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Management of chronic epilepsy

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Epilepsy can be defined pragmatically as the occurrence of at least two unprovoked epileptic seizures. It is the commonest serious neurological condition in adults, directly affecting over 400 000 people in the United Kingdom and up to 60 million people worldwide.[1] Prevalence of epilepsy in developed countries is about 0.5%; however, the lifetime risk of a person having a non-febrile epileptic seizure is much higher at 2-5%, implying, for most patients, remittance of the condition or premature death.

Risk of a second seizure occurring within two years of the first event is about 50%. Early treatment with antiepileptic drugs after the first seizure does not affect the long term prognosis, with 75-80% achieving remission at five years, irrespective of whether treatment began after the first seizure or only after a recurrence.[2 3] Treatment is therefore typically reserved for people who have had at least two seizures; the risk of a third seizure in these patients is over 70%. A tailored approach to treatment should always be adopted, since there could be circumstances in which treatment after a first seizure is appropriate (for example, presence of a structural lesion on neuroimaging) or deferred (for example, in those with very infrequent seizures).

Most people with epilepsy eventually become free of seizures on antiepileptic drugs. Nevertheless, about 20-30% of patients continue to have seizures despite treatment.[4] By extrapolating this proportion to the UK, an estimated 100 000 people with epilepsy need continuing, hospital based medical treatment. Of this group, over 35 000 will have more than one seizure a month. Epilepsy carries an increased risk of morbidity and premature mortality with standardised mortality rates two to threefold higher than the general population.[5 6] This raised risk is partly due to the underlying cause of the epilepsy but is also a direct result of seizures, such as an increased risk of accidents (including drowning) and sudden unexpected death in epilepsy (a condition that affects at least 500 people with epilepsy in the UK annually). On this basis, seizure remission, wherever possible, is a major goal.

The implications of chronic epilepsy extend beyond continued seizures, and encompass cognitive difficulties, mood disturbance, and lifestyle issues, the effective treatment of which involves a coordinated response from both primary and secondary care.

The purpose of this review was to examine the literature on how to manage adults with chronic epilepsy.

SUMMARY POINTS

- Epilepsy is common, affecting over 400 000 people in the United Kingdom
- Epileptic seizures are associated with an increased risk of morbidity and premature mortality
- Quality of life depends on seizure freedom and lack of adverse effects from drug treatment
- Comorbidities and the effects on lifestyle, mood, and relationships are also important
- Up to 75% of people with epilepsy become seizure-free on treatment
- Choice of drug treatment should be tailored to each person, as determined by their characteristics, the epilepsy syndrome, seizure types, lifestyle issues, and cotreatments
- Combination treatment could be needed for patients who do not respond to monotherapy
- Review diagnosis and treatment compliance for patients who do not respond to treatment
- Consider other treatment options, such as surgery, in people with chronic focal epilepsy

SOURCES AND SELECTION CRITERIA

This clinical review is based on personal experience, reference archives, and a wide literature search of PubMed using the search terms "adult epilepsy", "management of epilepsy", and "antiepileptic drugs". We also consulted guidelines from the International League against Epilepsy, American Academy of Neurology, PubMed search for adult epilepsy, and antiepileptic drug and clinical management guidelines from the National Institute for Health and Clinical Excellence (clinical guideline 137, 2012).

Who gets epilepsy?

The incidence of epilepsy is increased in childhood, at least partly because of brain malformations, perinatal cerebral insults, and genetic disorders, and in later life, usually as a result of cerebrovascular disease. Nevertheless, seizures could start at any age and may follow a cerebral insult, such as head injury, intracranial infections, or tumours. The risk of developing epilepsy increases in the presence of learning disability or after a prolonged or lateralised febrile convulsion in childhood. Genetic factors contribute either directly (for example, in the autosomal dominantly inherited condition tuberous sclerosis) or in a more complex pattern of polygenic inheritance. Overall, genetic factors are thought to contribute to about 40% of people with epilepsy.

What is the goal of epilepsy treatment?

