium channel	Focal, generalised	Yes	Yes
Oxcarbazepine (2000)	Blocks fast-inactivated state of sodium channel	Focal	Yes	Yes
Lacosamide (2008)	Blocks slow-inactivated state of sodium channel	Focal	Yes	
Gabapentin (1993)	Blocks high voltage-activated calcium channel	Focal	Yes	
Pregabalin (2004)	Blocks high voltage-activated calcium channel	Focal	Yes	
Levetiracetam (2000)	Modulates synaptic vesicle protein 2A	Focal, generalised	Yes	Yes
Topiramate (1995)	Various actions on multiple targets	Focal, generalised	Yes	Yes
Zonisamide (2005)	Various actions on multiple targets	Focal	Yes	

*Seizures are broadly classified into focal or generalised on the basis of the mode of onset.³ Focal (partial) epileptic seizures are conceptualised as originating within networks limited to one hemisphere and may be discretely localised or more widely distributed. Focal seizures may or may not lead to impairment of consciousness or awareness and may evolve to bilateral convulsive seizures (secondarily generalised tonic-clonic seizure). Generalised epileptic seizures are conceptualised as originating at some point within, and rapidly engaging, bilaterally distributed networks. Examples include (primarily) generalised tonic-clonic, absence, myoclonic seizures.

Europe (defined as a ≥50% reduction in seizure frequency) and median reduction in seizure frequency in the United States.⁴ A recent meta-analysis that evaluated the clinical effectiveness and tolerability of the newer AEDs included 62 placebo controlled studies in children and adults in terms of responder and withdrawal rates (table 2).⁵ Owing to methodological heterogeneity—such as in the range of dosages tested and of treatment durations (8-26 weeks)—and the small differences found, caution is needed in drawing comparisons between these drugs. In addition, the clinical relevance of the responder rate as a useful clinical end point remains questionable. The recent consensus from the International League Against Epilepsy⁶ proposes that a treatment’s success should be defined by sustained freedom from seizures, as that is the only efficacy outcome consistently associated with improved quality of life (and in the UK the only efficacy outcome that allows a patient to drive legally). Using this measure, another meta-analysis showed that the overall weighted pooled-risk difference in favour of the newer AEDs compared with placebo for

freedom from seizures during the limited study periods was only 6% (95% confidence interval 4% to 8%; number needed to treat in terms of freedom from seizures, 16).⁷

Monotherapy

Several of the newer AEDs have shown efficacy similar to that of the older drugs (mostly carbamazepine), and sometimes similar to that of each other, for the treatment of new onset focal epilepsy in adults in head to head monotherapy trials and have been approved for this indication in the UK and other European countries.⁸ These approved drugs include levetiracetam, lamotrigine, oxcarbazepine, and topiramate and in some countries gabapentin. Seizure-free rates for a year in this highly selective population have increased to about 60% as the design of the studies has evolved.⁹

However, although there is evidence of efficacy under controlled research conditions for these drugs, their clinical effectiveness and cost effectiveness have been poorly studied. The greater overall effectiveness for focal seizures (mostly in terms of better tolerability) of lamotrigine compared with carbamazepine, oxcarbazepine, and gabapentin in the randomised open-label Standard and New Antiepileptic Drugs (SANAD) study of 1721 patients arguably makes it the drug of first choice in this clinical setting.¹⁰ The SANAD study found that gabapentin had significantly inferior efficacy compared with carbamazepine, and most experts do not recommend gabapentin as initial monotherapy.

How safe are the newer antiepileptic drugs?

All AEDs are associated with a range of adverse effects, the main reason for withdrawal in regulatory trials.⁵ Many adverse effects were detected only during postmarketing surveillance, and their long term adverse effects (such as on bone health) are unknown.

