Efficacy and tolerability of the new antiepileptic drugs: comparison of two recent guidelines

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Background
Until the early 1990s six major compounds (carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproic acid) were available for the treatment of epilepsy. However, these drugs have pharmacokinetic limitations, teratogenic potential, and a negative effect on cognitive functions that impairs the quality of patients' lives and limits the use of these drugs in some patients. In addition, 20–30% of patients are refractory to these drugs.

Recent developments
The development of ten new antiepileptic drugs (vigabatrin, felbamate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide, and pregabalin) has expanded treatment options. The newer drugs may be better tolerated, have fewer drug interactions, and seem to affect cognitive functions to a lesser extent than old drugs. Guidelines on the use of new antiepileptic drugs have been developed in the USA and in the UK. Both guidelines offer a clear picture of the efficacy, safety, and tolerability of the new antiepileptic drugs and agree on their use as add-on treatment in patients who do not respond to conventional drugs. The guidelines differ in the type and strength of recommendations. Whereas the US guidelines recommend treatment in newly diagnosed epilepsy with a standard drug or a new drug depending on the individual patient's characteristics, the UK guidelines recommend that a new antiepileptic drug should be considered only if there is no benefit from an old antiepileptic drug, an old drug is contraindicated, there is a previous negative experience with the same drug, or the patient is a woman of childbearing potential.

Where next
The limited amount of information on the new antiepileptic drugs may explain the discrepancies among the two guidelines and between these and other recommendations. Comparative, pragmatic, long-term and open trials should be done to show long-term efficacy and comparative features of the new antiepileptic drugs, and to better assess the effect on quality-of-life, cost-effectiveness, tolerability, and teratogenic potential. In addition, the conflicts should be resolved between the needs of the regulatory bodies and those of the treating physicians. Finally, there is a need for trial designs to be standardised.

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Epilepsy is a common medical disorder (incidence 30–50 per 100 000 per year; prevalence 6–8 per 1000; cumulative incidence 3%)[1,2] requiring prolonged and sometimes lifelong drug therapy. Several antiepileptic drugs are available to the practising physician. Until the early 1990s there were six major compounds—carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproic acid. With these drugs, about 50% of patients with newly diagnosed epilepsy achieved seizure control immediately after starting drug treatment, and 20–30% of cases achieved remission after one or more changes of the daily dose or after switch to another compound. This leaves 20–30% of patients whose epilepsy does not benefit from the older antiepileptic drugs. Carbamazepine, phenytoin, phenobarbital and primidone are liver enzyme inducers. Combination therapy with other drugs metabolised through the same pathways (eg, oral anticoagulants, oral contraceptives, calcium channel antagonists, and antibacterial agents) may lead to a reduced efficacy of these compounds with a need to increase the daily dose for a successful therapeutic action. Sex steroids and vitamin D may also be affected, leading to sexual and reproductive dysfunction and osteomalacia. With the older drugs there is a two to four times increase in the number of newborns with minor or major malformations; this complication is most common with valproic acid. This drug is also a potent hepatic inhibitor with consequent interactions with other antiepileptic and non-antiepileptic drugs. Cognitive dysfunction has been also reported with almost all the older drugs. These limitations must be considered in the treatment of patients at risk—such as children, patients with intellectual deficits and learning disabilities, women of childbearing potential, and elderly people.

Since 1991, ten new drugs have been developed and marketed to reduce the number of patients with drug-resistant epilepsy. Evidence-based guidelines are thus needed to provide practising physicians with adequate knowledge of the comparative efficacy and safety of these compounds relative to the older drugs to facilitate the choice of the appropriate drug in the management of children and adults with newly diagnosed epilepsy and those who are unresponsive to the older drugs.

