Pharmacological management of epilepsy

Carole Brown  MSc Clin Pharm, MPS, PIP, PwSI epilepsy

There have been significant advances in the management of epilepsy since the appearance of bromide in 1857. In the last decade, many new drugs have been developed and general understanding of the condition has improved. Here, Pharmacist Epilepsy Practitioner, Carole Brown, considers the current choice of antiepileptic drugs (AEDs), mode of action, newer AEDs, when to start treatment, epilepsy guidelines, adverse effects of AEDs, generic substitution, therapeutic drug monitoring, driving, contraception and bone health.

Long-term antiepileptic drugs (AEDs) remain the mainstay of epilepsy treatment. AEDs eliminate or reduce seizure frequency in up to 60–70% of patients. Treatment for chronic diseases such as epilepsy means that patients often have complex medication regimens to incorporate into their daily routines. AED choice should be tailored to individual patient factors that may limit medication use such as tolerability, treatment adherence and side-effect profile. Non-adherence rates among patients with epilepsy range from 30–50%. Clinicians treating epilepsy patients note that non-adherent patients report more difficulty in attaining seizure control than patients adherent with their medication. Uncontrolled seizures lead to major morbidity and mortality, including physical injury such as head trauma, fractures and burns, also psychosocial problems such as depression and anxiety, decreased quality of life and sudden unexpected death. The key to compliance with epilepsy medication is concordance, ensuring that patients have a good understanding of the reasons for taking an AED. Intentional non-adherence can result in poor seizure control.

Ferrari et al. investigated factors associated with non-adherence in 385 patients with epilepsy. Non-adherence measured by the Morisky–Green test was 66.2%, a moderate to low result. Non-adherence was higher in men, younger patients and patients with uncontrolled seizures; increasing complexity was also associated with decreased treatment adherence. The conclusion was to have strategies to improve adherence in these groups. Less complex treatment regimens may result in better adherence and consequently in better seizure control.

When to start treatment for epilepsy and medication selection

Local guidelines – Epilepsy Guidelines, Calderdale and Huddersfield Foundation Trust (CHFT) 2011 – state that the decision to start AEDs should be made by the patient and epilepsy specialist. The patient needs to be committed to long-term medication in order to be compliant. Pharmacological treatment is guided by NICE guidance 2011 for first-line AED, adjunctive AEDs and avoidance of AEDs which may worsen seizures (see Table 2 [online at www.progressnp.com]).
**Review**

**Epilepsy management**

CHFT 2011 Guidelines for drug selection for monotherapy:

- *Focal and generalised seizures*: carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate
- *Primary generalised seizures*: sodium valproate, lamotrigine.
- *Uncertain seizure type*: sodium valproate, lamotrigine.

Side-effects and interaction profiles should direct the choice of drug for the individual patient. Elderly patients are particularly sensitive to AED adverse events so low doses are recommended and prescribing drugs with a high propensity of neurotoxicity should be avoided.

For provoked seizures caused by metabolic disturbances or drugs the provocative factor should be corrected or withdrawn; for alcohol withdrawal give benzodiazepines in the short term. AEDs are not indicated for concussive convulsions.

There is a distinction between treatment for primary and secondary generalised tonic-clonic seizures (TCS) as some AEDs exacerbate primary generalised TCS but are efficacious for secondary generalised seizures.

**AED reviews**

The relative risks and benefits of starting or withholding antiepileptic drug treatment in patients with few or infrequent seizures are unclear. Marson *et al.* compared the policies of immediate *versus* deferred treatment in such patients and assessed the effects of these policies on short-term recurrence and long-term outcomes. The conclusion was that immediate antiepileptic drug treatment reduced the occurrence of seizures in the next 1 to 2 years, but did not affect long-term remission in individuals with single or infrequent seizures.

The SANAD study (2007) compared the effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, and topiramate for treatment of partial epilepsy. Carbamazepine is widely regarded as first-line drug treatment for partial-onset seizures. Several newer drugs possess efficacy against these seizure types but previous randomised controlled trials have failed to inform a choice between these drugs. The aim was to assess efficacy with regards to longer-term outcomes, quality of life, and health economic outcomes. SANAD was an unblinded randomised controlled trial in hospital-based outpatient clinics in the UK. The study compared seizure control, adverse events, psychosocial outcome and costs. The authors concluded that lamotrigine was clinically better than carbamazepine for time-to-treatment failure outcomes and therefore a cost-effective alternative for patients diagnosed with partial-onset seizures.

