Chapter 28

Overview of established antiepileptic drugs

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Established antiepileptic drugs (AEDs) are those which were licensed before 2000. By now, substantial data have accumulated on them. Their pharmacokinetic properties are listed in Table 1, and indications and a guide to dosing in children, adults and adolescents are outlined in Tables 2 and 3, respectively. These drugs are not without their hazards and their optimum use must be governed by an appreciation of their potential for dose-related and idiosyncratic toxicity (Table 4). The clinical use of each drug will be considered, highlighting the practical problems likely to be encountered during every day clinical use.

Carbamazepine

Carbamazepine is indicated for focal seizures and generalised tonic-clonic seizures. It is not effective, and may even be deleterious, for some people with absences and myoclonic seizures.

Carbamazepine, as a strong auto-inducer, should be introduced in low dosage (100–200 mg daily) to allow tolerance to develop to its CNS side effects. The dose can then be increased in 1–2 weekly increments of 100–200 mg/day to a maintenance dose that completely controls seizures.

Diplopia, headache, dizziness, nausea and vomiting are the commonest side effects of carbamazepine, some of which may be due to its active epoxide metabolite. Peak levels often result in intermittent side effects occurring around two hours after dosing, necessitating administration three or four times daily in some. These problems can often be overcome by prescribing the controlled-release formulation, which can be given twice daily.

Carbamazepine can cause a range of idiosyncratic reactions, the most common of which is a skin rash, occurring in up to 10% of people exposed to it. Slow dosage titration reduces the risk. Rarely, it may cause more severe skin eruptions including erythema multiforme and Stevens-Johnson syndrome. Reversible mild leucopenia often occurs and has no clinical significance. Discontinuation of therapy is not required unless accompanied by evidence of infection or if the cell count is well below 2×10^9/L. Blood dyscrasias and toxic hepatitis occur very rarely.

There are some long-term problems with carbamazepine. As a strong enzyme inducer it has the potential to affect bone health in the long term and this needs to be taken into account particularly if lifelong treatment is a consideration. At high levels, carbamazepine has an antidiuretic hormone-like action that can result in fluid retention in people with cardiac failure and in the elderly. Mild hyponatraemia is usually asymptomatic, but if serum sodium falls below 125 mmol/L there might be confusion, peripheral oedema and worsening seizure control. Cardiac arrhythmia is also an occasional complication.

Table 1. Pharmacokinetics of established antiepileptic drugs.

DRUG	ABSORPTION (BIOAVAILABILITY)	PROTEIN BINDING (% bound)	ELIMINATION HALF-LIFE (hours)	ROUTE(S) OF ELIMINATION	COMMENTS
CARBAMAZEPINE	Slow absorption (75–85%)	70–80	24–45 (single) 8–24 (chronic)	Hepatic metabolism Active metabolite	Enzyme inducer Metabolic autoinduction
CLOBAZAM	Rapid absorption (90–100%)	87–90	10–30	Hepatic metabolism Active metabolite	Sedative Tolerance
CLONAZEPAM	Rapid absorption (80–90%)	80–90	30–40	Hepatic metabolism	Sedative Tolerance
ETHOSUXIMIDE	Rapid absorption (90–95%)	0	20–60	Hepatic metabolism 25% excreted unchanged	More rapid clearance in children
GABAPENTIN	Rapid initial absorption	0	5–7	Not metabolised Excreted unchanged	Limited absorption at high doses
LAMOTRIGINE	Rapid absorption (95–100%)	50–55	14–88	Hepatic metabolism by glucuronidation	Half-life dependent on co-medication
PHENOBARBITAL	Slow absorption (95–100%)	48–54	72–144	Hepatic metabolism 25% excreted unchanged	Enzyme inducer Sedative Tolerance
PHENYTOIN	Slow absorption (85–90%)	90–93	9–40	Saturable hepatic Metabolism	Enzyme inducer Elimination half-life concentration-dependent
SODIUM VALPROATE	Rapid absorption	88–92	7–17	Hepatic metabolism Active metabolites	Enzyme inhibitor Concentration-dependent protein binding
TIAGABINE	Rapid absorption	87–96	4–9	Hepatic metabolism	
TOPIRAMATE	Rapid absorption	15	12–30	Mostly hepatic metabolism, with renal excretion. No active metabolites	Cognitive slowing, kidney stones, weight loss. Clearance increased by enzyme inducers.
VIGABATRIN	Rapid absorption (60–80%)	0	5–8	Not metabolised 85% excreted unchanged	Visual field constrictions

Table 2. Dosage guidelines for established antiepileptic drugs in children.

