

New antiepileptic drugs

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New antiepileptic drugs (AEDs) are necessary for people with chronic epilepsy and for improving upon established AEDs as first-line therapy. Since 2000, ten new AEDs have been released in the UK. In chronological order these are: oxcarbazepine, levetiracetam, pregabalin, zonisamide, stiripentol, rufinamide, lacosamide, eslicarbazepine acetate, retigabine and perampanel. Two of these drugs, stiripentol and rufinamide, are licensed as orphan drugs for specific epileptic syndromes. Another drug, felbamate, is available in some EU countries. Their pharmacokinetic properties are listed in Table 1 and indications and a guide to dosing in adults and adolescents are given in Table 2. Known side effects are given in Table 3.

Complete freedom from seizures with the absence of side effects should be the ultimate aim of AED treatment and the new AEDs have not entirely lived up to expectations. Only a small number of people with chronic epilepsy have been rendered seizure free by the addition of new AEDs. Despite claims to the contrary, the safety profile of the new drugs is only slightly more favourable than that of the established drugs. The chronic side effect profile for the new drugs has also not yet been fully established.

New AEDs marketed in the UK

Eslicarbazepine acetate

Eslicarbazepine acetate is licensed as an add-on for focal epilepsy. It has similarities to carbamazepine and oxcarbazepine. As such it interacts with voltage-gated sodium channels and this is likely to be its main mode of action. There are no head-to-head comparisons between this drug and oxcarbazepine or carbamazepine but in the randomised clinical trial response was seen in some people that had not responded to carbamazepine or oxcarbazepine. Its tolerability and pharmacokinetic profile are similar to that of oxcarbazepine.

Lacosamide

Lacosamide is licenced as an add-on for focal epilepsy in people over the age of 16 years. Its putative mode of action is not shared with any other currently available AEDs as it enhances the slow inactivation of sodium channels.

The recommended doses are between 200 and 400 mg/day divided in two doses. It should be started at 50–100 mg/day and increased by 50 mg per day every one or two weeks.

Table 1. Pharmacokinetics of new antiepileptic drugs available in the UK.

Drug	Absorption (bioavailability)	Protein binding (% bound)	Elimination half-life (hours)	Route(s) of elimination	
Eslicarbazepine acetate	Rapid absorption	30–40	12–20	Urinary excretion	
Levetiracetam	Rapid absorption (95–100%)	<10	7–12	Urinary excretion	
Lacosamide	Rapid absorption	<15%	9–13	Urinary excretion	
Oxcarbazepine	Rapid absorption (95–100%)	35–40	8–10	Hepatic metabolism Active metabolite	
Perampanel	Rapid absorption	<90%	70–80	Mainly hepatic metabolism	
Pregabalin	Rapid absorption	<5	8–10	Urinary excretion	
Retigabine	Rapid absorption	60–80%	8–11	Mainly urinary excretion	
Zonisamide	Rapid absorption	40%	40–60	Urinary excretion	

Table 2. Dosage guidelines for new antiepileptic drugs in adolescents and adults.

Drug	Indications	Starting dose	Standard maintenance dose	Dosage interval
Eslicarbazepine acetate	Focal seizures	400 mg	800–1200 mg	bid
Levetiracetam	Focal seizures, generalised seizures	500 mg	1500–3000 mg	bid
Lacosamide	Focal seizures	100 mg	200–400 mg	bid
Oxcarbazepine	Focal and generalised tonic-clonic seizures	300–600 mg	1200–2400 mg	bid
Perampanel	Focal seizures	2 mg	4–10 mg	od or bid
Pregabalin	Focal seizures	100–150 mg	150–600 mg	bid
Retigabine*	Focal seizures	300 mg	450–900 mg	tds
Zonisamide	Focal seizures	50 mg	200–600 mg	bid

*No guidelines as yet

Table 3. Side effects of new antiepileptic drugs.