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Table 1. Serious and nonserious adverse events associated with the new antiepileptic drugs[3,8]

AED	Serious adverse events	Nonserious adverse events
Felbamate	Aplastic anaemia, hepatotoxicity	Gastrointestinal disturbances, anorexia, insomnia
Gabapentin	Aggression*	Weight gain, peripheral oedema, behavioural changes†
Lamotrigine	Rash, including Stevens Johnson and toxic epidermal necrolysis (high risk for children, also more common with concomitant valproic-acid use and low with slow titration); hypersensitivity reactions, including hepatic and renal failure, DIC, and arthritis	Tics† and insomnia
Levetiracetam	None	Irritability/behaviour change
Oxcarbazepine	Hyponatraemia (more common in elderly people), rash	None
Tiagabine	Nonconvulsive status epilepticus	Dizziness, asthenia
Topiramate	Nephrolithiasis, open angle glaucoma, hypohidrosis,† depression, psychosis	Metabolic acidosis, weight loss, language dysfunction, paraesthesia
Vigabatrin	Visual field defects, psychosis, depression	Weight gain
Zonisamide	Rash, renal calculi, hypohidrosis†	Irritability, photosensitivity, weight loss

AED=antiepileptic drug; DIC=disseminated intravascular coagulation. *Mostly in cognitively impaired patients; †predominantly children.

US and UK guidelines

Guidelines for the pharmacological treatment of epilepsy and, more specifically, for the use of the newer antiepileptic drugs, have been devised recently in the USA[3,4] and in the UK.[5,6] In the USA, the Therapeutic and Technology Assessment Subcommittee and the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society did a literature search for relevant articles on the efficacy, tolerability, and safety of seven new antiepileptic drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide). Felbamate was not considered in this review because it was addressed in a previous guideline.[7] The safety profile of the new antiepileptic drugs is summarised in table 1.[3,8] Placebo-controlled randomised clinical trials and active-control comparative studies in children and adults and for patients with partial and generalised seizures were reviewed. Each study was reviewed by three panel members who classified it as class I (best rating) through IV (lowest rating) according to standard classification criteria. Treatment of new onset epilepsy and treatment of refractory epilepsy were assessed in two separate publications.

In the UK, the National Institute for Clinical Excellence Committee examined randomised clinical trials and systematic reviews comparing new antiepileptic drugs with placebo, with older drugs, or with other new compounds. The UK guidelines did not consider zonisamide (not yet available in Europe) and felbamate (a last resort agent because of bone marrow and liver toxicity) but included vigabatrin in the review. Pregabalin has not been reviewed, possibly because of insufficient evidence at the time of preparation of the guidelines. The results of these studies were combined with information derived from other sources to provide recommendations on the use of new antiepileptic drugs in a more general context, including the overall modalities of drug treatment of epilepsy. In addition, the UK panel addressed quality-of-life and cost issues. Children and adults with newly diagnosed epilepsy and with different epilepsy syndromes were assessed separately.

Summary of evidence and recommendations

Newly diagnosed partial epilepsy

The new antiepileptic drugs seemed to be similar to the older compounds in efficacy, but superior in tolerability. Overall, evidence is insufficient to assess the effect of old and new drugs on quality of life. There is insufficient evidence to suggest differences in efficacy among newer antiepileptic drugs. On this basis, the US panel recommended patients with newly diagnosed (previously untreated) epilepsy to be treated with an older drug or with a new drug among lamotrigine, gabapentin, oxcarbazepine, or topiramate, depending on individual patients' characteristics (level A: drug established as effective; table 2). By contrast, the UK panel stressed the need to start treatment with an older drug (preferably carbamazepine or valproic acid) unless this is contraindicated for the potential for interactions with other drugs, there is a previous negative experience with the same drug, or the patient is a woman of childbearing potential, only after discussing the possible interactions with oral contraceptives and the teratogenic potential of each compound. Although there are few randomised clinical trials in children, partial seizures are thought to be similar in pathophysiology to childhood seizures and will probably respond to the same drugs.[9] These recommendations have been thus extended by both panels to cryptogenic and symptomatic partial epilepsies in children of different ages (table 2).

Newly diagnosed generalised epilepsy

On the basis of a class II evidence study, lamotrigine was found to be effective for the treatment of children with newly diagnosed absence seizures. The US panel recommended including lamotrigine in the options for this indication. Although in the UK lamotrigine and topiramate are licensed for use in idiopathic generalised epilepsy, the UK panel did not consider them first-line drugs. By contrast, gabapentin was not superior to placebo for the treatment of absence seizures and there is insufficient evidence for efficacy of any other new antiepileptic drug for the treatment of idiopathic and symptomatic generalised epilepsy.