DRUG	INDICATIONS	STARTING DOSE (mg/kg/day)	STANDARD MAINTENANCE DOSE (mg/kg/day)	DOSAGE INTERVAL
CARBAMAZEPINE	Partial and generalised tonic-clonic seizures	5	10–25	bid-qid
CLOBAZAM	Partial and generalised seizures	0.25	0.5–1	od-bid
CLONAZEPAM	Myoclonic epilepsy Lennox-Gastaut syndrome Infantile spasms Status epilepticus	0.025	0.025–0.1	bid-tid
ETHOSUXIMIDE	Generalised absences	10	15–30	od-bid
GABAPENTIN	Partial seizures	10	25–35	tid
LAMOTRIGINE	Partial and generalised seizures	with valproate 0.2 without valproate 2.0	1–5 5–15	od-bid
PHENOBARBITAL	Partial and generalised seizures Newborn seizures Status epilepticus	4	4–8	od-bid
PHENYTOIN	Partial and generalised tonic-clonic seizures Status epilepticus	5	5–15	od-bid
PRIMIDONE	Partial and generalised tonic-clonic seizures	10	20–30	od-bid
SODIUM VALPROATE	Partial and generalised seizures	10	15–40	od-tid
TOPIRAMATE	Partial and generalised seizures	2	3–6	od-bid
VIGABATRIN	Partial seizures Infantile spasms	40	50–100	bid

Table 3. Dosage guidelines for established antiepileptic drugs in adolescents and adults.

DRUG	INDICATIONS	STARTING DOSE	STANDARD MAINTENANCE DOSE	DOSAGE INTERVAL	TARGET RANGE
CARBAMAZEPINE	Partial and generalised tonic-clonic seizures	200 mg	400–2000 mg	*od-qid	25–50 μmol/L (6–12 mg/L)
CLOBAZAM	Partial and generalised seizures	10 mg	10–40 mg	od-bid	None
CLONAZEPAM	Myoclonic and generalised tonic-clonic seizures	1 mg	2–8 mg	od-bid	None
ETHOSUXIMIDE	Absence seizures	500 mg	500–2000 mg	od-bid	283–708 μmol/L (40–100 mg/L)
GABAPENTIN	Partial seizures	300–400mg	1800–3600 mg	tid	None
LAMOTRIGINE	Partial seizures and generalised tonic-clonic seizures	25mg	200–400mg	bid	6–16 mg/L
PHENOBARBITAL	Partial and generalised tonic-clonic, myoclonic, clonic and tonic seizures Status epilepticus	60 mg	60–240 mg	od-bid	40–172 μmol/L (10–40 mg/L)
PHENYTOIN	Partial and generalised tonic-clonic seizures Status epilepticus	200 mg	100–700 mg	od-bid	40–80 μmol/L (10–20 mg/L)
PRIMIDONE	Partial and generalised tonic-clonic seizures	250 mg	250–1500 mg	od-bid	23–55 μmol/L (5–12 mg/L)
SODIUM VALPROATE	All generalised seizures Partial seizures	500 mg	500–3000 mg	*od-bid	347–693 μmol/L (50–100 mg/L)
TIAGABINE	Partial seizures	5–10 mg	30–45 mg	tid	
TOPIRAMATE	Partial and generalised seizures	25 mg	100–400 mg	bid	6–74 μmol/L (2–25 mg/L)
VIGABATRIN	Partial seizures	500 mg	1000–4000 mg	od-bid	None

*od or bid with controlled-release formulation

Table 4. Side effects of established antiepileptic drugs.

