The place of the new antiepileptic drugs

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For many patients, better tolerability and reduced potential for drug interactions are favourable characteristics of the new antiepileptic drugs.

In the past 10 years, the number of drugs available in Australia to treat epilepsy has effectively doubled. Disappointingly, this has not been associated with a halving of the number of patients with medically refractory epilepsy. Yet each of the recently introduced antiepileptic drugs has particular characteristics that may merit its selection for individual patients.

Many neurologists regard antiepileptic drugs as 'new' even after 10 years of clinical use. This view is understandable given the recent experience of failure of two previous agents to provide long term safety. (Vigabatrin was introduced in the early 1990s, only to be found after several years to be associated with peripheral visual field loss, effectively curtailing its use. Only a few years later, felbamate, which was quickly becoming a popular antiepilepsy drug in the USA, was withdrawn because of rare fatalities due to hepatic failure or aplastic anaemia.) Additionally, the issues relevant to establishing when each of the new epileptic agents is best used clinically have only slowly and partially been resolved.

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The new antiepileptic drugs lamotrigine, gabapentin, topiramate (Topamax) and tiagabine (Gabitril) were introduced prior to 1999, each initially indicated as add-on therapy for partial onset seizures. Levetiracetam (Keppra) was introduced in 2003 and oxcarbazepine (Trileptal) in 2002. Pregabalin (Lyrica) has been approved for use as adjunctive therapy in adults with partial seizures with or without secondary generalisation; it has not yet been listed on the PBS.

The newest antiepileptic drugs on the PBS

Levetiracetam

Levetiracetam is indicated, as add-on therapy, for treating partial onset seizures that are not controlled satisfactorily by other antiepileptic drugs. It is well absorbed when taken by mouth and most is excreted unchanged by the kidneys.

For most patients, levetiracetam is well tolerated.[2] Adverse effects relate primarily to action on the central nervous system. Somnolence, asthenia, headache and dizziness are the most common unwanted effects, leading to discontinuation or dose reduction in approximately 5% of treated patients. Anxiety, irritability and depression occur less frequently; rash appears to be an uncommon adverse event. Levetiracetam is not associated with hepatic or renal dysfunction.

Levetiracetam does not induce enzymes responsible for drug metabolism so it does not alter the kinetics of other antiepileptic medications the patient is receiving. In adults, the dose range is from 1000 to 3000 mg per day, which is usually taken as two divided amounts. The onset of efficacy is rapid. Initiation with a high dose (e.g. 1000 mg twice daily) was seen to be well tolerated in clinical trials, but in clinical practice slower introduction – starting at 500 mg per day then increasing weekly or fortnightly – appears to improve tolerability.[1]

Oxcarbazepine

Oxcarbazepine is an effective treatment of partial onset seizures and primary generalised tonic–clonic seizures. Like levetiracetam, it is restricted for use in patients for whom other epileptic drugs have not provided satisfactory seizure control.

Oxcarbazepine was developed by modifying carbamazepine and has simpler metabolism and better tolerability. Oxcarbazepine is effectively a prodrug with a half-life of two hours; it is converted to an active metabolite, 10-hydroxycarbazepine, which exerts the clinical effects. This metabolite has a half-life of nine hours, so oxcarbazepine is administered twice daily. In adults, treatment can be commenced at 600 mg per day and increased weekly in 300 mg increments, depending on response and tolerability. The drug is almost completely absorbed orally. As the metabolism of oxcarbazepine has linear kinetics, the ratio of the administered dose to the blood concentration of the active metabolite is unchanged over the range used clinically, which is 600 to 2400 mg per day in adults.[3]

The adverse effects of oxcarbazepine are mostly dose related. Dizziness, fatigue, drowsiness and nausea are the most common. Rash is seen less frequently with oxcarbazepine than with carbamazepine, occurring in up to 10% of patients, usually in the first month of treatment. However, Stevens–Johnson syndrome has been reported so drug withdrawal should be considered and appropriate clinical monitoring undertaken if rash occurs. A patient who has suffered a rash on exposure to

Table. Adverse effects of the new antiepileptic drugs

Drug	Serious effects	Nonserious effects
Gabapentin	None	Dizziness, ataxia, fatigue, weight gain, mood change
Lamotrigine	Rash (rarely, Stevens–Johnson syndrome or toxic epidermal necrolysis)	Dizziness, ataxia, diplopia, insomnia
Levetiracetam	None	Somnolence, weakness, headache, depression
Oxcarbazepine	Rash, hyponatraemia	Fatigue, dizziness, nausea, nervousness
Tiagabine	Spike wave stupor	Dizziness, nervousness, depression
Topiramate	Kidney stones, open angle glaucoma (rare)	Weight loss, mild acidosis, paraesthesia

carbamazepine has a 30% risk of rash with oxcarbazepine.

