Efficacy of new antiepileptic drugs in different adulthood epilepsies

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ABSTRACT

Objectives: To present the current state of knowledge on the spectrum of efficacy of 9 new antiepileptic drugs (AEDs) in adult epilepsy.

Methods: The results of double-blind controlled clinical trials were combined with data from open-label studies or case series to assess the efficacy of new AEDs in adult epilepsies.

Results: All new AEDs were found effective in the adjunctive treatment of partial epilepsy. In the United States of America, only oxcarbazepine is approved as first-line therapy in partial onset epilepsy, while lamotrigine and felbamate are approved for conversion to monotherapy. However, comparative trials support the potential use of gabapentin, lamotrigine and topiramate as first-line drugs in partial epilepsy. There is no evidence of preferential efficacy of an AED in specific partial epilepsies. Meta-analysis of published trials showed only nonsignificant trends for differences in efficacy. Only some of the new AEDs have demonstrated efficacy in generalized epileptic syndromes and generalized seizure types. Felbamate, lamotrigine, and topiramate were effective in the Lennox-Gastaut syndrome and lamotrigine has also been found effective for generalized absence seizures. There is preliminary evidence for levetiracetam efficacy in juvenile myoclonic epilepsy and zonisamide efficacy in progressive myoclonus epilepsy. Gabapentin failed to demonstrate efficacy against primary generalized tonic-clonic or generalized absence seizures. No generalized epilepsy trials have been performed for tiagabine, oxcarbazepine or vigabatrin.

Conclusions: All the new AEDs are effective against partial epilepsy, but only some seem to have efficacy in generalized epilepsy. Additional investigations are needed to study specific efficacy of individual new AEDs in generalized epileptic syndromes.

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Since the early 1990’s at least 9 new anti-epileptic drugs (AEDs) have been marketed worldwide. They include felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), topiramate (Topamax), tiagabine (Gabitril), oxcarbazepine (Trileptal), levetiracetam (Keppra), zonisamide (Zonegran), and vigabatrin (Sabril). The profusion of new agents has resulted in a need for guidelines to direct the use of these agents. Ideally, guidelines should be evidence-based and derived from controlled blinded clinical trials. However, in the absence of data in specific categories, guidelines may have to be based on open-label studies, case series and anecdotal reports. This manuscript will summarize the current state of knowledge on efficacy of new AEDs in adult epilepsy syndromes.

Partial epilepsies. All the new anti-epileptic drugs were tested as adjunctive treatment in refractory partial onset seizures and were demonstrated effective in double-blind placebo-controlled trials. This has often been the basis for regulatory marketing approval and all the new AEDs drugs have approval as add-on agents in medically refractory partial epilepsy. The epileptic syndromes studied have been predominately partial cryptogenic and partial symptomatic, without regard to localization. Very limited information is available on new AED efficacy in specific syndromes, specific localizations, or specific age groups. No study has compared new AEDs directly for efficacy and tolerability as adjunctive therapy, but published add-on trials of different agents were compared in...
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meta-analysis.\textsuperscript{12,13} When examining the proportion of 50% responders, no statistically significant difference was found between the new drugs, even though the 50% responder rate ranged from 20-44%.\textsuperscript{12,13} However, based on the doses tested, there was a trend for topiramate, oxcarbazepine, vigabatrin, and levetiracetam to have a larger proportion of responders than tiagabine, zonisamide, lamotrigine and gabapentin. This finding may not be valid since the gabapentin and lamotrigine dosing was underestimated in the clinical trials, while topiramate dosing was overestimated in the pivotal double-blind trials. Seizure-free rates in these short-term studies were less than 10%, and usually less than 5%, in this refractory patient group. During long-term follow-up the seizure-free rates at best reach 13%.\textsuperscript{14,15} The comparative tolerability of the new AEDs has also been compared using meta-analysis of withdrawal rate in clinical trials.\textsuperscript{12,13} Similarly, there was no statistically significant difference between the new AEDs in this measure of tolerability. Overall, the withdrawal rate tended to be greater for the AEDs with larger responder rate. For example, topiramate and oxcarbazepine had relatively greater withdrawal rates than lamotrigine and gabapentin. This data should be interpreted with caution as well, since the current clinically recommended dose range for topiramate is much smaller than that used in the trials. Levetiracetam had the most favorable responder-withdrawal ratio.\textsuperscript{12}

Two of the new AEDS are now restricted due to potentially serious toxicity: felbamate because of aplastic anemia and liver failure,\textsuperscript{16} and Vigabatrin because of retinal toxicity and visual field constriction.\textsuperscript{17} As a result, both agents should be considered only as a last resort.