CARBAMAZEPINE	CLOBAZAM	CLONAZEPAM	ETHOSUXIMIDE	GABAPENTIN
* Diplopia	* Fatigue	* Fatigue	* Nausea	* Somnolence
* Dizziness	* Drowsiness	* Sedation	Anorexia	* Dizziness
* Headache	Dizziness	* Drowsiness	Vomiting	* Ataxia
* Nausea	Ataxia	Dizziness	Agitation	* Fatigue
Drowsiness	Irritability	Ataxia	Drowsiness	* Diplopia
Neutropenia	Aggression	Irritability	Headache	Paraesthesia
Hyponatraemia	Hypersalivation	Aggression (children)	Lethargy	Amnesia
Hypocalcaemia	Bronchorrhoea	Hyperkinesia (children)		
Orofacial dyskinesia	Weight gain	Hypersalivation		
Cardiac arrhythmia	Muscle weakness	Bronchorrhoea		
	Psychosis	Psychosis		
* Morbilliform rash	Rash	Rash	Rash	* Increased seizures
Agranulocytosis		Thrombocytopenia	Erythema multiforme	
Aplastic anaemia			Stevens-Johnson syndrome	
Hepatotoxicity			Lupus-like syndrome	
Photosensitivity			Agranulocytosis	
Stevens-Johnson syndrome			Aplastic anaemia	
Lupus-like syndrome				
Thrombocytopenia				
Pseudolymphoma				
Teratogenicity				

Above line: Dose-related; Below line: Idiosyncratic; *Commonest side effects

Table 4 (contd). Side effects of established antiepileptic drugs.

LAMOTRIGINE	PHENOBARBITAL	PHENYTOIN	PIRACETAM	PRIMIDONE
* Drowsiness	* Fatigue	* Nystagmus	* Diarrhoea	* Fatigue
* Diplopia	* Listlessness	* Ataxia	* Weight gain	* Listlessness
* Headache	* Tiredness	Anorexia	Insomnia	* Tiredness
* Ataxia	* Depression	Dyspepsia	Depression	* Depression
* Insomnia	* Insomnia (children)	Nausea	Hyperkinesia	* Psychosis
* Tremor	* Distractibility (children)	Vomiting		* Decreased libido
Nausea	* Hyperkinesia (children)	Aggression		* Impotence
Vomiting	* Irritability (children)	Depression		* Hyperkinesia (children)
Aggression	Aggression	Drowsiness		* Irritability (children)
Irritability	Poor memory	Headache		Nausea
	Decreased libido	Paradoxical seizures		Vomiting
	Impotence	Megaloblastic anaemia		Nystagmus
	Folate deficiency	Hypergylcaemia		Ataxia
	+ Neonatal haemorrhage	Hypocalcaemia		Folate deficiency
	Hypocalcaemia	Osteomalacia		Hypocalcaemia
	Osteomalacia	+ Neonatal haemorrhage		Osteomalacia
				Megaloblastic anaemia
				+ Neonatal haemorrhage
* Rash	* Macropapular rash	* Rash		Rash
Stevens-Johnson Syndrome	Exfoliation	* Acne		Agranulocytosis
Toxic epidermal necrolysis	Toxic epidermal	* Gum hypertrophy		Thrombocytopenia
Liver failure	necrolysis	* Coarse facies		Lupus-like syndrome
Aplastic anaemia	Hepatotoxicity	* Hirsutism		Teratogenicity
Pancytopenia	Frozen shoulder	Blood dyscrasias		
Multi-organ failure	Teratogenicity	Lupus-like syndrome		
		Reduced serum IgA		
		Pseudolymphoma		
		Peripheral neuropathy		
		Stevens-Johnson syndrome		
		Dupuytren's contracture		
		Hepatotoxicity		
		Teratogenicity		

Above line: Dose-related; Below line: Idiosyncratic; *Commonest side effects; + Maternal treatment

Table 4 (contd). Side effects of established antiepileptic drugs.