Side effects	Eslicarbazepine acetate	Levetiracetam	Oxcarbazepine	Lacosamide	Perampanel	Pregabalin	Retigabine	Zonisamide
Dose related	*Fatigue *Drowsiness Diplopia Dizziness Hyponatraemia Ataxia Nausea Nystagmus Tremor	Headache Asthenia Irritability Ataxia Drowsiness	*Fatigue *Drowsiness *Diplopia *Dizziness *Hyponatraemia Ataxia Nausea Nystagmus Tremor	* Nausea * Dizziness * Headache * Lethargy * Diplopia	*Drowsiness *Ataxia *Lethargy *Blurred vision Irritability Weight gain	*Dizziness Drowsiness Ataxia Weight gain Diplopia Tremor Abnormal thinking	*Drowsiness *Dizziness *Slurred speech *Ataxia *Tremor *Diplopia	Drowsiness Dizziness Anorexia Memory impairment Ataxia Confusion Word-finding difficulties Concentration impairment Agitation Depression
Idiosyncratic or chronic effects			Rash				Urinary tract symptoms Skin and retinal discoloration	Skin rash Blood dyscrasias

*Commonest side effects

No drug-drug interactions are known but there are suggestions of pharmacodynamic interaction with traditional sodium channel blockers such as carbamazepine and oxcarbazepine.

Lacosamide commonest side effects are dizziness, headaches, nausea, and diplopia. It seems better tolerated if no traditional sodium channel blockers are used concomitantly. No idiosyncratic side effects have yet been associated with this drug. It should be used with caution in people with a history of cardiac conduction problems as it is known to increase the PR interval in some people.

Levetiracetam

Levetiracetam, a piracetam derivative, is a broad-spectrum drug indicated both as a first-line drug and as an add-on drug. Its mode of action is not fully understood. It has a binding site in the brain for which the natural ligand is the synaptic vesicle protein SV2A but it is not known if this is related to its mode of action.

The recommended doses are between 1000 and 3000 mg/day divided into two doses although some people respond to doses outside this range. Levetiracetam should be started at 500 mg/day divided into two doses and increased by 250–500 mg/day every week up to 1000–1500 mg/day in the first instance.

Levetiracetam is well tolerated overall and no idiosyncratic side effects have yet been described. Somnolence, dizziness, asthenia, ataxia, insomnia, behavioural problems (particularly irritability, usually of a transient nature) and mood changes are the most common side effects. No definite pharmacokinetic interactions have yet been identified.

Oxcarbazepine

Oxcarbazepine, the 10-keto analogue of carbamazepine, has a similar mechanism of action to carbamazepine. Its indications are very similar to those of carbamazepine; it is effective in focal seizures with or without secondary generalisation and may worsen absences and myoclonic seizures.

The recommended doses are between 600 and 2400 mg/day divided into two doses. Oxcarbazepine should be started at 300 mg/day and increased by 300 mg/day each week, up to 900 mg/day in the first instance.

Oxcarbazepine weakly induces hepatic enzymes, and so is likely to have fewer drug interactions than carbamazepine. A high dose of the oral contraceptive pill is advised to give protection against pregnancy. Oxcarbazepine exhibits less autoinduction than carbamazepine. Its safety profile is very similar to that of carbamazepine apart from hyponatraemia, which is more pronounced with oxcarbazepine and allergic skin reactions which are less common. Cross-sensitivity is seen in less than one-third of people hypersensitive to carbamazepine. There are indications of teratogenicity in animal models, particularly at high doses but to date no concerns have been raised in humans.

Perampanel

Perampanel has been licenced for the adjunctive treatment of refractory focal epilepsy. It is the first licenced drug that interacts with glutamate receptors. Its effective dose is likely to be somewhere between 4 and 12 mg/day. The commonest treatment emerging events so far seen are drowsiness, ataxia, lethargy, irritability, weight gain and blurred vision. No clinically significant pharmacokinetic interaction has yet been seen. It has a very prolonged half-life and can be given in a once-a-day regimen.

Pregabalin

Pregabalin has been licensed for the adjunctive treatment of refractory focal epilepsy. People with comorbid generalised anxiety seem to particularly benefit from it. Pregabalin is closely related to gabapentin, it is also a structural analogue of the neurotransmitter GABA that does not seem to affect transmitter response. It modulates calcium channels by binding to a subunit of Ca⁺ and this action is thought to be the basis of its antiepileptic mechanism.

The recommended dosages are between 150 and 600 mg divided into two doses, although some people may respond to doses outside this range. Pregabalin would normally be started at 50 or 75 mg bid and increased in incremental steps of 50 mg every two weeks up to 600 mg according to clinical need. Pregabalin is available in 25, 50, 75, 100, 150, 200 and 300 mg tablets.

Overall pregabalin is well tolerated and so far no idiosyncratic side effects have been described. Dizziness, drowsiness, ataxia, tremor and diplopia are the most common side effects. Weight gain, particularly with higher doses can be a major issue for some people. No pharmacokinetic interactions have yet been identified. In addition to its use in epilepsy, pregabalin has also been indicated for neuropathic pain and in generalised anxiety disorders.

