Epilepsy is a common neurological disorder. As many as 1 in 20 of the general population have a fit at some time in their lives, and at any one time around 200 000 people in the UK are taking antiepileptic drugs. On treatment at least two-thirds of patients are likely to be free of attacks and eventually almost two-thirds are likely to be fit-free on no medication. In this article we review the drugs used to control epilepsy and consider how and when they can be withdrawn.

BACKGROUND
Seizure disorders can be divided into two main groups – idiopathic generalised epilepsies and localisation-related epilepsies. Idiopathic generalised epilepsies, which are mostly genetic in origin, are often associated with characteristic generalised spike wave on electroencephalography (EEG). They include childhood absence seizures (petit mal), juvenile myoclonic seizures and tonic-clonic seizures.

Localisation-related epilepsies have a focus (origin) of activity, such as a tumour or scar tissue caused by trauma or a stroke, from which the epileptic activity begins and then spreads. These epilepsies include simple partial seizures that often begin with an aura and do not proceed to unconsciousness, complex partial seizures in which the activity spreads out from the focus and consciousness is impaired, and secondarily generalised seizures in which the activity spreads to the other hemisphere of the brain and there are generalised tonic-clonic seizures.

STARTING TREATMENT
In the UK a single seizure in someone who recovers fully is not usually pursued. Investigation, and so the possibility of treatment, is reserved for those who do not fully recover, or who have had two or more seizures within a year.

Before beginning therapy it is essential that the diagnosis is confirmed, and for this a specialist (such as a neurologist) opinion should be sought. Initially, the diagnosis will be based on a detailed description of events given by the patient and by any eye-witnesses. Where there is doubt, it is best to wait for a further description or until an episode has been seen before making the definitive diagnosis.

Diagnosis should not be based solely on EEG because between 10 and 15% of the general population may have an ‘abnormal’ EEG, and about 15% of people with epilepsy never have specific epileptiform discharges. However, an EEG is useful for differentiating between typical absence seizures and complex partial seizures in patients with seizures occurring without an aura that are characterised by a brief period of absence, or between primary and secondarily generalised seizures in patients with tonic-clonic seizures without an aura.

Computed tomographic (CT) scanning as the sole basis of diagnosis is also unreliable; the frequency of abnormalities found in CT scanning in people with epilepsy varies greatly. A CT scan is indicated in a patient with late onset epilepsy who has focal seizures, because it may detect a tumour.

ANTIEPILEPTIC TREATMENT
Antiepileptic therapy aims to prevent seizures while keeping the patient free of unwanted effects. The initial choice of antiepileptic drug depends on the type of epilepsy and any special needs of the patient. It also depends on the likelihood of troublesome unwanted effects.

In women, the choice will be influenced by the concomitant use of the oral contraceptive pill and by the possibility of pregnancy (to be discussed in detail in a forthcoming article). Carbamazepine, phenytoin and barbiturates (phenobarbitone and primidone) all induce hepatic microsomal enzymes and therefore speed the metabolism of oestrogens and progestagens and may make oral contraception with a combined oral contraceptive (COC) or a progestagen-only pill (POP) unreliable. This risk can be reduced by using sodium valproate, which does not affect oral contraceptive efficacy, or by using a higher dose of a COC (50µg or 100µg of oestrogen) or double the dose of a POP. The newer add-on antiepileptic drugs gabapentin, lamotrigine and vigabatrin do not induce liver enzymes.

Initially, antiepileptic drugs should be prescribed singly using the lowest dose to obtain complete seizure control with minimum unwanted effects. A single drug will suffice in about 80% of patients, leaving around 20% needing a second drug to bring the fits under acceptable control. Localisation-related epilepsy is more likely to be refractory.