SODIUM VALPROATE	TIAGABINE	TOPIRAMATE	VIGABATRIN
* Tremor	* Dizziness	* Anorexia	* Drowsiness
* Weight gain	* Headache	* Weight loss	* Fatigue
* Hair loss	* Tremor	* Impaired concentration	* Headache
Anorexia	* Difficulty concentrating	* Impaired speech	* Ataxia
Dyspepsia	Light-headedness	* Paraesthesias	* Nystagmus
Nausea	* Nervousness	Kidney stones	* Diplopia
Vomiting	Asthenia	Impaired memory	* Irritability
Alopecia	Abnormal thinking	Ataxia	* Depression
Peripheral oedema			Psychosis
Drowsiness			Aggression
Hyperammonaemia			Weight gain
Amenorrhoea			Stupor
			Tremor
			Impaired concentration
Acute pancreatitis	Increased seizures		* Visual field defects
Hepatotoxicity	Non-convulsive status		Increased seizures
Thrombocytopenia			
Stupor			
Encephalopathy			
Teratogenicity			
Polycystic ovarian syndrome			

Above line: Dose-related; Below line: Idiosyncratic; *Commonest side effects

As well as inducing its own metabolism, carbamazepine can accelerate clearance of a number of other lipid-soluble drugs including the oral contraceptive pill, necessitating, for most women, a daily oestrogen dose of 50 µg or more. Other affected drugs include sodium valproate, ethosuximide, corticosteroids, anticoagulants, antipsychotics and cyclosporin. Drugs that inhibit carbamazepine metabolism and which may result in toxicity include phenytoin, cimetidine, danazol, dextropropoxyphene, diltiazem, erythromycin, isoniazid, verapamil and viloxazine. The less common neurotoxic interaction with lithium (confusion, disorientation, drowsiness, ataxia, tremor, hyperreflexia) is not associated with altered concentrations of either drug.

The substantial variation in carbamazepine concentrations in any given individual over the course of the day – as much as 100% with twice-daily dosing using the regular release formulations – makes the interpretation of levels problematical. In most people, the dosage can be titrated adequately on clinical criteria alone. Exceptions include people with learning disabilities, those in whom adherence to treatment is suspect, and those taking a cocktail of AEDs likely to interact with each other.

Clobazam

Clobazam is a useful adjunctive drug in refractory epilepsy although the majority of responders will develop tolerance to its antiepileptic action. Nevertheless, a useful proportion (up to 20–30%) will become and stay seizure-free in the long term. There is some evidence that the intermittent use of clobazam reduces the likelihood of tolerance. Short-term administration, e.g. 10–20 mg daily for 3–7 days, can be useful in women with catamenial seizures and as 'cover' for special events such as holidays, weddings and surgery. A single dose of 20–30 mg can have a prophylactic action if taken immediately after the first seizure in people who suffer regular clusters of complex partial or secondary generalised seizures.

Clobazam's structure differs from that of other benzodiazepines, and this may account for its lesser propensity to cause sedation. Nevertheless, tiredness, irritability and depression are commonly reported. Occasionally deterioration in behaviour and mood disturbance can occur, particularly in people with learning disabilities in whom clobazam should probably be avoided. Withdrawal seizures can also be a problem.

Clonazepam

Clonazepam has efficacy against absences, myoclonic jerks and tonic-clonic seizures. Sedation and tolerance, however, substantially reduce its usefulness. Few people respond well to this drug but nearly 50% will have an exacerbation of seizures when it is withdrawn. Accordingly, clonazepam now has a limited role in the management of epilepsy, possibly limited to refractory myoclonic seizures. Like other benzodiazepines, clonazepam should only be prescribed as a last resort in people with learning difficulties.

Ethosuximide

Ethosuximide is only indicated in the treatment of absence seizures. Slow introduction is sensible to minimise the development of gastrointestinal and CNS side effects. In children over six years, 500 mg daily is a reasonable starting dose, with further increments as necessary to a maximum of 1–2 g per day. The dose can be increased every 2–4 weeks according to clinical need.

Side effects usually involve the gastrointestinal tract (nausea, vomiting, abdominal pain) or CNS (lethargy, dizziness, and ataxia). Blood dyscrasias have been reported rarely. Drug monitoring is not indicated unless for checking of adherence to treatment. Ethosuximide itself

does not interfere with drug metabolism, but provides a target for enzyme inducers such as phenytoin and carbamazepine, or inhibitors such as sodium valproate.