Valproate is considered a drug of first choice for patients with generalised-onset seizures, and SANAD notes its broad spectrum of efficacy means it is recommended for patients with seizures that are difficult to classify. Lamotrigine and topiramate also exhibit a broad spectrum of activity. The SANAD group comment that valproate is better tolerated than topiramate and more efficacious than lamotrigine, and should remain the drug of first choice for many patients with generalised and unclassified epilepsies. However, the potential adverse effects of valproate during pregnancy, mean that the benefits for seizure control in women of childbearing age should be considered very carefully.

A study by Zeng *et al.* evaluated the long-term effectiveness of five AEDs – carbamazepine, lamotrigine, oxcarbazepine, topiramate and valproate – for monotherapy of adults with focal epilepsy. The study size was 654 patients. Results showed lamotrigine was the most effective, topiramate less so, oxcarbazepine was more effective than valproate but less effective than lamotrigine in preventing the first seizure.

**Adverse effects of AEDs**

As a general rule AEDs should be started at a low dose and titrated gradually at doses no higher than recommended by the manufacturer. Patients should be warned of possible side-effects (see Tables 3 and 4) and given instructions to seek urgent medical advice if rash, bruising or somnolence occur. If there are multiple concomitant medications, AEDs that do not have drug–drug interactions are preferred.

Anticonvulsant hypersensitivity syndrome (AHS), anhidrosis and hepatic/pancreatic failure occur more often in children than in adults. AHS is a potentially fatal, but rare, reaction that can manifest as a rash, fever, tender lymphadenopathy, hepatitis or eosinophilia.

Rufinamide is recommended in NICE guidance 2011† to be prescribed only when other appropriate drug combinations have proved inadequate or have not been tolerated. Its use for adjunctive treatment of drug-resistant focal seizures with or without secondary generalisation is restricted to adults aged 18 years or older. Patients should be monitored for: QT interval prolongation; changes in vision or retinal pigment, and blue-grey discolouration of nails, lips and skin. The dose should be reduced by 50% in moderate or severe hepatic impairment or renal impairment if eGFR is less than 50mL/min/1.73m².

Rufinamide is licensed for the adjunctive treatment of seizures in Lennox–Gastaut syndrome in patients over 4 years of age, weight over 30kg. The dose is 200mg twice daily increased in 200mg increments according to response. Main side-effects include nausea, constipation, weight loss. Patients who are concerned about hypersensitivity syndrome (possibly including rash and fever) should be advised to seek immediate medical attention. Its use is restricted to when other AEDs are unsatisfactory. Avoid in severe liver impairment, careful dose titration in mild to moderate impairment.
Vigabatrin should not be prescribed unless all other drug combinations are ineffective or not tolerated. It should be initiated and supervised by a specialist. About one-third of patients treated with vigabatrin have suffered visual field defects. Prominent behavioural side effects have occurred in some patients.

Newer AEDs
Eslicarbazepine is licensed for adjunctive treatment in adults with focal seizures. Its mechanism of action is blockade of the voltage-gated sodium channel. The active metabolite has a linear pharmacokinetic profile, a half-life of 20–24 hours, so it can be administered once a day. It has a low potential for drug–drug interactions.13 Efficacy and safety have been assessed in four randomised clinical trials: patients with improvements over 50% ranged between 17–43%. Adverse effects were mild to moderate – commonly dizziness, somnolence, diplopia, abnormal co-ordination, blurred vision, vertigo. A study to evaluate eslicarbazepine, at doses between 400mg and 1200mg in stroke patients over a 2-year period, found that hyponatraemia developed in four out of 32 patients, and was symptomatic in three patients. Hyponatraemia symptoms can be subtle and delayed, therefore monitoring of