In all people with epilepsy, the goal should be to achieve seizure freedom. Reducing a person's seizures by 50%, for example, from six seizures to three seizures a month might have a minimal effect on quality of life.[7] This is largely because of the restrictions to a person's lifestyle that remain until seizure freedom, such as the inability to drive, difficulties obtaining work, and maintaining a relationship. Nevertheless, antiepileptic drugs have both idiosyncratic and often more predictable chronic side effects, and seizure freedom should not be relentlessly pursued at the expense of quality of life; intrusive side effects also have a negative effect on quality of life.[7] Common side effects that lead to withdrawal of drug treatment include drowsiness, dizziness, lethargy, and cognitive slowing. These side effects are a particular concern for combination antiepileptic drug treatment.

How is epilepsy managed?

The diagnosis of epilepsy is clinical—that is, it is made on the basis of a description of the seizure by both a patient and a witness. It is mandatory to try to obtain a witness

Box 1 | : Information needs

General epilepsy information
Explanation of what the condition is
Classification
Investigations
Syndrome
Epidemiology
Prognosis
Genetics
Sudden unexpected death in epilepsy

Antiepileptic drugs
Choice of drug
Efficacy
Side effects
Adherence
Drug interactions
Free prescriptions

Seizure triggers
Lack of sleep
Alcohol and recreational drugs
Stress
Photosensitivity

First aid
General guidelines

Issues for women
Contraception
Preconception
Pregnancy and breastfeeding
Menopause

Lifestyle
Driving regulations
Employment
Education
Leisure
Relationships
Safety at home

Possible psychosocial consequences
Perceived stigma
Memory loss
Depression
Anxiety
Maintain mental wellbeing
Self esteem
Sexual difficulties
Support organisations
Address and telephone numbers

description, which is often more informative than the person's account of the event, which may be confounded by loss of awareness, confusion, and amnesia. Investigations such as a brain scan by magnetic resonance imaging or an electroencephalography recording should be used to corroborate clinical suspicion and not as screening tests, owing to the presence of both false positive and false negative information. Patients should be referred to a specialist for evaluation if a seizure is suspected, but drug treatment is typically started only after a second seizure. The choice of initial monotherapy has been guided by several important studies (including, most recently, SANAD[8 9]) and advice from the National Institute for Health and Clinical Excellence (NICE).[10] The antiepileptic drug strategy should be tailored to each patient's seizure type, epilepsy syndrome, cotreatment, comorbidity, lifestyle issues, and preferences (box 1).

Specialists should adjust the dose of the selected drug to achieve optimal seizure control, making increments if seizures continue in the absence of side effects and, for some drugs such as phenytoin, being guided by assays of serum drug concentrations. Zealous adherence to quoted therapeutic ranges of serum antiepileptic concentrations is, however, not appropriate. These data should always be secondary to the clinical picture of whether the person continues to have seizures or dose related side effects from antiepileptic drugs. Blood levels of antiepileptic drugs should also be monitored to detect non-adherence to the prescription, suspected toxicity, and in the management of specific clinical conditions such as status epilepticus, organ failure and pregnancy, in which serum levels may fall resulting in the re-emergence of seizures.

Treatment should be initiated and continuing therapy should be planned by the specialist. If management is straightforward, continuing drug treatment can be prescribed in primary care if local circumstances or licensing allow. The duration of each treatment trial before deciding on continuing or changing to an alternative drug depends on the occurrence of side effects and seizure frequency. For example, it will take longer to establish whether a drug has been effective in a patient with very infrequent seizures than in a patient with daily or weekly seizures.

What affects seizure control and prognosis in chronic epilepsy?

Several factors influence prognosis, and specifically, the chance of patients becoming seizure-free. Perinatal neurological insult and learning disability are associated with an increased risk of developing chronic epilepsy. Only about 10% of people with an epileptic structural lesion on magnetic resonance imaging, such as hippocampal sclerosis, achieve seizure freedom with drug treatment alone. For some of these, epilepsy surgery offers the best chance of becoming seizure-free and improving quality of life.[11]

An important factor in the probability of subsequent remission is the frequency of seizures within the first six months after seizure onset; 95% of patients with two seizures in the first six months achieve a five year remission, compared with only 24% of those with more than ten seizures.[12] The probability of seizure remission decreases significantly with each successive treatment failure. About 50% of people become seizure-free with their first antiepileptic drug, whereas only 11% who discontinued the first appropriate drug owing to a lack of efficacy become seizure-free on a second drug, and only 4% become seizure-free on a third drug or beyond.[13] A recent series of studies has suggested, however, that this view is overly pessimistic. For example, in a review of the effect of 265 drug changes in 155 people with chronic epilepsy, 16% were rendered seizure-free after introduction of one drug, whereas a further 21% had a considerable reduction in seizure frequency. Overall, 28% of the cohort was rendered seizure-free by one or more changes to their drug treatment.[14]

What are the factors to consider if seizure control is suboptimal?