Gabapentin

Gabapentin may occasionally be useful as a second-line treatment of focal seizures. It is of no use in other seizure types. The initial dose is 300–400 mg/day and the titration rate consists of weekly dose increases of 300–400 mg up to 2400–3600mg/day in first instance. In view of its short elimination half-life a three times daily dosage is recommended.

Gabapentin is not metabolised, exhibits no protein binding and does not induce hepatic enzymes. Its potential for drug interaction is small and, to date, no clinically significant interaction with other drugs has been reported. Gabapentin may, therefore, be a useful add-on drug in people with a high risk of drug interactions. There is no need to measure levels as a guide to dosing.

Side effects of gabapentin are mainly related to the CNS and these include drowsiness, dizziness, diplopia, ataxia and headaches. Gabapentin is associated with weight gain, particularly at high doses. It may also occasionally worsen seizures, particularly myoclonic seizures. Gabapentin treatment has not been associated with any serious idiosyncratic reaction to date.

Lamotrigine

Lamotrigine is a first-line drug for people with focal seizures and with generalised seizures.

The recommended starting dose as monotherapy is 25 mg/day. If the person is taking concomitant sodium valproate then the starting dose should be 25 mg/day on alternate days. The maximum recommended dose as monotherapy is 400–500 mg/day in two divided doses but no more than 200 mg/day if the person is taking concomitant valproate. Treatment should be slowly titrated upwards over a period of several weeks as too rapid titration may be associated with an increased incidence of adverse events, particularly skin rash.

Lamotrigine does not seem to interact with other concomitantly administered AEDs, although it may increase levels of an active metabolite of carbamazepine. Hepatic enzyme inducers, however, increase lamotrigine clearance, reducing its half-life. Hence, higher doses of lamotrigine need to be used with concomitant enzyme inducing drugs such as phenytoin and carbamazepine. Inhibitors of hepatic enzymes, such as sodium valproate, block the metabolism of lamotrigine so that reduced doses of lamotrigine have to be used if both drugs are given together. Oral contraceptives containing oestrogen may increase the metabolism of lamotrigine.

Headaches, drowsiness, ataxia, diplopia, insomnia, nausea and dizziness are the most common acute adverse effects of lamotrigine, particularly during dose escalation. A skin rash is the commonest idiosyncratic side effect and affects up to 5% of people exposed to it. The incidence is higher when lamotrigine is used in combination with sodium valproate or if larger initial doses of lamotrigine are used. Rarely, it may cause more severe idiosyncratic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, aplastic anaemia and liver failure.

Phenytoin

Phenytoin is now a last resort option for focal and tonic-clonic seizures in view of its chronic toxicity and kinetic profile. Phenytoin is one of a handful of drugs that switches from first-order to saturation kinetics at therapeutic dosage. Accordingly, at higher levels a moderate increment

in dose can produce an unexpectedly large rise in the level with accompanying neurotoxicity. Conversely, levels can fall precipitously when the dose is reduced modestly, resulting sometimes in unexpected deterioration in seizure control. The dosage producing the same levels, therefore, varies substantially among different individuals.

Phenytoin can produce a range of dose-related and idiosyncratic adverse effects including rash, hepatotoxicity and blood dyscrasias. Reversible cosmetic changes (gum hyperplasia, acne, hirsutism, facial coarsening), although often mild, can be troublesome. Phenytoin is an enzyme inducer and as such may impact on bone health. Symptoms of neurotoxicity (drowsiness, dysarthria, tremor, ataxia, cognitive difficulties) become increasingly likely with higher levels but the diagnosis of phenytoin toxicity should be made on clinical grounds and not assumed from a high level. The person may complain of mental slowing and unsteadiness, and neurological examination may show cerebellar signs. Permanent cerebellar damage may be a consequence of chronic toxicity, so it is important to examine regularly the person taking it. In some of these people, cerebellar atrophy will be apparent on brain imaging, although hard evidence for cause and effect is not readily available. A paradoxical increase in seizure frequency may also occur with marked phenytoin toxicity.

It can accelerate the metabolism of a number of lipid-soluble drugs, including carbamazepine, sodium valproate, ethosuximide, anticoagulants, steroids and cyclosporin. Due to its saturable metabolism, phenytoin provides a target for drugs such as allopurinol, amiodarone, cimetidine, imipramine and some sulphonamides. Protein binding displacement interactions with AEDs are only clinically relevant when there is concomitant enzyme inhibition, as is the case with the combination of phenytoin and sodium valproate.