<table>
<thead>
<tr>
<th>AED</th>
<th>Adverse reactions</th>
<th>Life threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Idiosyncratic (rash), sedation, headache, ataxia, nystagmus, diplopia, tremor, impotence, hyponatraemia</td>
<td>AHS, hepatic failure, haematological</td>
</tr>
<tr>
<td>Clobazam</td>
<td>Severe sedation, fatigue, drowsiness, behavioural and cognitive impairment, restlessness, coordination disturbances. Tolerance and withdrawal syndrome</td>
<td>None</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>As for clobazam</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Weight gain, peripheral oedema, behavioural changes, impotence</td>
<td></td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Dizziness, diplopia, can occasionally cause rash</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Idiosyncratic (rash), insomnia, dizziness, diplopia, headache, ataxia, asthenia, blurred vision, may exacerbate myoclonic seizures</td>
<td>AHS, hepatic failure, haematological</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Irritability, behavioural and psychotic changes, asthenia, dizziness, somnolence, headache</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Idiosyncratic (rash), headache, dizziness, nausea, somnolence, ataxia and diplopia, hyponatraemia</td>
<td>AHS, haematological</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Idiosyncratic (rash), severe drowsiness, sedation, impairment of cognition and concentration, hyperkinesias and agitation in children, shoulder hand syndrome</td>
<td>AHS, haematological</td>
</tr>
<tr>
<td>Phenytin</td>
<td>Idiosyncratic (rash), ataxia, drowsiness, lethargy, sedation, encephalopathy, gingival hyperplasia, hirsutism, dysmorphism, rickets, osteomalacia</td>
<td>AHS, hepatic failure, haematological</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Weight gain, myoclonus, dizziness, somnolence, ataxia, confusion</td>
<td>Renal failure, congestive heart failure</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Somnolence, anorexia, fatigue, nervousness, difficulty with concentration / attention, memory impairment, psychomotor slowing, metabolic acidosis, weight loss, language dysfunction, renal calculi, acute angle-closure glaucoma and other ocular effects</td>
<td>Hepatic failure, anhidrosis</td>
</tr>
<tr>
<td>Valproate</td>
<td>Nausea, vomiting, dyspepsia, weight gain, hair loss</td>
<td>Hepatic and pancreatic failure</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Idiosyncratic, drowsiness, anorexia, irritability, photosensitivity, weight loss, renal calculi</td>
<td>AHS, anhidrosis</td>
</tr>
</tbody>
</table>

Table 3. Adverse reactions associated with antiepileptic drugs
serum sodium in patients taking eslicarbazepine is recommended, especially in the elderly.\textsuperscript{14}

Levetiracetam monotherapy outcomes from an epilepsy clinic were studied in 228 patients, 70.6\% of whom had partial-onset seizures, 25.9\% had idiopathic generalised epilepsies and 3.5\% unclassified GTCS.\textsuperscript{15} Seizure freedom was achieved in around half of patients on a median dose levetiracetam of 1000mg/day. This was more likely to occur in those taking the drug as first monotherapy and in those with fewer than five pre-treatment seizures. The drug was withdrawn in 16.2\% of patients; 50\% of these developed neuropsychiatric symptoms, eg depression, mood swings, irritability, depression. Lacosamide is a unique functionalised amino acid specifically synthesised for use as an AED. It was approved in 2008 as adjunctive therapy for partial-onset seizures with or without secondary generalisation, and restricted for specialist use in refractory epilepsy in people with epilepsy aged over 16 years. Its mechanism of action is to increase slow inactivation of the voltage-gated sodium channel.\textsuperscript{16} The pharmacological response to lacosamide differs from sodium-channel blocking AEDs.\textsuperscript{8} The drug does not interact with other AEDs, and its anticonvulsant effect is possibly antagonised by MAOIs and tricyclic-related antidepressants, mefloquine, antipsychotics and orlistat. There is a risk of PR interval prolongation, and it is contraindicated in second or third degree AV block.\textsuperscript{17} A study comparing efficacy and safety of lacosamide in 118 paediatric and adult patients with uncontrolled epilepsy, showed lacosamide was well tolerated in adults as in previous trials, adverse events occurring at a low frequency, related to the nervous and gastrointestinal systems, included dizziness, headache, nausea, diplopia and somnolence, with dyspepsia onset occurring during the titration period.\textsuperscript{18} The discontinuation rate due to side-effects was 8.5\%. A 50\% seizure reduction was achieved by around half of patients on a median dose levetiracetam of 1000mg/day. This was more likely to occur in those taking the drug as first monotherapy and in those with fewer than five pre-treatment seizures. The drug was withdrawn in 16.2\% of patients; 50\% of these developed neuropsychiatric symptoms, eg depression, mood swings, irritability, depression.