Is the diagnosis correct?

A patient's failure to respond to adequate trials of

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- Diagnosis, treatment, and management of echinococcosis (*BMJ* 2012;345:e3866

antiepileptic drugs should prompt specialists to review the diagnosis. One study showed that up to 20-30% of people attending tertiary referral centres with presumed chronic epilepsy did not in fact have the condition, with the most common differential diagnoses being dissociative seizures and neurocardiogenic or cardiac syncope.[15]

Is the drug treatment appropriate?

Some antiepileptic drugs could exacerbate seizure disorders if used injudiciously. The most common examples are the use of carbamazepine, oxcarbazepine, phenytoin, pregabalin, and gabapentin in primary generalised epilepsy, all of which can exacerbate not only absences and myoclonic jerks but also convulsive seizures.[16] Therefore, a patient's seizure disorder must be classified accurately, although this is not possible in some instances and drugs with a broad spectrum of activity should be used (table).

What other medications and illnesses need to be considered?

Other non-epilepsy drugs may lower the seizure threshold, including antimalarial compounds (such as chloroquine, mefloquine), smoking cessation drugs (such as bupropion), antidepressants, and antipsychotics (such as amitriptyline and clozapine). Use of these drugs should be questioned if seizure control is suboptimal. Systemic illnesses, such as sepsis, renal or hepatic disease, or an endocrine disturbance, may cause treatment failure and should be investigated.

Is adherence to treatment adequate?

If there are doubts about adherence to treatment, the patient and carer should be questioned sensitively about this. Serum concentrations of antiepileptic drugs can also be obtained. Inspecting the packaging and drugs themselves may rarely yield prescribing or dispensing errors. If adherence is a problem, consider using dossett boxes, prepackaged treatment packs, and reminder services (such as alarms or regular, timed text messages).

Has the patient had a good trial with a maximally tolerated dose of all major antiepileptic drugs?

People with poorly controlled epilepsy are usually under the care of a specialist neurology team. If seizures continue despite a maximally tolerated dose of individual first line drugs, specialists should trial a combination of two first line drugs for that seizure type. The chance of dual therapy controlling seizures, if monotherapy has been unsuccessful, is 10-15%. If dual therapy does not help, the drug which seems to have the most effect and fewest side effects should be continued, and the second drug should be gradually replaced with an adjunctive drug. NICE guidelines may help in selecting an alternative, second line antiepileptic drug (table).[10] The chance of a 50% reduction in seizures from the addition of a second line drug is 20-50%, with the chance of the patient becoming seizure-free less than 10%.

If the second line drug is effective, consider withdrawing the initial drug. Prescription of an unhelpful second line drug should not be continued. If adjunctive treatment is ineffective or not tolerated, discuss this with the person, and possibly refer them to a tertiary epilepsy specialist. Current NICE guidelines recommend other antiepileptic drugs to consider at this point for focal epilepsy, such as lacosamide, eslicarbazepine acetate, pregabalin, zonisamide, retigabine, and tiagabine, as well as the older substances phenobarbitone and phenytoin.[10]

Over the past 20 years, the number of antiepileptic drugs available has increased markedly (see figure and table). Similarities exist between drugs in terms of efficacy and indications, but there is a wide range of dosing strategies, pharmacokinetic and pharmacodynamic interactions, and side effect profiles. This complexity has led to a degree of "prescribing paralysis" among non-specialists, and clinicians will often retreat to established and trusted drugs, rather than considering more contemporary and newly licensed drugs.

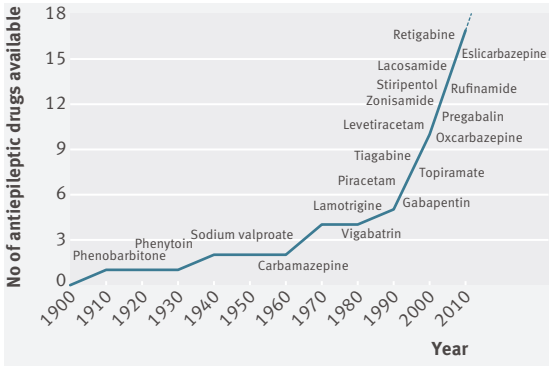
Which drug should the patient try next?