Phenobarbital

Phenobarbital is an established treatment for focal and tonic-clonic seizures but is seldom currently used in developed countries due to its potential to cause neurotoxicity.

Phenobarbital is an easy drug to use clinically. To minimise sedation, a low dose should be started (30 mg in adolescents and adults), which can be increased gradually (15–30 mg incremental steps) according to clinical requirements. The value of measuring its levels is limited, as concentration associated with seizure control varies considerably. In addition, the development of tolerance to its CNS side effects makes the toxic threshold imprecise.

The major problem in the clinical use of phenobarbital is its effect on cognition, mood and behaviour. It can produce fatigue, listlessness and tiredness in adults and insomnia, hyperactivity and aggression in children (and sometimes in the elderly). Subtle impairment of memory, mood and learning capacity can occur. Depression may be a consequence of long-term use and arthritic changes, frozen shoulder, and Dupuytren's contracture can be associated problems. Tolerance develops to the deleterious cognitive effects of the drug but also to its efficacy in some people. Phenobarbital is an enzyme inducer and can accelerate the metabolism of many lipid-soluble drugs and has an impact on bone health.

Piracetam

Piracetam is only indicated as an adjunctive treatment in refractory myoclonus. It has no use in other seizure types. The usual starting dose is 7.2 g daily in two or three divided doses, increased weekly by 4.8 g/day according to clinical response. Effective doses are usually between 12 and 24 g/day and this bulk is one of the limiting factors of the use of this drug. Piracetam is generally well tolerated. The commonest side effects are diarrhoea, weight gain, insomnia, and depression. Hyperkinesia has been reported with very high doses. There are no known drug interactions with piracetam.

Primidone

Primidone is metabolised to phenobarbital and its efficacy is similar to that of phenobarbital, but it is not as well tolerated. There is therefore nothing to recommend it over phenobarbital for people in whom treatment with a barbiturate is contemplated.

Sodium valproate (valproic acid)

Sodium valproate is a broad spectrum AED effective over the complete range of seizure types, with particular value in the idiopathic generalised epilepsies. It use in women of childbearing potential, however, is problematic in view of its potential teratogenicity.

The starting dose of sodium valproate for adults and adolescents should be 500 mg/day for one or two weeks, increasing in most people to 500 mg twice daily. The controlled release formulation can be given once daily. Alterations thereafter should be made according to clinical need. Since the drug can take several weeks to become fully effective, frequent dosage adjustments shortly after initiating therapy may be unwarranted. As valproate does not exhibit a clear-cut concentration-effect-toxicity relationship and the daily variation in the level at a given dose is wide, routine monitoring is not helpful unless used as a check of adherence to therapy.

Side effects of sodium valproate include dose-related tremor, weight gain due to appetite stimulation, thinning or loss of hair (usually temporary), and menstrual irregularities including amenorrhoea. Polycystic ovarian syndrome has been reported in some women. Sedation is an uncommon complaint, although stupor and encephalopathy can occur, albeit rarely, possibly as a consequence of underlying carnitine deficiency. Hepatotoxicity, histologically a microvesicular steatosis similar to that found in Reye's syndrome, affects fewer than one in 20,000 exposed individuals. Children under three years of age receiving AED polypharmacy are the highest risk group. Mild hyperammonaemia without hepatic damage is seen in up to 10% of people taking it. This is usually transient, but occasionally can present clinically with confusion, nausea and vomiting and clouding of consciousness. Other sporadic problems include thrombocytopenia and pancreatitis. Valproate is far more teratogenic than other commonly used AEDs and this needs to be taken into account when treating women of childbearing age.

Sodium valproate can inhibit a range of hepatic metabolic processes, including oxidation, conjugation and epoxidation reactions. Targets include other AEDs, particularly phenytoin, phenobarbital, carbamazepine epoxide, and lamotrigine. Aspirin displaces sodium valproate from its binding sites on plasma protein and inhibits its metabolism. Sodium valproate, however, does not interfere with the hormonal components of the oral contraceptive pill.