Table 4. Adverse effects associated with AEDs used as adjunctive therapy, second or third line

<table>
<thead>
<tr>
<th>AED</th>
<th>Adverse reactions</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eslicarbazepine</td>
<td>Gastrointestinal disturbances, dizziness, drowsiness, headache, impaired coordination, tremor, visual disturbances</td>
<td>Rash; avoid in severe renal impairment</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Nausea, changes in appetite, weight increase, aggression, dizziness, drowsiness</td>
<td>Avoid in severe hepatic failure and moderate or severe renal failure</td>
</tr>
<tr>
<td>Primidone</td>
<td>See phenobarbital, also nausea, visual disturbances</td>
<td>Reduce dose in hepatic impairment may precipitate coma</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Diarrhoea, dizziness, tiredness, tremor, emotional lability,</td>
<td>Avoid in acute porphyria, avoid abrupt withdrawal</td>
</tr>
</tbody>
</table>

Perampanel is an orally active, non-competitive glutamate receptor antagonist. It demonstrates novel pharmacology and is the first licensed drug that specifically and selectively inhibits the AMPA-type of glutamate receptor. Perampanel is licensed for adjunctive treatment of partial-onset seizures, with or without secondary generalised seizures, in patients with epilepsy aged 12 years and older. It is administered orally, once daily, typically at bedtime.\textsuperscript{19}

Tiagabine is used as an adjunctive treatment for focal seizures with or without secondary generalisation not controlled by other AEDs. (Around 30\% of seizures are resistant to treatment.) The use of tiagabine should be avoided in absence, myoclonic, tonic and atonic seizures due to risk of seizure exacerbation. It has a favourable safety profile. The suggested titration is in 5mg increments to minimise CNS-related side effects. It should not be used in patients with severely impaired liver function. The pharmacokinetics are unaffected in patients with renal impairment or renal failure.\textsuperscript{20}

Topiramate is an effective antiepileptic drug given alone or as adjunctive treatment in generalised tonic-clonic seizures or focal seizures without secondary generalisation. It is also licensed for prophylaxis of migraine. The drug has two unusual non-neurological side effects – urolithiasis and body weight loss.\textsuperscript{21} It is recommended to ensure adequate hydration, especially when undertaking strenuous activity or in a warm environment.

Zonisamide, first approved in 1989, is a benzisoxazole derivative with a unique chemical structure, predictable dose-dependent pharmacokinetics and multiple complementary mechanisms of action. There have been over two million patient years of experience of zonisamide for treatment of epilepsy and it has International League Against Epilepsy (ILAE) level A evidence for efficacy/effectiveness as initial monotherapy for adults with partial-onset seizures. It is not known to be associated with clinically significant drug–drug interactions.\textsuperscript{22} Zonisamide displays predictable dose-dependent pharmacokinetics, a half-life of 60 hours allowing
once or twice daily administration. The most frequently reported adverse effects are somnolence, dizziness and anorexia/weight loss.23

On the horizon
Brivaracetam was filed for approval to treat partial-onset seizures in epilepsy patients over 16 years old, supported by data from phase III studies. In January 2016 the European commission licensed brivaracetam as adjunctive therapy for adult epilepsy patients with uncontrolled partial-onset seizures.

The drug shows high water solubility and modest lipophilicity. No dose adjustment is required for renal impairment, and for patients with hepatic impairment a starting dose of 50mg/day may be considered.24 The dose range is 50mg to 200mg/day taken twice daily. It is a highly selective, reversible, high affinity synaptic vesicle protein 2A (SV2A) ligand with higher potency at the binding site than levetiracetam. Dizziness and somnolence are very common side-effects; common side-effects include decreased appetite, irritability and anxiety.