FIRST-LINE DRUGS
For patients with idiopathic generalised epilepsies sodium valproate is often recommended as the treatment of choice because carbamazepine is ineffective for the treatment of absence and myoclonic epilepsies. However, in a recent randomised, open, multicentre study in 281 patients with newly diagnosed idiopathic generalised tonic-clonic seizures or partial seizures attending 22 neurology outpatient clinics, sodium valproate and carbamazepine were equally effective regardless of seizure type and equally well tolerated in the long term. ethosuximide is a useful alternative in children with absence seizures only. It has no action on tonic-clonic or partial seizures.

For localisation-related epilepsies carbamazepine, sodium valproate, phenytoin and phenobarbitone are all effective, and probably equally so. In one study carbamazepine, phenytoin and phenobarbitone were similarly effective. In another equal efficacy was shown for carbamazepine and sodium valproate, although in a third study carbamazepine was more effective than sodium valproate in the treatment of complex partial seizures. However, these drugs differ in their.

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unwanted effects and ease of use, and because of this carbamazepine and sodium valproate have become the drugs of first choice.

**Sodium valproate** – The manufacturer recommends a starting dose in adults of 600mg daily, increasing by 200mg increments once every 3 days to a maximum of 1000–2500mg daily until either seizures cease or unwanted effects develop. Several of our consultants follow a different regimen, starting with a dose of 500mg as a single dose daily, increasing in 500mg increments to a maximum of 2500mg daily in two divided doses. If this regimen works there seems no place for the long-acting formulation of sodium valproate. Common unwanted effects of sodium valproate include weight gain (due to increased appetite), hair thinning and, at higher doses, tremor. Hepatotoxicity occurs rarely; most reports have been in children, particularly those below age 3 and those with severe learning difficulties, many of whom may have a coexisting metabolic disorder. Sodium valproate may cause thrombocytopenia and pancreatitis. Platelet function should be monitored before major surgery.

**Carbamazepine** – The manufacturer recommends starting with 100mg twice daily (in adults), then if seizures continue increasing the dose gradually every few weeks up to a maximum of 800–2000mg daily in two divided doses. Slowly increasing the dose may help to avoid some of the common CNS unwanted effects such as dizziness, nausea, headache and drowsiness. Carbamazepine causes rash in 5–10% of patients. It induces hepatic microsomal enzymes and so speeds its own metabolism and that of phenobarbitone, sodium valproate and lamotrigine and also the oral contraceptive pill, corticosteroids, theophylline and warfarin. Surprisingly, carbamazepine inhibits the metabolism of phenytoin. Idiosyncratic reactions to carbamazepine include Stevens-Johnson syndrome, exfoliative dermatitis and hepatitis. Neutropenia and hypoaetraemia are common with high doses of carbamazepine but are usually clinically unimportant.

**SECOND-LINE DRUGS**

**Phenytoin** often proves difficult to use because it has unpredictable pharmacokinetics and so the optimum dose is hard to determine. The manufacturer recommends a starting dose in adults of 200mg daily, increasing by 25–100mg increments every 7–10 days, up to a maximum of 500mg. Cosmetic changes such as gum hypertrophy, acne, hirsutism and facial coarsening are common, as are unwanted psychological effects such as aggression, sedation, impaired memory and depression. All these problems make phenytoin a less attractive alternative than either carbamazepine or sodium valproate for patients with newly diagnosed epilepsy.

**Phenobarbitone** affects cognition and behaviour and is no longer considered a first-line drug. It should be reserved for those patients who cannot tolerate other antiepileptic therapy.

**Primidone** is partly metabolised in the liver to phenobarbitone. Its efficacy is similar to that of phenobarbitone but it is more expensive and has an even higher incidence of unwanted effects. It is not recommended.

**ADD-ON DRUGS**

Three new antiepileptic drugs, vigabatrin, lamotrigine and gabapentin, have been introduced in the UK over the past few years for use as add-on therapies for partial or secondarily generalised seizures. They appear to be equally effective. The benzodiazepines, clobazam and clonazepam are used differently.