Table 2. Summary of the US and UK guideline recommendations for use of new antiepileptic drugs

Drug	Newly diagnosed epilepsy				Refractory epilepsy							
	Partial, mixed		Absence		Partial		Partial monotherapy		Idiopathic generalised		Symptomatic generalised	
	US	UK	US	UK	US	UK	US	UK	US	UK	US	UK
Felbamate*	No	NA	No	NA	Yes†	NA	Yes	NA	No	NA	Yes‡	NA
Gabapentin	Yes§	No	No	No	Yes	Yes¶	No	No	No	No	No	No
Lamotrigine	Yes§	Yes‖	Yes§	Yes‖	Yes	Yes**	Yes	Yes	No	Yes**	Yes	Yes**
Levetiracetam	No	No	No	No	Yes	Yes††	No	No	No	No	No	No
Oxcarbazepine	Yes	Yes¶	No	No	Yes	Yes¶	Yes	Yes¶	No	No	No	No
Tiagabine	No	No	No	No	Yes	Yes‖	No	No	No	No	No	No
Topiramate	Yes§	Yes¶	No	No	Yes	Yes**	Yes§	Yes¶	Yes‡‡	Yes‡‡**	Yes	Yes**
Vigabatrin§§	NA	No	NA	No	NA	Yes	NA	No	NA	No	NA	Yes¶¶
Zonisamide	No	NA	No	NA	Yes‖‖	NA	No	NA	No	NA	No	NA

None of the new drugs is recommended as first choice in newly diagnosed epilepsy by the UK guidelines (see text). NA=not available. *Patients unresponsive to standard drugs in whom the risk/benefit ratio supports use;[7] †only patients >18 years; ‡only patients >4 years with Lennox-Gastaut syndrome; §indication not approved by FDA; ¶only patients ≥6 years; ‖only patients ≥12 years; **only patients >2 years; ††only patients ≥16 years; ‡‡only generalised tonic-clonic seizures; §§in the UK the indications are limited to adjunctive use after failure of all other appropriate drug combinations; ¶¶only West syndrome; ‖‖only adults.

Refractory partial epilepsy

In the absence of a standard definition of refractory epilepsy, the US panel defined drug resistance as failure to respond to three or more drugs. The UK guidelines did not provide a definition of drug resistance, but they recommend repeated monotherapy trials before starting an add-on therapy.

Both guidelines concluded that add-on clinical trials have shown efficacy for all new antiepileptic drugs, and that these drugs can be recommended as add-on therapy in patients with refractory partial epilepsy. Except for levetiracetam, a dose-response effect and a dose-dependent adverse event rate are present for all compounds. However, between-drug comparisons are prevented by the different study populations, the variable drug schedules, and the differing titration rates. On this basis, both guidelines suggest the use of all new antiepileptic drugs as add-on treatment for refractory partial epilepsy. The role of the new drugs as monotherapy in these patients (assessed for lamotrigine, oxcarbazepine, and topiramate) is uncertain because the results of regulatory trials (short-lasting and only in adults) cannot be easily transferred to clinical practice. Even with these limitations, the US panel recommended the use of oxcarbazepine and topiramate (level A) and lamotrigine (level B: drug probably effective) as monotherapy in refractory partial epilepsy. In the UK guidelines, vigabatrin was recommended as a first-line therapy for children with West syndrome. The UK panel also recommended that "... people who do not derive worthwhile benefits in terms of significant seizure reduction or improvement in quality of life should not continue with that regimen in the long term ... [and] ... should revert to treatment with the regimen that had proved most effective ... and has the least side effects". In addition, in the absence of compelling evidence of advantage in terms of efficacy among new antiepileptic drugs, the UK guidelines suggest a cost-minimisation approach to decide in which order the drugs should be tried.

Refractory generalised epilepsy

Only a few trials investigated the effects of topiramate (effective) and gabapentin (ineffective) in refractory generalised epilepsy. On this basis, the US panel recommended the use of topiramate alone for the treatment of children and adults with this disorder (level A). Topiramate and lamotrigine are effective against drop attacks in patients with Lennox-Gastaut syndrome and have been recommended for the treatment of children and adults with this disorder (level A).

Treatment of special populations

Children and patients with learning disabilities and intellectual deficits

Although these patients have been shown to benefit from new antiepileptic drugs to the same extent as adults with epilepsy, and beneficial effects were obtained on behavioural symptoms with lamotrigine and gabapentin, safety and tolerability concerns have been raised by the UK panel. In addition, there is no strong or consistent evidence of a difference between drugs in their effects on cognitive functions. However, none of the guidelines mentioned differential modes of treatment in these specific subgroups.