Therapeutic drug monitoring (TDM)
The pharmacokinetics of AEDs vary, resulting in wide differences in the plasma steady-state concentration in patients receiving the same dose. This variability will affect the degree of pharmacological response, as the concentration of the drug in plasma is in equilibrium with that in the brain. Toxic effects will correlate with the plasma level rather than the prescribed dose. However, therapeutic decisions must be based on evaluation of clinical response rather than plasma drug measurements alone.25 Therapeutic ranges for AEDs represent the range at which most patients respond. If a patient is well controlled at a subtherapeutic level then there is no need to increase the dose. The type and severity of epilepsy affect the response to any given plasma drug concentration.26 It is proposed that any concentration up to the upper limit should be considered potentially therapeutic. Pharmacodynamic tolerance is seen with the benzodiazepines and barbiturates. Therapeutic and/or toxic effects may diminish over time despite stable concentrations in the blood due to adaption mechanisms. The development of pharmacodynamic tolerance to the sedative effects of benzodiazepines in patients on chronic treatment means they tolerate concentrations which would be toxic if prescribed acutely to a patient. The therapeutic efficacy of their chronic treatment is often limited by diminished efficacy. With phenobarbital, tolerance to sedative effects does not entail a simultaneous loss in anticonvulsant activity. The value of TDM is greatest for phenytoin for which the relationship between plasma concentration and effect is relatively consistent.

<table>
<thead>
<tr>
<th>Epilepsy medicine</th>
<th>Daily dose</th>
<th>Approximate risk</th>
<th>% risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Any</td>
<td>Two in a hundred</td>
<td>2.4</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Below 400mg</td>
<td>Two in a hundred</td>
<td>2.4</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Above 400mg</td>
<td>Six in a hundred</td>
<td>5.9</td>
</tr>
<tr>
<td>Valproate</td>
<td>Above 1100mg</td>
<td>Ten in a hundred</td>
<td>10.7</td>
</tr>
</tbody>
</table>

Table 5. Risk of major congenital malformations associated with epilepsy medicine monotherapy29

Special populations
Pregnancy
The UK Epilepsy and Pregnancy Register was set up to find out more about having epilepsy and taking epilepsy medicines during pregnancy (Table 5).27

The teratogenic risk associated with sodium valproate is higher than with other AEDs both as monotherapy and polytherapy. The teratogenic effect of sodium valproate is dose dependent and greatest for daily doses >1100mg. High congenital malformation (CM) rates associated with prenatal sodium valproate exposure are more likely to be related to the total daily dose rather than peak serum concentrations. Prescribing controlled-release sodium valproate or administering it in multiple divided doses does not reduce the risk of congenital malformations.28

In a Drug Safety Update published on 17 February 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) says that children exposed to valproate in utero are at high risk of developmental disorder in up to 30–40% of cases and congenital malformations in up to 10% of cases.29 Valproate is associated with a dose-dependent risk of abnormal pregnancy outcomes whether taken alone or in combination with other medicines. This prompted a review of all women of childbearing age taking valproate to ensure that they were using effective contraception and that they were informed of the risks associated with valproate during pregnancy and the need for regular review of treatment.

Elderly
In elderly patients all AEDs are introduced with caution, and health-care professionals need to remain vigilant to increased sedation, confusion and mental sedation. Pharmacokinetic factors are diminished, of these creatinine clearance is the most significant. The general advice ‘start low go slow’ is particularly relevant in the elderly. AEDs cause drowsiness and co-ordination problems in the elderly, which can lead to falls and fractures.

Practical considerations
Interactions
Enzyme induction is the main cause of drug-drug interactions for AEDs. The effect is to increase the rate of
metabolism of the affected drug causing a reduction in plasma level and a potential reduction in the therapeutic response.

Interactions between AEDs are subject to individual variability; primarily they are pharmacokinetic, although pharmacodynamic interactions can also have some clinical impact. A marked elevation of a low AED plasma concentration may improve seizure control or therapeutic response, whereas a small elevation of a near toxic plasma level of drug may precipitate toxicity. So although a small change in blood level of AED may have little clinical effect in the majority of patients there may be a profound effect in some patients.  

An important objective of AED treatment is to minimise the risks of drug interactions, both with AEDs and concomitant medication. For example, the addition of lamotrigine to patients already on valproate is a risk factor for development of skin rash, however, there is no risk if valproate is introduced to lamotrigine. Valproate inhibits the metabolism of lamotrigine; drug levels can be increased two-fold, a consequence of inhibition of lamotrigine metabolism through UGT1A4 glucuronidation. During combination therapy valproic acid synergistically enhances the antiepileptic activity (partial and generalised seizures) and toxicity of lamotrigine, a consequence of a pharmacodynamic interaction.