Idiosyncratic reactions

Such reactions are unpredictable adverse effects independent of dosage.¹¹ The most common of these is rash, which develops in 3-5% of patients taking lamotrigine, zonisamide, or oxcarbazepine but in <1% of those taking

Table 2 | Meta-analysis of responder rate and withdrawal rate for newer antiepileptic drugs as add-on therapy for uncontrolled focal epilepsy in randomised controlled trials (modified from Costa et al, 2011⁵)

	Gabapentin	Lacosamide	Levetiracetam	Lamotrigine	Oxcarbazepine	Pregabalin	Topiramate	Zonisamide
Data for responder rate*								
Trials/patients (n/n)	6/1187	3/1092	10/1693	12/1314	2/961	6/1867	10/1312	4/850
Responder rates for drug/placebo (%)	19.9/10.9	37.7/22.6	40.1/17.0	28.3/15.1	39.5/16.6	37.2/15.2	44.8/15.2	32.6/13.1
Odds ratio (95% CI)	2.08 (1.47 to 2.96)	2.06 (1.54 to 2.76)	3.75 (2.71 to 5.20)	2.34 (1.66 to 3.30)	3.30 (1.80 to 6.08)	3.61 (2.21 to 5.89)	4.31 (3.07 to 6.06)	2.99 (2.07 to 4.32)
Number needed to treat	19 (14-31)	10 (8-15)	8 (8-10)	12 (10-18)	9 (7-15)	10 (8-13)	9 (8-10)	12 (10-16)
Data for withdrawal rate†								
Trials/patients (n/n)	6/1206	3/1105	10/1721	13/1767	2/961	6/1867	10/1312	4/850
Withdrawal rates for drug/placebo (%)	8.8/10.0	21.2/12.9	11.7/11.6	16.5/14.1	41.1/19.9	23.2/17.1	16.5/6.9	20.6/12.9
Odds ratio (95% CI)	0.99 (0.66 to 1.5)	1.8 (1.26 to 2.56)	0.97 (0.69 to 1.36)	1.19 (0.90 to 1.57)	2.27 (1.62 to 3.17)	1.52 (1.17 to 1.98)	2.38 (1.54 to 3.65)	1.59 (1.08 to 2.34)
Number needed to harm	NA	19 (13-42)	NA	NA	10 (8-15)	19 (13-47)	26 (20-43)	23 (9-119)

CI=confidence interval; NA=not applicable.

*Responders had at least a 50% reduction in seizure frequency.

†Withdrawals were mostly because of adverse events.

topiramate, levetiracetam, gabapentin, or pregabalin.¹² Lamotrigine and oxcarbazepine can rarely lead to Stevens-Johnson syndrome or toxic epidermal necrolysis. Other rare idiosyncratic reactions include hepatitis, pancreatitis, and blood dyscrasias.

Ophthalmic effects

Rare cases of acute angle-closure glaucoma and myopia have been reported with topiramate.

Neurotoxicity

Typical dose related symptoms including nausea, diplopia, dizziness, headache, tiredness, somnolence, sedation, and ataxia can occur with all AEDs.¹³

Renal calculi

Topiramate and zonisamide carry a small (1%) risk of symptomatic renal calculi as both drugs inhibit carbonic anhydrase.

Cardiac effects

Minor prolongation in the PR interval has been observed in clinical studies with lacosamide.

Psychiatric effects

Topiramate is associated with anorexia, weight loss, word finding difficulties, and neuropsychiatric complications. Behavioural problems, such as agitation, aggression, hostility, psychosis, anxiety, and depression, have been reported in patients treated with levetiracetam. Zonisamide can also produce or exacerbate psychiatric comorbidities, particularly depression.¹⁴ The US Food and Drug Administration analysed data from 199 placebo controlled trials of 11 AEDs and found an increase in risk of suicidal behaviour or ideation among patients receiving them (0.43%) compared with those receiving placebo (0.22%).¹⁵ A community based case-control study in treated epilepsy documented increased risk of suicidal behaviour associated with some newer AEDs (such as topiramate, levetiracetam) only in patients with a high risk of depression.¹⁶

Teratogenicity

Recent data from EURAP, the largest international prospective cohort study of 3909 pregnancies, reported that in utero exposure to lamotrigine monotherapy was associated with an overall, dose dependent rate of major fetal malformation at 1 year of age that ranged from 2% (<300 mg/day) to 4.5% (≥300 mg/day). This was less than that with carbamazepine (3.4% to 8.7%), phenobarbital, (5.4% to 13.7%) and particularly sodium valproate (5.6% to 24.2%).¹⁷ The UK pregnancy register reported a rate of major fetal malformation for untreated women with epilepsy (n=239) of 3.5% (95% confidence interval 1.8% to 6.8%).¹⁸ Children exposed to lamotrigine in utero had similar IQs at age 3 years to those exposed to phenytoin and carbamazepine, which was around 10 percentage points higher than those taking high dose sodium valproate.¹⁹ Data from the US and UK pregnancy registries indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester.²⁰ Sufficient data for other newer AEDs are lacking, although preliminary experience from the UK

pregnancy registry has suggested a low risk of teratogenicity with levetiracetam.²¹

What are the precautions?