Stiripentol

Stiripentol is licensed as an orphan drug for Dravet's syndrome when used in conjunction with sodium valproate and clobazam. It is an aromatic alcohol and is unrelated to any other AED. Its mode of action is unknown.

Retigabine

Retigabine has just been licensed as add-on for focal epilepsy. It is the first drug licensed which acts as a modulator of potassium channels. Effective dose is likely to be somewhere between 600 and 1200 mg a day. The commonest emerging treatment side effects are CNS-related and drowsiness, dizziness, slurred speech, ataxia, tremor and diplopia. It also causes urinary tract symptoms in some people. No clinically significant pharmacokinetic interaction has yet been seen. An unexpected side effect has recently been associated with the chronic use of retigabine and this consists of a blue skin discoloration and pigmentary changes in the retina. The mechanism of this is unknown. It is likely that this will limit the use of the drug.

Rufinamide

Rufinamide is licensed as an orphan drug for the Lennox-Gastaut spectrum when used as an adjunctive. It is a triazole derivative and is unrelated to any other AED. Its mode of action is unknown.

Zonisamide

Zonisamide, a sulphonamide analogue which inhibits carbonic anhydrase, is a potent blocker of the spread of epileptic discharges. This is believed to be mediated through action at voltage-sensitive sodium channels. It is currently indicated for people with focal seizures with or without secondary generalisation but it is likely to be a broad-spectrum drug. It can be effective in generalised seizures particularly myoclonic seizures. Recommended doses are between 200 and 500 mg/day, although some people may derive benefit from doses outside this range. The recommended starting dose for most people is 50 mg once daily, titrating upwards every two weeks in 50 mg/day increments until seizure control is achieved or side effects develop. Its long elimination half-life allows once-daily dosing.

Zonisamide may increase phenytoin levels by about 10–15%. Zonisamide metabolism is induced by carbamazepine, barbiturates and phenytoin and higher doses may be necessary during co-administration with these AEDs.

Side effects include dizziness, drowsiness, headaches, hyporexia, nausea and vomiting, weight loss, skin rashes, irritability, impaired concentration and fatigue. These are mostly transient and seem to be related to the dose and rate of titration. Nephrolithiasis has also been reported, particularly in Caucasians and people starting it should increase their fluid intake to reduce this risk. It is not recommended for women of child-bearing age as there are issues about its teratogenic potential.

AEDs marketed elsewhere

Felbamate

Felbamate is a di-carbamate closely related to meprobamate. Its exact mechanism of action is not known but it appears to reduce seizures both by increasing seizure threshold and by inhibiting seizure spread.

It is a drug with a broad spectrum of action but due to its safety profile it is used as a drug of last resort in people with intractable epilepsy, particularly in those within the Lennox-Gastaut spectrum. The usual dose is between 2400 and 4800 mg/day. The recommended starting dose for most people is 400 mg once daily, titrating upwards every week in 400 mg/day increments up to 2400 mg/day in two or three divided doses. After that the dose can be increased by 600 mg/day each week until seizure control is achieved or side effects develop.

Felbamate exhibits significant pharmacokinetic interactions with phenytoin, carbamazepine and valproic acid: plasma phenytoin concentrations rise by 20% upon introduction of felbamate; plasma carbamazepine concentrations are reduced by 20–25% but there is a concurrent increase in the concentrations of 10,11-epoxi-carbazepine, a metabolite of carbamazepine; plasma valproate concentrations increase by about 50% during co-medication with felbamate. The exact mechanism of these pharmacokinetic interactions is unknown but their magnitude requires dosage adjustments. Felbamate metabolism is also inducible by carbamazepine and phenytoin, and higher doses of felbamate may be necessary during co-administration with these AEDs.

The most frequently reported side effects during felbamate therapy have been neurological (diplopia, insomnia, dizziness, headache and ataxia), and gastrointestinal (anorexia, nausea and vomiting). A major use-limiting problem is its potential to cause aplastic anaemia and liver failure, affecting as many as one in 3000 people exposed to the drug. Hence, it seems prudent to limit its use to severe intractable cases where potential benefit outweighs the risk.

Antiepileptic drugs currently in development

At present there are not many potential antiepileptic compounds undergoing clinical evaluation and there is only one, brivtiracetam which is in the final stages of development.