**Generic substitution of AEDs**

Generic substitution is cost effective for many medications, however, in the case of AEDs two parameters, the bioavailability and secondly the drug’s therapeutic range, need to be considered (see Table 6). The solubility of phenytoin in gastrointestinal fluids appears to be the main reason for the variation in bioavailability of different formulations. Monitoring blood levels can be useful; however, caution is needed in patients with low albumin or renal failure as the consequent reduction in blood plasma protein binding can cause misinterpretation of total concentration.

Different AEDs vary considerably in their characteristics, which influence the risk, if switching between different manufacturers’ medicines, of causing adverse effects or loss of seizure control. AEDs with nonlinear pharmacokinetics, such as phenytoin, mean that slight differences between different versions of the same drug such as particle size or dissolution rate may lead to significant differences in bioavailability. The bioequivalence for most AEDs has not been evaluated in patients with epilepsy or in special populations such as the elderly or those on polytherapy.  

Bioequivalence of a generic drug is established by comparing pharmacokinetic parameters relating to the active ingredient, which must not vary between 80% and 125% after single/repeated administration of both products. Theoretically, plasma drug levels could be up to 45% lower than another generic, however, plasma drug levels usually vary by only 5–7%.  

The bioequivalence of drugs varies from patient to patient, which may or may not correspond to the average therapeutic range of the drug.  

Recent problems in the supply chain for community pharmacy have caused shortages of particular brands; explanation of the problem by the prescriber can allay the potential anxieties caused by a switch of a branded generic if the AED is in category 2 or 3. Category 1 contains phenytoin capsules, which are manufactured by a sole manufacturer – Flynn pharmaceuticals. There is a choice of brands for carbamazepine, and it is important to maintain continuity between secondary and primary care. Different preparations of carbamazepine vary in bioavailability, so it is prudent to avoid changing the formulation.

**Drugs and driving**

Recent legislation from March 2015 states that it is illegal to drive if unfit to do so as a result of taking legal or illegal drugs.  

The restrictions include medicines prescribed for epilepsy such as clonazepam and diazepam. The upper plasma levels of the drugs specified in the legislation are: clonazepam 50μg/L and diazepam 550μg/L. Patients should be advised about the new regulations, and reassured that if they take their medicines in accordance with the prescription and they not subject to sedative or cognitive side-effects then driving is permissible. These medications are often taken at night as they can have sedating side-effects. However, in some patients the sedative effects may still be apparent the next day. Caution is needed if clonazepam is withdrawn as it can cause rebound insomnia. Patients would be able to raise a statutory medical defence providing the drug was lawfully prescribed for medical purposes and taken in accordance with the advice of the prescriber.

<table>
<thead>
<tr>
<th>MHRA / CHM: Three risk-based categories:</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Maintain continuity of a specific manufacturer’s product</td>
<td>Phenytoin, carbamazepine, phenobarbitone, primidone</td>
</tr>
<tr>
<td>2. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient and/or carer, taking into account seizure frequency and treatment history</td>
<td>Valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate</td>
</tr>
<tr>
<td>3. It is usually unnecessary to maintain continuity of brand unless there are specific concerns such as patient anxiety</td>
<td>Levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin</td>
</tr>
</tbody>
</table>

**Table 6.** Classification of risk of switching between different manufacturers for AEDs  

www.progressnp.com
Driving regulations say that a person who suffers from epilepsy may qualify for a group 1 licence if she or he has been free from any epileptic attack for one year.

A person who has suffered from a single unprovoked epileptic seizure will qualify for a licence if he or she has been free from further attacks for a 6-month period, provided that there are no further clinical factors or investigations that may suggest an unacceptably high risk of a further seizure occurring, in which case they cannot drive for 12 months. A person who has suffered an epileptic attack whilst asleep must also refrain from driving from 1 year from the date of the attack, unless they have had an attack whilst asleep more than 3 years ago and have not had any awake attacks since that sleep attack.

Any change or dose reduction of AED by the physician means the licence is revoked for 12 months as per the epilepsy regulations but re-application can be earlier once treatment has been reinstated for 6 months and as long as there have been no further seizures in the 6-month period after recommencing treatment.