Precautions relate to potential adverse effects as discussed above. Examples are outlined as follows.

Rash

Closely monitor patients with a history of allergic rash when introducing an AED as they have an approximate fivefold increased risk of developing another rash.¹² Avoid oxcarbazepine in patients with a history of rash induced by carbamazepine because of a cross sensitivity rate between these drugs of 25-31%.

Cardiac problems

For patients with a history of cardiac problems, including conduction block, taking drugs known to prolong the PR interval, and for those aged over 65, use lacosamide cautiously and perform electrocardiography before starting treatment and after titration to optimal dosage.

History of psychiatric illness

Avoid topiramate, levetiracetam, and zonisamide, or, if essential, use these cautiously.

History of renal calculi

Avoid topiramate and zonisamide as they inhibit carbonic anhydrase; advise all patients taking these drugs to avoid dehydration.

Renal impairment

For patients with renal impairment prescribe lower doses of gabapentin, levetiracetam, and pregabalin as these are predominantly excreted unchanged in the urine.

Interaction with oral contraceptives

As oxcarbazepine and topiramate (at daily doses above 200 mg) selectively induce the breakdown of the oestrogenic component of oral contraception,¹³ patients taking oral contraception need formulations with higher doses (50 µg) of oestrogen, with subsequent adjustment of hormones depending on any breakthrough bleeding; other contraceptive measures must be taken until the menstrual pattern has been stable for at least three months. As the oestrogenic component of oral contraception significantly increases the metabolism of lamotrigine, the dosage of lamotrigine may need adjustment when starting combined oral contraception (to maintain seizure control) and when stopping the pill (to minimise adverse effects of lamotrigine).²²

Pregnancy

Limited data are available on the teratogenic risk of the newer AEDs. Counsel women of childbearing potential on pregnancy matters early.²³ Advise them to plan pregnancy, so that any changes to their regimen of AED treatment can be made before conception (because teratogenesis may occur early in the first trimester). Treatment with AEDs should be continued during pregnancy on the basis that seizures, especially convulsive seizures, are more harmful

Table 3 | Advantages and disadvantages of the established and newer antiepileptic drugs

	Advantages	Disadvantages
Older antiepileptic drugs		
Carbamazepine	Cost effective for new onset focal seizures	Dizziness, headache, drowsiness, diplopia, rash, hyponatraemia, osteoporosis, enzyme induction, blood dyscrasias
Phenobarbital	Broad spectrum of activity; once daily; cheap	Sedation, behavioural disturbances, hyperactivity, rash, teratogenesis, osteoporosis, folate deficiency, enzyme induction, Dupuytren's contracture
Phenytoin	Once daily; rapid titration; intravenous formulation available; cheap	Headache, dizziness, ataxia, rash, gum hyperplasia, hirsutism, acne, osteoporosis, peripheral neuropathy, enzyme induction, saturation kinetics, cerebellar atrophy
Sodium valproate	Cost effective for new onset generalised seizures; broad spectrum of activity; rapid titration; few interactions	Nausea, diarrhoea, lethargy, drowsiness, weight gain, thrombocytopenia, alopecia, tremor, extrapyramidal symptoms, enzyme inhibition, teratogenesis
Newer antiepileptic drugs		
Gabapentin	Low risk of allergic reactions; low risk of drug interaction	Drowsiness, dizziness, ataxia, weight gain, diarrhoea, dose adjustment needed in renal impairment
Lacosamide	Low risk of drug interaction; intravenous formulation available	Dizziness, headache, diplopia, nausea, vomiting, tremor, rash, minor prolongation in the PR interval
Lamotrigine	Cost effective for new onset focal seizures; broad spectrum; few interactions; better tolerated than older drugs; low risk of teratogenicity	Headache, insomnia, diplopia, dizziness, ataxia, rash, interacts with combined contraception pill
Levetiracetam	Broad spectrum of activity; intravenous formulation available; low risk of drug interaction	Somnolence, headache, neuropsychiatric and behavioural effects such as aggression, depression, dose adjustment needed in renal impairment
Oxcarbazepine	Better tolerated than older drugs	Dizziness, nausea, vomiting, headache, drowsiness, rash, hyponatraemia, interacts with combined contraception pill
Pregabalin	Low risk of allergic reactions; low risk of drug interaction	Dizziness, somnolence, headache, ataxia, weight gain, peripheral oedema, sexual dysfunction, dose adjustment needed in renal impairment
Topiramate	Broad spectrum; weight loss in obesity	Dizziness, paraesthesia, somnolence, confusion, fatigue, weight loss, renal stones, neuropsychiatric effects, interacts with combined contraception pill
Zonisamide	Broad spectrum; once daily; weight loss in obesity; low risk of drug interaction	Anorexia, dizziness, fatigue, nausea, vomiting, weight loss, renal stones, rash, neuropsychiatric effects especially depression