Hyponatraemia is associated with oxcarbazepine – about 2.5% of patients have a serum sodium level of 125 mmol/L or less. For most patients this does not produce symptoms, but it appears prudent to measure the sodium level after a maintenance dose is reached as a baseline for possible future reference. Particular care regarding hyponatraemia should be taken in patients who have renal disease or are concomitantly taking diuretics or NSAIDs.[4]

Although oxcarbazepine does not induce enzyme activity to the same degree as carbamazepine, it does increase the metabolism of ethinyloestradiol, impairing the efficacy of the oral contraceptive pill. Oxcarbazepine (which is an inhibitor of the P450 isoform CYP2C19) can increase phenytoin concentration to a moderate degree when these two medications are coadministered.[5]

Extending spectrum of clinical use

The indications for use of lamotrigine and topiramate have been extended since each agent was introduced as add-on therapy for refractory partial-onset seizures. Both are now recognised as broadspectrum antiepileptic drugs. Lamotrigine may be used to treat patients with epileptic seizures that are not controlled satisfactorily by other antiepileptic drugs. For topiramate, the additional indications are treatment of primary generalised tonic–clonic seizures and Lennox-Gastaut syndrome.

Monotherapy

A new antiepileptic drug is usually added to a patient's current antiepileptic drug treatment, which allows the efficacy and tolerability of the newly added medicine to be assessed. If there is a satisfactory response, consideration of withdrawal of the other antiepileptic drugs is worthwhile – particularly to minimise the risk of teratogenesis. There is potential for seizure recurrence as doses are lowered, so some patients opt to leave their medications unchanged or defer withdrawal until a time when the consequence of recurrence may not be a critical event in their life. The withdrawal of the other drugs is done singly and at a rate dependent on the pharmacokinetics of each agent.

How do the new antiepileptic drugs compare?

Comparison of the new antiepileptic drugs as treatment of refractory partial-onset epilepsy has been attempted by comparing results from independent placebo-controlled studies – that is, not from head to head studies. No statistically significant differences have been found in efficacy. It appears that levetiracetam and topiramate may be the more potent agents, while lamotrigine and levetiracetam are more tolerable. Topiramate has efficacy for primary generalised tonic–clonic seizures. Clinical reports indicate lamotrigine may be effective for patients with juvenile myoclonic epilepsy or childhood absence epilepsy.[6] Seizure exacerbation has been reported following commencement of lamotrigine, oxcarbazepine and tiagabine. This undesirable outcome appears to be uncommon.

Gabapentin, lamotrigine, topiramate and oxcarbazepine have evidence of efficacy as treatment for new onset epilepsy. However, none of the trials comparing these new drugs with phenytoin, carbamazepine or sodium valproate have found any of the new drugs to be superior.[7]

Deficiencies of the new antiepileptic drugs, compared with the older drugs, are the absence of long term safety or teratogenesis data, relative expense, and the lack of correlation between plasma concentration and clinical effect and titration rates. Plasma concentration monitoring may be useful for patients receiving lamotrigine during pregnancy. Monitoring of reliability of intake of these agents often relies on the reports of the patient or a family member. Favourable characteristics of the new drugs are often better tolerability and reduced drug interactions. Potential adverse effects of these agents are listed in the Table.

There are numerous potential combinations of antiepileptic drugs. Lamotrigine and sodium valproate appear to have a synergistic effect in controlling seizures that is not completely explained by the kinetic interaction between the two agents. Hopefully, further synergistic combinations will be identified by careful clinical observation.

Conclusion

These new antiepileptic drugs have resulted in a small number of patients becoming seizure free and a moderate number benefiting from improved tolerability without lessening seizure control. Surgery should be considered when partial-onset seizures are not controlled after adequate trials of two appropriate drugs.[8] Although the new antiepilepsy drugs may not have achieved the high hopes entertained at the time of their introduction, these agents are valuable for individual patients in a manner that is not clearly reflected by analysis of clinical trial data. Moreover, these agents have provided additional tools for researching the pathophysiology of epilepsy. MT

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DECLARATION OF INTEREST: Dr McLaughlin has received speaker fees from the manufacturers of tiagabine, topiramate, oxcarbazepine, levetiracetam and sodium valproate. He has been a member of company sponsored Australian advisory boards for tiagabine, topiramate, oxcarbazepine, levetiracetam and vigabatrin.