Bone health

It is increasingly recognised that epilepsy patients are at increased risk of osteopenia and osteoporosis. However, there are numerous confounders and much of the work has been conducted in refractory patients or those in long-term care. A cross-sectional study showed that patients with epilepsy have lower bone mineral density (BMD) and vitamin D levels. Multiple AEDs, enzyme-inducing AEDs and generalised seizures were all associated factors.

There have been reports of decreased BMD, osteopenia, osteoporosis and fractures and bone-related sequelae with patients on long-term therapy with carbamazepine, eslicarbazepine, oxcarbazepine, phenytoin, phenobarbital and sodium valproate. AEDs are thought to affect bone health through disturbance of mineral metabolism and acceleration of bone turnover mechanisms. Osteomalacia is a rare effect of primidone. Chronic metabolic acidosis associated with topiramate and zonisamide increases the risk of renal stone formation and may potentially lead to osteopenia. The effect of topiramate on bone-related sequelae has not been systematically investigated; there is insufficient evidence for levetiracetam. Lamotrigine does not appear to be associated with effects on bone.

The MHRA highlighted the effects on bone and advised that long-term treatment with phenytoin, carbamazepine, primidone and sodium valproate are associated with decreased bone mineral density, which may lead to osteopenia, osteoporosis and increased fractures, particularly in those patients immobilised for long periods, have inadequate sun exposure or inadequate dietary calcium intake.

CHFT guidelines for vitamin D deficiency in primary care mention AEDs (including enzyme inducers phenytoin, phenobarbital, primidone, and carbamazepine, as well as valproate, an enzyme inhibitor) as a risk factor for vitamin deficiency. Vitamin D status is assessed if 25-hydroxyvitamin D (25-(OH) D) is deficient – defined as a plasma level less than 30 nmol/L. In such cases high-dose vitamin D is indicated – 40 000 units for 7 weeks (as 20 000 unit capsules, two per week; 40 000 unit capsule once a week, or calciferol oral solution). The NICE clinical guideline for management of epilepsy (2012) recommends monitoring vitamin D, calcium and alkaline phosphatase every 2 to 5 years for patients taking enzyme-inducing AEDs. During epilepsy reviews advice on diet and weight-bearing exercise should be given for prevention of vitamin D deficiency, along with advice about over-the-counter vitamin D supplements. Certain supplements are gelatine free, so suitable for vegetarians.

Contraception

The effectiveness of combined oral contraceptives, progesterone-only oral contraceptives, contraceptive patches and vaginal rings can be considerably reduced by AEDs that induce liver enzymes. Lamotrigine concentrations are halved through glucuronidation induction by COCPs containing ethinylestradiol/levonorgestrel. Health-care professionals should warn patients about this and be aware that lamotrigine dosing may need to be altered accordingly if these medications are used together. This effect is negated when lamotrigine is prescribed with sodium valproate, which inhibits lamotrigine glucuronidation.

Levonorgestrel-containing IUDs can be safely used with AEDs.

Depression and epilepsy

Antidepressants can have a slight effect on the seizure threshold, however, rational use of antidepressant medication can improve quality of life for patients with epilepsy.39 Research from three studies with SSRIs showed no significant increase in seizure frequency. Existing evidence on effectiveness of antidepressants in treating depressive symptoms associated with epilepsy is very limited.40 Further clinical trials in large cohorts of patients are required to better inform treatment policy in the future. Anxiety and depression are common in patients with epilepsy; an antidepressant that has the minimum effect on the seizure threshold should be selected. For example, the SSRIs citalopram and sertraline have a minimal effect on seizures unless taken in high doses.

Several AEDs also function as mood stabilisers,41 which means that some patients may be managed on one drug; this applies also to some patients also diagnosed with non-epileptic attack disorder (NEAD). Common
side-effects of medication, such as drowsiness, can lower the seizure threshold in susceptible patients. Tricyclic antidepressants may require downward dose adjustment if concurrently administered with AEDs metabolised by cytochrome P-450. In the case of phenytoin and carbamazepine this can lead to unintended toxicity from the antidepressant.