to the mother and fetus than are the drugs themselves; however, treatment should be tapered to a minimal effective dose before pregnancy, if possible to a single AED. Supplemental folic acid is advised ($\geq 400 \mu\text{g}$ daily) before conception and during pregnancy to reduce the risk of major congenital malformation.²⁴ Offer prenatal diagnosis using targeted fetal ultrasonography to detect any major structural abnormalities. After delivery, encourage all mothers to breast feed their babies. If the AED dose, particularly that of lamotrigine, has been increased during pregnancy, consider a reduction in dosage after delivery.

Breast feeding

Lamotrigine can accumulate in the breastfed baby because of slow elimination. However, few data relate to the other newer AEDs. As a general rule, if the baby is noted to be drowsy or sedated, breast feeding should be alternated with bottle feeding or discontinued.

How are the newer antiepileptic drugs taken and monitored?

All the newer AEDs discussed in this article are taken orally. Oxcarbazepine and levetiracetam are available in liquid formulations. Lacosamide is also available as a syrup and by intravenous injection. An intravenous formulation of levetiracetam has been licensed in Europe for patients aged ≥ 4 years when oral administration is temporarily not feasible.

In general, start newer AEDs at low dosage, with increments over several weeks to establish an effective and tolerable regimen.¹³ Some agents, such as gabapentin and levetiracetam, can be started at effective doses with or without rapid titration, whereas others, such as lamotrigine and topiramate, require slow titration to reduce the risk of rash and cognitive impairment, respectively. Slow titration will also facilitate the development of tolerance to sedation and will ensure early detection of potentially serious idiosyncratic reactions.

Once the target dosage has been reached, adjust the dose further on the basis of seizure control and tolerability. Routine measurement of serum concentrations of the newer AEDs is not recommended (and not available in most clinical settings), as they do not correlate well with efficacy or side effects.²⁵ However, serum concentrations of lamotrigine fall dramatically during pregnancy, in patients who have recently started taking an oral contraceptive containing oestrogen, and in women just before the onset of the menses. Lamotrigine monitoring is particularly helpful in guiding dosing during pregnancy.²⁴ Such monitoring is not available routinely across the UK and is best performed with advice from an epilepsy specialist. Arguably, however, lamotrigine concentrations should be measured before conception, regularly throughout pregnancy, and in the puerperium.²⁵

How cost effective are the newer antiepileptic drugs?

Whether the better tolerability and interaction profile of newer AEDs are worth the higher price has been much debated. High quality cost effectiveness studies are lacking. The guidelines from the National Institute for Health and Clinical Excellence (NICE) included cost utility analyses of AEDs and found lamotrigine to be the most cost effective monotherapy (although carbamazepine may be as cost effective).²⁶ However, such cost utility analyses often do not adequately account for indirect or "hidden" costs such as interactions between drugs and long term adverse effects. Moreover, generic formulations are becoming available for many of the newer AEDs, thus driving down prescription costs.

How do the newer antiepileptic drugs compare with the established ones?

Given the limited number of comparative studies, AED treatment for the individual patient is not based entirely on these and depends also on the patient's age, weight, sex, comorbidities, and perceived differences in adverse effects, propensity for interactions, and cost. Owing to the absence of adequate evidence, judgments about treatment choice (in an attempt to be rational) are based on what we think we know about these other factors. Table 3 lists some advantages and disadvantages of the established and newer AEDs.