Several drugs have been tested in head-to-head monotherapy comparisons in new onset partial epilepsy.\textsuperscript{5,18,25} The comparator was most often carbamazepine or another older AED, but in some instances the new drugs were compared directly.\textsuperscript{19} Gabapentin, lamotrigine and oxcarbazepine have been found equally effective to carbamazepine, yet with less adverse effects.\textsuperscript{5,18,22,25-27} Lamotrigine and gabapentin were equally effective and no different in adverse effects.\textsuperscript{19} In the newly diagnosed epilepsy population, responder rates usually were around 70-80%, and seizure free rates were in the range of 50-60%. For patients who fail one AED due to lack of efficacy, the odds of becoming seizure-free with a second AED are reduced to approximately 11%.\textsuperscript{28}

In the United States of America, comparative trials have not been accepted as the basis for monotherapy approval. Only placebo or pseudo-placebo controlled studies have been accepted, because they can demonstrate superiority. Based on this type of study, oxcarbazepine was approved for new onset monotherapy and lamotrigine was approved for withdrawal to monotherapy.\textsuperscript{29,31}

A lot less is known about the specific efficacy of new anti-epileptic drugs in generalized seizure types and generalized epileptic syndromes. The preponderance of evidence suggests that gabapentin, tiagabine, oxcarbazepine and vigabatrin are not effective in generalized seizure, and may even worsen some seizure types. However, primary generalized tonic-clonic seizures may respond to agents effective in partial-onset seizures. This latter statement is based more on circumstantial evidence than rigorous controlled trials. Felbamate, lamotrigine, topiramate, levetiracetam and zonisamide all appear to have some efficacy in generalized-onset seizures and generalized epileptic syndromes. Controlled trials confirming this efficacy are available only for felbamate in Lennox-Gastaut syndrome,\textsuperscript{32} Lamotrigine in Lennox-Gastaut syndrome\textsuperscript{33} and generalized typical absence seizures,\textsuperscript{34} and topiramate in generalized-onset tonic-clonic seizures\textsuperscript{35} and Lennox-Gastaut syndrome.\textsuperscript{36} There is preliminary support for efficacy of topiramate, levetiracetam and zonisamide for generalized myoclonic seizures and the syndrome of juvenile myoclonic epilepsy (JME).\textsuperscript{37} Lamotrigine may also be effective in JME, but appears to be relatively less useful for myoclonic seizures and occasionally aggravates them.\textsuperscript{38-40} If generalized myoclonic seizures are the primary seizure type in JME, lamotrigine may not be the most appropriate choice. The response rate is not known for newly diagnosed generalized epilepsy, but one study suggested no difference from partial epilepsy.\textsuperscript{28} The seizure-free rate with lamotrigine treatment for absence seizures was 64%.\textsuperscript{34}

New AED selection. In new onset partial epilepsy, the choice of new AED will be based on efficacy and safety/tolerability data, as well pharmacokinetic considerations. For example, in situations where a rapid intervention is required, lamotrigine and topiramate may be inappropriate because they require a long titration. Oxcarbazepine can be started at a therapeutic dose and would be the most appropriate for partial epilepsy. Levetiracetam, zonisamide and tiagabine do not have sufficient new onset monotherapy data. When several anti-epileptic drug options exist for a particular seizure type or epileptic syndrome, co-morbidity and adverse effects may be the key determinant of the most appropriate choice. For example, the presence of obesity and migraine in a patient with JME may favor the use of topiramate. On the other hand, a history of cognitive dysfunction and drowsiness with other anti-epileptic drugs may argue for the use of lamotrigine, which is less sedating in comparative studies.\textsuperscript{41,42}

In conclusion, new AEDs are all effective for adjunctive therapy in partial epilepsy. Monotherapy data, and data in generalized seizure types and epileptic syndromes are available only for select AEDs (Table 1). There is a need for investigation of the new AEDs in specific syndromes to improve existing therapeutic guidelines.
Table 1 - Efficacy of new AEDs in some seizure types.

<table>
<thead>
<tr>
<th>AED</th>
<th>Partial</th>
<th>Primary GTC</th>
<th>Generalized myoclonic</th>
<th>Generalized absence</th>
</tr>
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<tbody>
<tr>
<td>Felbamate*</td>
<td>Effective</td>
<td>Effective</td>
<td>Effective</td>
<td>Effective</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Effective</td>
<td>?</td>
<td>Not effective</td>
<td>Not effective</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Effective</td>
<td>Effective</td>
<td>?Partially effective</td>
<td>Effective</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Effective</td>
<td>Effective</td>
<td>?Effective</td>
<td>?Effective</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Effective</td>
<td>?</td>
<td>Not effective</td>
<td>Not effective</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Effective</td>
<td>?</td>
<td>Not effective</td>
<td>Not effective</td>
</tr>
<tr>
<td>Levetiracetam</td>
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<td>Effective</td>
<td>Effective</td>
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<tr>
<td>Zonisamide</td>
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<td>Effective</td>
<td>Effective</td>
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</tr>
<tr>
<td>Vigabatin*</td>
<td>Effective</td>
<td>?</td>
<td>Not effective</td>
<td>Not effective</td>
</tr>
</tbody>
</table>

*AED - antiepileptic drug; GTC - generalized tonic clonic.

**References**