**Vigabatrin** – The manufacturer recommends a starting dose of 2000mg daily (in one or two doses), increasing by 500mg every few weeks to a maximum of 4000mg daily. However, several of our consultants use a smaller starting dose (500–1000mg daily) to minimise the unwanted behavioural effects. Unwanted effects of vigabatrin include drowsiness, fatigue, irritability, weight gain and psychosis, which limit its use.

**Lamotrigine** – The half-life of lamotrigine is affected by other anticonvulsants; it is 15 hours when given with enzyme inducers (carbamazepine, phenytoin, phenobarbitone) and 72 hours with sodium valproate. In a patient already taking sodium valproate, the manufacturer recommends starting with 25mg on alternate days for 2 weeks, then 25mg once daily for 2 weeks, increasing to a maintenance of 100–200mg daily in two doses. For those already on an enzyme inducer it is 50mg daily for two weeks, then 100mg daily in two doses, increasing to a maintenance of 200–400mg daily. Lamotrigine can precipitate carbamazepine toxicity, so if unwanted effects such as double vision appear the dose of carbamazepine should be reduced. Lamotrigine causes mild maculopapular rash in about 5% of patients, the incidence of which can be reduced by beginning with a low dose. Much more rarely it causes severe allergic rash.

**Gabapentin** – On starting therapy the manufacturer recommends that the dose be increased rapidly from 300mg as a single dose on day one to 600mg in two doses on day two, 300mg in three doses on day three and so on to a maintenance dose of 1200mg a day (in three doses). Several of our consultants use a slower incremental regimen, increasing to 1200mg over 2 weeks. The dose can be increased as needed to a maximum of 2400mg a day given in three doses. Gabapentin is excreted unchanged in the urine, so the dose should be reduced in people with renal impairment. The most common unwanted effects with gabapentin are somnolence, dizziness and ataxia.

**Clobazam**, a benzodiazepine and so unrelated to vigabatrin, lamotrigine or gabapentin, can be used intermittently as add-on therapy in people with refractory epilepsy, particularly when seizures are difficult to predict, such as around menstruation or during clusters. If it is taken continuously tolerance usually develops and this limits its usefulness. Clobazam may be less sedating than clonazepam.

**Clonazepam**, also a benzodiazepine, is used particularly in children with myoclonic or tonic-clonic seizures. Sedation and
tolerance are common and withdrawal seizures are a problem. It should be used rarely.

**PLASMA CONCENTRATION MONITORING**
Measurement of the plasma concentrations of antiepileptics is not necessary. For most drugs, it is best to titrate the dose against clinical effect and unwanted effects. If a patient is seizure-free and there are no unwanted effects, no adjustment in dosage is needed and there is no indication to measure drug plasma levels. Measurement is needed, however, in patients with continuing seizures to check compliance, and in those taking phenytoin if there is a suspicion of problems because of its complicated pharmacokinetics.

**HOW LONG SHOULD TREATMENT CONTINUE?**
In most children who have taken antiepileptics for 2 years or so, drugs can be withdrawn over 2–3 months without risk of seizures. Moreover, 2 years after stopping treatment around 75% of children with epilepsy are still seizure-free. It is not so clear when withdrawal should be attempted in adults. In a large prospective study 1013 patients were randomised to slow withdrawal of treatment or continuation of existing therapy. By 2 years 78% of those still on treatment and 59% in whom it had been withdrawn were still seizure-free. Thereafter the difference between the two groups diminished. As the livelihoods of many adult patients depend on their being seizure-free, they may not be so ready to risk drug withdrawal until doctors can more easily identify those at risk of seizure recurrence.

**TREATMENT FAILURE**
Around 80% of patients with newly diagnosed epilepsy become seizure-free on monotherapy. Therefore, if seizures continue it is important to establish whether the diagnosis is correct, the patient is taking the drug prescribed and the dose of treatment is correct. Seizure control may be improved by changing to an alternative first-line antiepileptic (i.e. carbamazepine for sodium valproate or vice versa). If this does not help then the two first-line drugs can be given together. If control still does not improve a second-line antiepileptic, the addition of a newer drug such as vigabatrin, lamotrigine or gabapentin, or the intermittent addition of a drug such as clobazam can be tried.