Choice of drug in newly diagnosed epilepsy

Based on a systematic review and consideration of clinical benefits, harms, and cost effectiveness, the updated NICE guidelines recommend offering carbamazepine or lamotrigine as first line treatment to children, young people, and adults with newly diagnosed focal seizures; if

these are unsuitable or not tolerated, NICE recommends levetiracetam (if its acquisition cost falls to at least 50% of the value at June 2011), oxcarbazepine, or sodium valproate.²⁶ The American Academy of Neurology supports starting treatment with the older AEDs and lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patients' characteristics.²⁷ The International League against Epilepsy adopts a stricter classification of evidence, supporting only carbamazepine, phenytoin, and valproic acid as initial monotherapy for partial onset seizures in adults and lamotrigine and gabapentin for older people.²⁸ On the basis of the double blind, randomised monotherapy study of levetiracetam versus extended release carbamazepine in newly diagnosed epilepsy, which fulfilled the strict criteria of the International League against Epilepsy, levetiracetam can also be recommended for this indication.⁹ These differing recommendations may reflect fundamental differences in the purposes of the various guidelines and in the approaches adopted by the groups developing them.

Choice of drug in uncontrolled epilepsy

As very few head to head comparisons of new AEDs exist for the treatment of drug resistant epilepsy, choice remains largely empirical. The increasing number of

available agents has encouraged consideration of their different mechanisms of action (table 1) in optimising their efficacy in combination. The broad spectrum AEDs levetiracetam, topiramate, and zonisamide, which have multiple mechanisms of action, are often chosen in drug resistant epilepsy.²⁹

Our case scenario

Treatment with AEDs is indicated for our patient with recurrent focal seizures, the latest of which seem to have developed into a secondarily generalised seizure (epileptic seizure with focal onset and subsequent bilateral convulsion). On the basis of this review and in line with NICE guidance, given the patient's childbearing potential, the drug of choice would be lamotrigine, preferably maintained at <300 mg/day. Ideally, monitor the concentration before conception, during pregnancy, and in the puerperium. We do not recommend carbamazepine for her because of its comparatively higher risk of fetal malformation (when the dose is ≥ 400 mg/day) and enzyme induction of the oestrogenic component of her oral contraception. Levetiracetam can also be considered because it is effective as controlled release carbamazepine and preliminary data suggest a low risk of teratogenicity, although NICE asserts that it is not as cost effective as lamotrigine at June 2011 unit costs.

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TIPS FOR PATIENTS

Drug treatment aims at preventing the development and spread of seizures (the electrical consequence of an underlying process in the brain) but does not affect the underlying cause of the epilepsy

Keep a diary of any seizures and side effects you have experienced and discuss the record with your general practitioner or epilepsy specialist during consultations

Discuss the common problems associated with your treatment with your general practitioner before starting any new drug

If you think you are experiencing a side effect with your epilepsy treatment, discuss this as soon as possible with your general practitioner or epilepsy specialist

If you are a woman you should seek advice on contraception to ensure that the epilepsy treatment does not interfere with your oral contraception and request referral to an epilepsy specialist if you are planning a pregnancy

Health problems that arise months or years after taking an unchanged treatment schedule are unlikely to be the result of the antiepileptic drugs but should be discussed with your doctor as they may affect your epilepsy treatment

Adding another medicine can sometimes interfere with the epilepsy drugs, producing side effects or reducing the efficacy of these drugs and thus worsening seizure control. Check this specifically with your doctor when he or she recommends starting you on any new drug

Very rarely an epileptic seizure can affect the function of the heart, lungs, or brain, resulting in sudden death, and so taking the antiepileptic drugs is essential

TIPS FOR GENERAL PRACTITIONERS

Refer patients with suspected epilepsy to a specialist in epilepsy care for diagnosis, investigation, and treatment

If problems arise, seek advice from the appropriate neurologist or local epilepsy specialist nurse

Refer patients planning a pregnancy to an epilepsy specialist for advice, optimisation of the antiepileptic drug regimen, and initiation of folic acid

When introducing adjunctive treatment in a patient with drug resistant epilepsy it may be necessary to reduce the dose of one of the other drugs, particularly if this is being taken at a high dose, to facilitate optimal tolerability