Tiagabine

Tiagabine is last resort drug for focal seizures with or without secondary generalisation. It has no use in any other seizure type.

The recommended dose is between 30 and 45 mg/day, although higher doses (up to 80 mg/day) have been used. Tiagabine should be started at 10 mg/day in two divided doses, and increased by 5–10 mg/day each week up to 30 mg/day in the first instance. Doses above 30 mg/day should be given in three divided doses.

Tiagabine does not affect levels of carbamazepine or phenytoin, but may reduce the plasma concentration of valproate by about 10%, which is unlikely to be of clinical importance.

Enzyme-inducing AEDs, however, decrease the half-life of tiagabine and people taking such drugs as concomitant medication may need to take tiagabine three times a day from the beginning of treatment.

Side effects of tiagabine are primarily CNS-related and are more common during drug titration; the main side effects are sedation, headache, tiredness and dizziness. Tremor, diarrhoea, irritability, confusion, and depression are seen occasionally. Exacerbations of seizures and cases of non-convulsive status epilepticus have also been reported.

Topiramate

Topiramate is licensed as a first-line drug for people with focal seizures with or without secondary generalisation and for generalised seizure disorders.

Recommended doses are between 75 and 300 mg, although some people may derive benefit from a dose that is outside this range. The recommended starting dose for most people is 25 mg once daily, titrating upwards every two weeks in 25 mg/day increments up to 200 mg/day in two divided doses. After that, the dose can be increased by 50 mg each week until seizure control is achieved or side effects develop.

Topiramate exhibits linear pharmacokinetics with low levels of protein binding. It has minimal interaction with other AEDs, although hepatic enzyme inducers accelerate its metabolism. Because of this, topiramate doses may need to be adjusted downwards if people are coming off carbamazepine or phenytoin.

Most of the acute and dose-related side effects of topiramate are CNS-related including dizziness, drowsiness, headaches, irritability, cognitive slowing and speech impairment. These are usually transient and in some people seem to be related to the dose and rate of titration. Paraesthesia and nephrolithiasis have also been reported and are likely to be due to topiramate's carbonic anhydrase inhibitory action. People starting topiramate should increase their fluid intake to reduce the risk of kidney stones. Initial weight loss is seen in up to 40% of people and is usually not problematic. No idiosyncratic side effects have yet been described. Topiramate is teratogenic in some animal models and it is not recommended as a first-line option in women of childbearing potential.

Vigabatrin

Vigabatrin is now a last resort treatment for people with focal seizures. It is, however, still a first-line treatment for infantile spasms, particularly those associated with tuberous sclerosis. It has no use in primary generalised epilepsy and may worsen myoclonic seizures. Tolerance may develop in up to one-third of initial responders.

The recommended dose is 1000–2000 mg/day, although doses of up to 4000 mg/day in two divided doses can be used if necessary. Treatment should be started with a low dose (250–500 mg/day), and titrated slowly upwards over a period of several weeks until therapeutic response is achieved. Too rapid titration may be associated with an increased incidence of adverse events.

The addition of vigabatrin reduces plasma concentrations of phenytoin. The mechanism is unknown but may be due to decreased phenytoin absorption. Usually this has no clinical significance, but occasionally an increase in phenytoin dose is necessary if seizures increase a few weeks after the introduction of vigabatrin. The corollary of this effect is that plasma phenytoin concentrations rise after the withdrawal of concomitant vigabatrin therapy. Vigabatrin has no other known pharmacokinetic interactions. There is no need to measure the plasma concentration to guide dosing.

Sedation, dizziness and headache are the most commonly reported adverse effects, particularly when doses are being increased. Tolerance often develops and the symptoms are frequently self-limiting. These symptoms can usually be avoided by introducing the drug gradually. Allergic skin rashes are extremely rare. Up to 10% of people taking vigabatrin develop a change in mood, commonly agitation, ill temper and disturbed behaviour, depression or, more rarely, paranoid and psychotic symptoms. Visual field defects have been associated with long-term treatment with vigabatrin in up to 40–50% of people and this limits the use of the drug to those cases in which potential benefit outweighs risk.