With a large number of drugs to choose from, how do specialists choose drugs rationally—that is, tailor the choice of treatment to an individual? Many placebo controlled trials of adjunctive antiepileptic drugs have formed the bases on which individual drugs have been licensed. Establishing which drug is the most effective and well tolerated by comparing these trials is difficult because of different

NICE guidelines on antiepileptic drug treatment[10]

Epileptic seizure type	First line treatment	Adjunctive treatment	Other drugs to consider on referral to tertiary care	Do not consider (may worsen seizures)
Generalised tonic-clonic	Carbamazepine, lamotrigine, oxcarbazepine,* sodium valproate	Clobazam, lamotrigine, levetiracetam, sodium valproate, topiramate	—	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin
Tonic or atonic	Sodium valproate	Lamotrigine*	Rufinamide*, topiramate*	Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, vigabatrin
Absence	Ethosuximide, lamotrigine,* sodium valproate	Ethosuximide, lamotrigine,* sodium valproate	Clobazam, clonazepam, levetiracetam,* topiramate,* zonisamide*	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin
Myoclonic	Levetiracetam,* sodium valproate, topiramate*	Levetiracetam, sodium valproate, topiramate*	Clobazam, clonazepam, piracetam, zonisamide*	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin
Focal	Carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate	Carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, topiramate	Eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, retigabine, tiagabine, vigabatrin, zonisamide	—

*At the time of publication of NICE guidelines in January 2012, this drug did not have UK marketing authorisation for this indication or population.



Antiepileptic drugs available in the UK over the past 20 years, in addition to acetazolamide, clobazam, clonazepam, and ethosuximide

trial designs, patient selection, and outcome measures. Nevertheless, detailed analysis shows no clear statistical difference between the drugs in terms of efficacy and tolerability,[17 18] and therefore one drug cannot be stated as conclusively better than another.

Head to head trials of adjunctive and combination treatments offer greater potential for establishing a drug hierarchy. Few such studies exist, and those that have been undertaken frequently evaluate outcome measures other than seizure frequency, such as mood changes and aggression.[19] These goals are laudable but do little to inform which drug or combination to recommend next for people with refractory epilepsy to improve seizure control.

In reality, the choice of the third or fourth antiepileptic drug or beyond is complex and involves looking at the evidence, clinical experience, and individual characteristics and concerns. For example, in people with comorbidities such as migraine, choosing a drug with adjunctive preventative properties for migraines may be beneficial (such as topiramate, sodium valproate, pregabalin, or gabapentin). In people with anxiety or depression, compounds that are also indicated for generalised anxiety disorder (such as pregabalin) or other drugs with mood stabilising properties (such as valproate and lamotrigine) may be worth considering earlier than other substances. In people with an elevated body mass index, consider avoiding pregabalin, sodium valproate, and gabapentin, and consider instead topiramate and zonisamide, which are commonly associated with weight loss.

The presence of cotreatments, particularly those affected by enzyme inducing drugs, may influence the choice of drug. Oral anticoagulants may need an increased dose to maintain appropriate anticoagulation levels, and hormonal contraceptives are rendered less effective, even with a dose adjustment, in the presence of drugs such as carbamazepine, phenytoin, and higher dose topiramate. Other drugs with favourable pharmacokinetics, such as levetiracetam, may be better choices. Teratogenicity is a clear concern with all drugs, and particularly in combinations including sodium valproate.[20]

How can the total drug load be minimised?

It is important to reduce and discontinue antiepileptic drugs if their prescription has not aided seizure control and they are suspected of giving rise to adverse effects. Reduction of the number of antiepileptic drugs frequently results in patients feeling better and improved seizure control.[21] The rate at which these drugs should be withdrawn in this situation is controversial and should be planned and supervised by specialist services. Some drugs can be safely withdrawn fairly rapidly, but conventional withdrawal occurs over a period of weeks. This period is particularly important in the withdrawal of benzodiazepines and barbiturates, which could precipitate status epilepticus if withdrawn too rapidly.[22] Making only one drug change at a time is recommended, to determine cause and effect if there is any improvement or deterioration.

