

## New antiepileptic drugs

J.W. SANDER

Institute of Neurology, University College London, National Hospital for Neurology and Neurosurgery, Queen Square, London, and Epilepsy Society, Chalfont St Peter, Bucks

---

New antiepileptic drugs (AEDs) are necessary for patients with chronic epilepsy and for improving upon established AEDs as first-line therapy. In the last decade, nine novel AEDs have been released in the UK. These are in chronological order of appearance: oxcarbazepine, levetiracetam, pregabalin, zonisamide, stiripentol, rufinamide, lacosamide, eslicarbazepine acetate and retigabine. Two of these drugs, stiripentol and rufinamide, have been licensed as orphan drugs for specific epileptic syndromes. Another drug, felbamate, is available in other countries. Their pharmacokinetic properties are listed in Table I, and indications and a guide to dosing in adults and adolescents are outlined in Table II. Known side effects are given in Table III. Other compounds are currently in different phases of development and may become available in the future.

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 patients 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 not yet been fully established.

### New AEDs marketed in the UK

#### *Eslicarbazepine acetate*

Eslicarbazepine acetate is a new drug, licensed as an add-on for focal epilepsy, which 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, a functionalised amino-acid, is a second line drug for focal epilepsy in patients over the age of 16 years. Its putative mode of action is not shared with any other currently available AEDs. It is said to enhance the slow inactivation of sodium channels and to modulate collapsing response mediator protein-2 (CRMP-2), although it is not known how this contributes to its antiepileptic action.

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 I.** Pharmacokinetics of new antiepileptic drugs available in the UK.

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

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

<b>Drug</b>	<b>Indications</b>	<b>Starting dose</b>	<b>Standard maintenance dose</b>	<b>Dosage interval</b>
<b>Eslicarbazepine acetate</b>	Focal seizures	400 mg	800–1200 mg	bid
<b>Levetiracetam</b>	Focal seizures, generalised seizures	500 mg	1500–3000 mg	bid
<b>Lacosamide</b>	Focal seizures	100 mg	200–400 mg	bid
<b>Oxcarbazepine</b>	Focal and generalised tonic-clonic seizures	300–600 mg	1200–2400 mg	bid
<b>Pregabalin</b>	Focal seizures	100–150 mg	150–600 mg	bid
<b>Retigabine*</b>				
<b>Zonisamide</b>	Focal seizures	100 mg	200–600 mg	bid

\*No guidelines as yet

**Table III.** Side effects of new antiepileptic drugs.

Side effects	Eslicarbazepine acetate	Levetiracetam	Oxcarbazepine	Lacosamide	Pregabalin	Retigabine	Zonisamide
<b>Dose related</b>	<ul style="list-style-type: none"> <li>* Fatigue</li> <li>* Drowsiness</li> <li>Diplopia</li> <li>Dizziness</li> <li>Hyponatraemia</li> <li>Ataxia</li> <li>Nausea</li> <li>Nystagmus</li> <li>Tremor</li> </ul>	<ul style="list-style-type: none"> <li>Headache</li> <li>Asthenia</li> <li>Irritability</li> <li>Ataxia</li> <li>Drowsiness</li> </ul>	<ul style="list-style-type: none"> <li>* Fatigue</li> <li>* Drowsiness</li> <li>* Diplopia</li> <li>* Dizziness</li> <li>* Hyponatraemia</li> <li>Ataxia</li> <li>Nausea</li> <li>Nystagmus</li> <li>Tremor</li> </ul>	<ul style="list-style-type: none"> <li>* Nausea</li> <li>* Dizziness</li> <li>* Headache</li> <li>* Lethargy</li> <li>* Diplopia</li> </ul>	<ul style="list-style-type: none"> <li>* Dizziness</li> <li>Drowsiness</li> <li>Ataxia</li> <li>Weight gain</li> <li>Diplopia</li> <li>Tremor</li> <li>Abnormal thinking</li> </ul>	<ul style="list-style-type: none"> <li>Drowsiness</li> <li>Dizziness</li> <li>Slurred speech</li> <li>Ataxia</li> <li>Tremor</li> <li>Diplopia</li> </ul>	<ul style="list-style-type: none"> <li>Drowsiness</li> <li>Dizziness</li> <li>Anorexia</li> <li>Memory impairment</li> <li>Ataxia</li> <li>Confusion</li> <li>Word-finding difficulties</li> <li>Concentration impairment</li> <li>Agitation</li> <li>Depression</li> </ul>
<b>Idiosyncratic</b>			Rash				<ul style="list-style-type: none"> <li>Skin rash</li> <li>Blood dyscrasias</li> </ul>

\*Commonest side effects

No drug-drug interactions are known. Its commonest side effects are dizziness, headaches, nausea, and diplopia. No idiosyncratic side effects have yet been associated with this drug. The drug should be used with caution in patients with a history of cardiac conduction problems as it is known to increase the PR interval in some patients.

#### *Levetiracetam*

Levetiracetam, a piracetam derivative, is a broad-spectrum drug indicated both as a first-line drug and as an add-on drug. No mode of action for levetiracetam has yet been advanced. It has a binding site in the brain for which the natural ligand is the synaptic vesicle protein SV2A although 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) are the most common side effects. No definite pharmacokinetic interactions have yet been identified, but there are reports of potential pharmacodynamic interactions with carbamazepine and phenytoin.

#### *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 partial 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 patients hypersensitive to carbamazepine. There are indications of teratogenicity in animal models, particularly at high doses, and caution should be used in humans.

#### *Pregabalin*

Pregabalin has been licensed for the adjunctive treatment of refractory focal epilepsy. It 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<sup>+</sup> and this action is thought to be the basis of its antiepileptic mechanism.

The recommended doses 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, seems to be a chronic side effect of this medication. No pharmacokinetic interactions have yet been identified. In addition to its use in epilepsy, pregabalin has also been indicated for neuropathic pain and there are studies to suggest that it might be useful in generalised anxiety disorders.

#### *Stiripentol*

Stiripentol is licensed as an orphan drug for severe myoclonic epilepsy of infancy (SMEI) 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 during the clinical trial development programme were CNS-related and drowsiness, dizziness, slurred speech, ataxia, tremor and diplopia. It also seems to cause urinary tract infection in some people. No clinical significant pharmacokinetic interaction has yet been seen.

#### *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 effect is believed to be mediated through action at voltage-sensitive sodium channels. It is used as a second-line drug for patients with focal seizures with or without secondary generalisation. Anecdotal reports of its efficacy in other seizure types, particularly myoclonic seizures, need to be formally tested. Recommended doses are between 200 and 500 mg/day, although some patients may derive benefit from doses outside this range. The recommended starting dose for most patients is 100 mg once daily, titrating upwards every two weeks in 100 mg/day increments until seizure control is achieved or side effects develop. Its long elimination half-life allows once-daily dosing.

Zonisamide does not affect levels of carbamazepine, barbiturates or valproate, but may increase the plasma concentration of phenytoin by about 10–15%. Zonisamide metabolism is, however, induced by carbamazepine, barbiturates and phenytoin and higher zonisamide doses may be necessary during co-administration with these AEDs.

Side effects of zonisamide 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. 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 an effective drug with a broad spectrum of action but due to its safety profile it is used as a drug of last resort in patients with intractable epilepsy, particularly in patients with Lennox-Gastaut syndrome. The usual dose is between 2400 and 4800 mg/day. The recommended starting dose for most patients 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-epoxy-carbamazepine, 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 4000 patients 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 several potential antiepileptic compounds undergoing clinical evaluation. These include: perampanel, brivirtacetam and ganaxalone, which are in the final stages of development.