Educating patients with epilepsy, their families and carers can reduce stigma associated with the condition. Provision of information about AEDs and epilepsy should be clearly written, easy to understand and culturally relevant. Epilepsy Action and the National Society for Epilepsy are excellent sources of information for epilepsy. Good seizure control improves quality of life for patients with epilepsy.

Models of care
A structured management system for epilepsy has been established in primary care in Calderdale. As with other chronic diseases, an annual review is desirable. The shared management system identifies all patients with epilepsy, records demographic data and validates the classification of seizures and syndromes. This advises monitoring seizure frequency, aiming to improve control by adjustments to medication, minimising side-effects of medication and drug interactions. Drug therapy is tailored to the individual to optimise quality of life and avoid toxicity. Therapeutic drug monitoring is conducted where indicated and routine blood tests are done as per NICE guidance. Where structured withdrawal from medication is appropriate it is facilitated with patient consent and clinical support from neurologists. Discussion of lifestyle interventions and dissemination of information to help improve quality of life for patients with epilepsy is an important aspect of care. Women’s issues are addressed and the needs of patients with learning disabilities including their careers. It is ensured that written protocols are in place for epilepsy patients prescribed rescue medication and carers given appropriate training. The pharmacist with a special interest in epilepsy (PwSI) implements clinical care plans in primary care agreed with the consultant neurologists and general practitioner; these are discussed with the patient and carers.

Conclusion
The treatment of epilepsy has been transformed since the serendipitous discovery of phenobarbitone in 1912, both in the spectrum of medication available and improved knowledge of how best to use AEDs. Improving access to specialist information, as provided by the PwSI epilepsy service in primary care, encouraging adherence to medication combined with a rational combination of AED and concomitant medication, minimising side-effects and addressing any modifiable risk factors and addressing psychological issues can serve to optimise care for the patients with epilepsy.

References, Tables 1 and 2 are online only, available free to view on the Progress in Neurology and Psychiatry website www.progressnp.com

Ms Brown is the Pharmacist Epilepsy Practitioner for Calderdale.

Declaration of interests
No conflicts of interest were declared.

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References

<table>
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<th>Blockage / inhibition of neuronal voltage-operated sodium channels</th>
<th>Blockage / inhibition of neuronal calcium channels</th>
<th>Blockage / inhibition of neuronal potassium channels</th>
<th>Potentiates inhibitory transmission</th>
<th>Reduces excitatory transmission</th>
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<td>Oxcarbazepine***</td>
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<td>Vigabatrin***</td>
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</table>

***primary action, **probable action, *possible action

Table 1. Proposed mechanisms of antiepileptic drug (AED) action

5,6
## Seizure type

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>First-line AEDs</th>
<th>Adjunctive AEDs</th>
<th>Other AEDs that may be considered on referral to tertiary care</th>
<th>Do not offer AEDs (may worsen seizures)</th>
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<tbody>
<tr>
<td>Generalised tonic-clonic</td>
<td>Carbamazepine, lamotrigine, oxcarbazepine, sodium valproate</td>
<td>Clobazam, lamotrigine, levetiracetam, sodium valproate, topiramate</td>
<td>(If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy suspected) carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin</td>
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<tr>
<td>Tonic or atonic</td>
<td>Sodium valproate</td>
<td>Lamotrigine</td>
<td>Rufinamide, topiramate</td>
<td>Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, vigabatrin</td>
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<tr>
<td>Absence</td>
<td>Ethosuximide, lamotrigine, sodium valproate</td>
<td>Ethosuximide, lamotrigine, sodium valproate</td>
<td>Clobazam, clonazepam, levetiracetam, topiramate, zonisamide</td>
<td>Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin</td>
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<tr>
<td>Myoclonic</td>
<td>Levetiracetam, sodium valproate, topiramate</td>
<td>Levetiracetam, sodium valproate, topiramate</td>
<td>Clobazam, clonazepam, piracetam, zonisamide</td>
<td>Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin</td>
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<td>Focal</td>
<td>Carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate</td>
<td>Carbamazepine, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, topiramate</td>
<td>Eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin tiagabine, vigabatrin</td>
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<td>Prolonged or repeated seizures and convulsive status epilepticus in the community</td>
<td>Buccal midazolam, Rectal diazepam, Intravenous lorazepam</td>
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</table>

**Table 2.** AED options by seizure type recommended by NICE⁸