Fatigue, stress, flashing lights and hypoglycaemia can precipitate seizures, at least in some patients, as can drugs that lower the seizure threshold, such as xanthine derivatives and ciprofloxacin. These should be avoided wherever possible. If seizures continue 6 months after starting therapy, total seizure suppression becomes less likely and re-referral to a specialist should be considered.

**EPILEPSY AND EMPLOYMENT**
The diagnosis of ‘epilepsy’ can have profound social consequences (e.g. discrimination, exclusion from certain jobs) and personal implications (e.g. feelings of insecurity). A person with epilepsy is barred from some occupations such as the armed forces. It is usual not to employ patients in a job that may be potentially hazardous for someone with ‘active’ epilepsy (e.g. on a building site), although this restriction is open to abuse. Finally, there are restrictions when jobs depend on being able to drive. In law a person with epilepsy cannot drive a private motor vehicle unless he or she has been free of epileptic seizures for 2 years (on or off treatment). However, if attacks occur only at night the person may drive even though the seizures continue, provided this pattern has been established for at least 3 years. People with a past history of seizures can now obtain a Large Goods and Passenger Carrying Vehicles (LGV/PCV) licence if they have been free from any epileptic seizures for 10 years, have not taken any medication for 10 years and have been declared fit to drive after a medical examination by a consultant nominated by the Driver and Vehicle Licensing Authority (DVLA). It is up to the person who has had the seizure to inform the DVLA. Patients can obtain information about epilepsy from the British Epilepsy Association.

**CONCLUSION**
Patients with epilepsy require sensitive management founded on detailed knowledge. Drug treatment, which should be started only when the diagnosis is clear, should aim to keep the patient fit-free and with the minimum of unwanted effects. Eventually, for many patients, it should be possible to stop treatment without fits returning. Sodium valproate is the drug of choice for idiopathic generalised epilepsies. Carbamazepine and sodium valproate seem to be equally effective for the treatment of localisation-related epilepsies, and in most patients either, used alone, will bring the seizures under control. If fits persist, the two may be combined. Alternatively, and where the patient has partial or secondarily generalised seizures, one of several add-on drugs (vigabatrin, lamotrigine, gabapentin) is worth trying. Ethosuximide is useful for childhood absence seizures.

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10. Brodie MJ. Established anticonvulsants and treatment of
REFRACTORY EPILEPSY

19. Folic Acid to Prevent Neural Tube Defects

CORRECTION: In our article Folic Acid to Prevent Neural Tube Defects (21 April, page 31) we wrongly stated that folic acid preparations containing 400µg were not available on prescription. Although the preparations are not listed as prescription drugs in the Drug Tariff, MIMS or the British National Formulary, the Prescription Pricing Authority has told us that 400µg folic acid supplements can be prescribed and dispensed on the NHS. The cost of a 13-week course of folic acid (91 tablets or capsules) starting 1 week before conception ranges from about £2.20 to £4. Women who would be required to pay a £4.75 prescription charge can buy these products more cheaply over the counter.

MEDICAL ABORTION

Medical abortion with mifepristone + gemeprost, which we discussed last year (Vol 31 No 2, page 5), is still available to only a minority of women with unwanted pregnancies, although it is now two years since mifepristone was licensed in the UK. A new booklet from the Birth Control Trust1 gives practical advice on setting up an early abortion service, emphasising for example the need for fast referral (since the method can be used only in the first 9 weeks of pregnancy) and a high nurse:patient ratio. Running an Early Abortion Service also describes how the method works and reviews its acceptability to women. Its perceived advantages, and the problems encountered (e.g. severe pain, heavy bleeding) are illustrated by accounts of the experiences of three young women.

Drug treatment of epilepsy

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