If a clinical problem occurs after an antiepileptic drug monotherapy or multidrug regimen has been stable for some years, the problem is unlikely to be caused by the antiepileptic drugs

Routine therapeutic drug monitoring of antiepileptic drugs is not necessary. Use monitoring only to ask a clinical question, such as whether the patient is complying with the treatment

If a patient is considering stopping treatment, advise him or her to discuss the risks with an epilepsy specialist before finalising the decision

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▶ Oral antiplatelet agents clopidogrel and prasugrel for the prevention of cardiovascular events (*BMJ* 2011;342:d3488)

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A PATIENT'S JOURNEY

Juvenile myoclonic epilepsy

Nicola Morrison,¹ Rhys Thomas,² Phil Smith³

Diagnosed with epilepsy in her twenties, Nicola Morrison was told it was likely to be life long. She describes how she has grown up alongside the seizures

I was 27 years old, had been married about a year, and was living in Inverness when I was diagnosed with epilepsy. I had moved to the area when we got married but didn't know anyone, and it was all very new to me. I was working in a school for children with special needs, which I loved, and was just beginning to find my feet and gain a little confidence. Although I had experienced a seizure when I was about 14, it was investigated with electroencephalography and doctors concluded that it was not epilepsy, highly likely to be a one off, and may even have been a reaction to a dose of antisickness medication following a minor knee operation. Several months into married life, I began to have more and more frequent jerks, predominantly in my right arm. I ignored them for a while but they became too regular and too disruptive to do so for long. I couldn't serve up food on to plates without spilling it and hot drinks were also dangerous. I recalled the jerks from stressful situations during my university days, but I had never put two and two together.

Restriction

I have never really been one to talk about my epilepsy; I guess at times it has been my way of coping. I don't think

I have been in denial but I just talk myself through things at my own pace over and over again in my head, coming to terms with the constraints the condition imposes on me. When I was diagnosed, I remember coming home from the hospital after seeing the consultant and being devastated because I would no longer be able to drive. My husband, John, worked away for two weeks at a time so I was going to have to sort out lifts for work and in an instant I felt like all my independence had been taken away from me. It wasn't so much the epilepsy as its practical repercussions. I don't remember being given any information at the time about epilepsy in general. We weren't fortunate enough to have an epilepsy nurse specialist in Inverness ten years ago, so there really wasn't any support for me or my husband that we knew of. Since then I have used the Epilepsy Action website (www.epilepsy.org.uk), watched related television programmes, and listened to radio programmes, and I guess I have just had more time to come to terms with my diagnosis.

First and second pregnancies

A very low dose of sodium valproate controlled my myoclonic seizures for my first year but by then I was thinking of starting a family and so was taken off the drug by my general practitioner. I remained free of seizures throughout my first pregnancy but went back on to sodium valproate when my daughter was three months old because the seizures recurred. I didn't appear to suffer from any

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This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance.

To share more people's experience of epilepsy go to: www.healthtalkonline.org/Nerves_and_brain/Epilepsy

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- ▶ Facial disfigurement (*BMJ* 2011;343:d5203)
- ▶ Sir Karl Popper, swans, and the general practitioner (*BMJ* 2011;343:d5469)

side effects but more drug changes were inevitable as I was planning another pregnancy. Also, I had my first tonic-clonic seizure a year or so later. Planning was the name of the game and so I was trialled on levetiracetam by yet another consultant. The dose for this increased dramatically throughout my pregnancy. I think I was on the highest dose the drug was licensed for—and still it did not control the seizures. With hindsight, I don't think anything would have controlled them, but looking back I can see how I became a different person. I lost a lot of confidence and became anxious about everything, to the point of really not wanting to do anything or go anywhere. That was just not like me. I was tired all the time and just wanted to sleep, but I was the sole carer for two weeks each month. Eventually we had to move closer to my family and friends. We managed to find two friends in particular who were willing to stay overnight and make sure I was OK with the two little ones when John was away working.

Support and progress

Moving has been frustrating at times. First, we went from Inverness to Aberdeen where we received excellent care and advice with research projects on the go and nurse specialists available when I needed them. They were particularly supportive during my second pregnancy (a 24 hour answer phone was available) as drug treatment during pregnancy was a field they were researching. It made me feel like somebody knew what they were talking about and that gave me a feeling of security.