What about epilepsy surgery?

In focal epilepsy, if satisfactory seizure control cannot be achieved by antiepileptic drugs, consider an evaluation for epilepsy surgery. This treatment is especially indicated if a lesion with concordant clinical features has been detected on magnetic resonance imaging, but should be considered in patients with a focal onset epilepsy and ongoing seizures despite optimal doses of two to three antiepileptic drugs (as monotherapy or in combination).

How often should people with epilepsy be reviewed?

Current NICE guidelines recommend that all people with epilepsy should have a yearly structured review. In adults, this review may be undertaken by a general practitioner or specialist, depending on how well the epilepsy is controlled and the presence of specific lifestyle issues, such as consideration of pregnancy, driving regulations, or drug cessation (box 2). At this review, people should have access to written and visual information, counselling services, timely and appropriate investigations, and tertiary services (box 1). In particular, if seizures are not controlled or diagnosis is uncertain, patients should be referred to tertiary services for further assessment.[10]

What should an epilepsy review include?

Pharmacological aspects

At the annual epilepsy review, the person's treatment should be discussed. This discussion will include an evaluation of the effectiveness of the prescribed drugs and presence of adverse effects. Common side effects to almost all drugs include drowsiness, dizziness, and lethargy; these effects, in addition to specific side effects for each drug, should be actively sought. The effect of comorbidities and use of cotreatments should be reviewed, such as the oral contraceptive pill or anticoagulants. Routine monitoring of antiepileptic drugs is not indicated because it is unlikely to alter drug management in isolation.

Box 2 | Triggers for referral to secondary care

- All patients with a suspected epileptic seizure
- All patients who continue to have epileptic seizures (that is, active epilepsy)
- Patients who have possible side effects, both acute and chronic, from drug treatment
- Patients with stable epilepsy but a change of circumstances, such as pregnancy
- Consideration of treatment withdrawal
- Patients needing additional specialist information, such as preconception counselling

Non-pharmacological aspects

The implications and consequences of chronic epilepsy should be considered, which often are more devastating than the seizures themselves. Patients should be given general safety advice about cooking with a microwave oven, safe bathing, and recreational activities. The driving regulations should be discussed if appropriate, and patients should be reminded that a one year period of seizure freedom is required before being eligible to drive. Issues regarding epilepsy, antiepileptic drugs, contraception, and pregnancy should be considered in women of childbearing age and further advice sought from a specialist if relevant. A discussion of reasonable expectations and limitations with regard to the prognosis and the prospects for independent living, leisure and social life, and employment is also important. For patients and their families, the support of an epilepsy specialist nurse[23] and of voluntary organisations, such as the Epilepsy Society (www.epilepsysociety.org.uk) or Epilepsy Action (www.epilepsy.org.uk), are invaluable.

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CASE REPORT A few hours from disaster

1 Bilious vomiting in a neonate should be treated as a surgical emergency until proved otherwise. The causes include intestinal malrotation and volvulus, duodenal atresia, jejunoileal atresia, meconium ileus, and necrotising enterocolitis.
2 Intestinal malrotation is a congenital anomaly of midgut rotation. Malrotation, with or without volvulus, is responsible for a large proportion of cases of neonatal bilious vomiting and should always be excluded first.
3 All patients with suspected malrotation require an upper gastrointestinal contrast study, and this remains the investigation of choice. Several other modalities may be used, including radiography, ultrasound, and computed tomography, although these tests can appear normal and often require experienced interpretation.
4 Intestinal malrotation is a surgical emergency. A Ladd's procedure should be performed as urgently as possible. This procedure reduces any volvulus present and restores blood supply and function to the small bowel.

STATISTICAL QUESTION

Open clinical trials

Options *b*, *c*, *d*, and *e* are all true, whereas *a* is false.

PICTURE QUIZ

Another patient with low back pain

1 Metastatic compression of the cauda equina at the level of the fourth lumbar vertebra.
2 Steroids, analgesia, and assessment for definitive treatment
3 Spinal surgery or radiotherapy.
4 The patient needs bed rest and nursing flat with two hourly log rolls while the stability of the spinal column is assessed. Consider using a brace if necessary. Prophylactic tinzaparin and antithromboembolism stockings are also recommended.