Women of childbearing age

The UK panel noted that preliminary data from the UK Epilepsy and Pregnancy Register suggests crude rates for risks of major congenital malformations being 4% with monotherapy and 6·3% with duotherapy or polytherapy (comparative rate in untreated women with epilepsy, 0·9%). The rate was 2·3% for carbamazepine, 3% for lamotrigine, and 7·2% for valproic acid. These findings are in keeping with other reports that show that multiple drug therapy and higher daily doses may be associated with higher risks.[10] Few data are available for the other new antiepileptic drugs to fully assess their teratogenicity. This should introduce a note of caution in their use in women of childbearing potential. The UK panel also emphasised the potential for drug interactions of some newer anticonvulsants (namely

oxcarbazepine and topiramate), which may be of relevance in women taking oral contraceptives.

Elderly people

The US panel highlighted the potential for drug interactions in elderly people. They also recommended caution in the use of liver-enzyme inducers and other drugs that may interact with others. However, it is still uncertain whether the new drugs should be preferred to the old drugs in elderly people because, except for lamotrigine (which compared favourably with carbamazepine), most of the information has been obtained from mixed populations.

Discrepancies between the US and UK guidelines and other recommendations

The UK guidelines seem to contrast with the Scottish Intercollegiate Network Guidelines (SIGN),[11] which expand on the use of drugs in a synthesised management of epilepsy and suggest using lamotrigine and oxcarbazepine as first-line treatments for partial and symptomatic generalised seizures and lamotrigine as first-line treatment for idiopathic generalised seizures. However, a revised version of the UK guidelines is forthcoming, having a format comparable to the SIGN guidelines. The US guidelines are at odds with the FDA recommendations (table 2) and with an expert consensus[12] that recommended using valproic acid and carbamazepine as first line for generalised and partial epilepsies. These differences may be explained by the paucity of evidence-based findings, on which some medical decisions (like the choice of the first-line treatment) rest. The limited amount of scientific information may also explain why the guidelines pay little attention to selected populations like elderly people and patients with learning disabilities.

Conclusions

The US and the UK guidelines on the use of the new antiepileptic drugs for the treatment of epilepsy are both useful instruments for practising physicians (epileptologists, neurologists, child neurologists, neurosurgeons and—to some extent—family practitioners) because they are evidence-based, fairly comprehensive, and up-to-date. However, the guidelines diverge on the management of newly diagnosed epilepsy. As compared with the US guidelines, which links the choice of a new antiepileptic drug to the individual patient situation, the UK panel is more explicitly conservative by recommending the use of the new drugs as first choice only in specific clinical conditions. A patient with epilepsy should be treated with a new antiepileptic drug under the following conditions: (1) the person has not benefited from an old antiepileptic drug; (2) an old antiepileptic drug is unsuitable because there are contraindications, there could be interactions with other drugs, there is proof of poor tolerability, or the patient is a woman of childbearing potential, only after assessment of risks and benefits. Treatment benefit means seizure freedom or at least significant seizure reduction, improvement in quality of life, and presence of minimal adverse reactions. This is also the view of this reviewer, because the new drugs are shown to be neither superior nor equivalent to the traditional drugs (comparative trials were not powered to detect superiority or equivalence), their long-term safety is still poorly understood, their teratogenic potential is ill-defined, and the cost is significantly higher than that of the old drugs.

Future studies should be comparative, pragmatic, long-term, and open trials, which are needed to show the long-term efficacy of the new antiepileptic drugs, to show their comparative features, and to better assess their effect on quality of life, their cost-effectiveness, their tolerability, and their teratogenic potential. A large randomised trial is ongoing in the UK comparing long-term outcome and cost-effectiveness of standard and new drugs in clinical practice.[5] In addition, the conflicts should be solved between the needs of the regulatory bodies (requiring the use of placebo as a proof of efficacy) and those of the treating physicians (requiring data on the long-term efficacy of the new drugs and their use in patients different from those of randomised trials). Finally, physicians need to agree on the definition of drug resistance, significant seizure reduction, improved quality of life, and drug contraindications and tolerability. There is also a need for standardisation of the trial design, with special reference to the target population, the outcome measures and the follow-up duration, and for the study of selected epilepsy syndromes.

Conflict of interest

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