We then moved to Cardiff where the most frustrating part was the delay in seeing a consultant; apparently my

FURTHER READING**Web based resources for patients and health professionals**

Epilepsy Action (www.epilepsy.org.uk) is the largest member led epilepsy organisation in the UK and has an active web forum as well as a helpline.

Epilepsy Society (formally the National Society for Epilepsy) (www.epilepsysociety.org.uk) is a medical charity focusing on research and awareness campaigns.

UK Epilepsy and Pregnancy Register (www.epilepsyandpregnancy.co.uk) has a free helpline for clinicians and patients to discuss epilepsy drugs in pregnancy. Their registry is one of the first and one of the largest in the world and the source of much of what is known regarding the safety of antiepileptic drugs in pregnancy.

Epilepsy Bereaved (www.sudep.org) is a voluntary organisation that works to support bereaved families and prevent unnecessary deaths from sudden unexpected death in epilepsy (SUDEP) and other epilepsy deaths.

notes took almost nine months to appear. My general practitioner was great in understanding my situation and frustrations, helping me to balance it all with being careful as a busy mum. After my last change in medication we would speak over the phone to change doses as requested by the consultant. This saved her surgery time and saved me finding time to go to the surgery without the children in tow.

My job just now is at home with the children and it gives me so much flexibility in keeping my epilepsy under control. If I am tired, I can do less about the house or go to bed for an hour when the little one is at nursery and my seizures have been far less frequent. I had been having myoclonic jerks up to five or six times a day about a year ago (although this may have been a side effect of the drugs), but I haven't had any since being put on zonisamide. My last tonic-clonic seizure was in October 2010. It sounds like a cliché but I do feel I am getting my life and my old self back.

Reflection

What do I know now that I wish I had been told at the time? That there is no quick fix. Everyone is different, I know, but personally I like to be told things straight. I might not like what I hear initially, but I am not someone who finds it easy to read between the lines. I wish someone could have told me at the beginning of my journey with epilepsy that there is often no quick and easy cure. It is often about "playing around" with drugs until doctors find the ones that suit you. Even then, there is no guarantee that you can remain on those drugs for the rest of your life. Depending on your type of epilepsy it may get worse at different stages in your life; it may not, but be as prepared for it as possible.

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A DOCTOR'S PERSPECTIVE

450 000 people are estimated to have epilepsy within the UK and a further one in twenty people has a seizure in their life time. Epilepsy remains poorly understood (even within some medical circles) despite its high prevalence and its long term nature, and stigma is common. To many people a bigger cause of isolation, stress, and stigma than the diagnosis itself is the ineligibility to drive that accompanies epilepsy. There are only so many places a free bus pass can get you to in rural Scotland—particularly when trying to navigate a pram through the public transport system.

Nicola's story of a delayed diagnosis of juvenile myoclonic epilepsy is very typical, yet she has had her own difficulties to face. Myoclonic jerks are often not recognised for what they are, or are not sought by the consulting physician. Her type of epilepsy—despite starting in her teenage years—would not be expected to remit; therefore when choosing an antiepileptic drug, the clinician must consider the possibility of future pregnancy. In retrospect, Nicola was lucky not to be taking sodium valproate when she was pregnant, as we now know it to be not just physically but cognitively teratogenic. It is always a difficult decision to change antiepileptic medication to become pregnant—and one to be made (as far as possible) in close collaboration with the prospective mother, providing her with as much information as possible. We do not often counsel people to come off their drugs, but undoubtedly some people do and never let us know about it.

Epilepsy is not one condition but an umbrella of many disorders each with the same symptom: seizures. A consequence of this is that, even with an electroclinical syndromic diagnosis like juvenile myoclonic epilepsy, people respond differently to medication, making it very difficult to match the right person to the right drug. It can be enormously stressful when the drug control fails after a period of months or years and it is not clear what to do next. Uncertainty in the absence of good evidence often results in a variety of clinical approaches and patients can feel like the doctors are "experimenting" on them until either good seizure control is achieved, or either party loses enthusiasm for further drug changes.

Nicola's story is the description of a journey where she has overcome the shock of diagnosis, faced the trial of social restrictions (like driving), navigated the apparent inequalities of NHS care, and still remained a mother, wife, and teacher—rather than being labelled as a person with epilepsy.

Rhys Thomas and Phil Smith