Newer antiepileptic drugs and recent advances in drug therapy of epilepsy

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Nine new antiepileptic drugs (AEDs) have reached the market during the last decade and thus markedly increased treatment options for patients with epilepsy. Felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, and zonisamide are all different drugs and their merits need to be assessed individually. However, being newer AEDs, they share some features that distinguish them from the older generation AEDs: For obvious reasons, our information on long-term efficacy and toxicity is limited and we know less about rare adverse effects and efficacy and toxicity in special populations. Aplastic anemia with felbamate and visual field restrictions caused by vigabatrin were all identified after the introduction of the drugs and can serve as examples of the problems to predict the risks for adverse effects with new compounds. Due to these serious adverse effects, the use of felbamate and vigabatrin is very restricted. The role of the other new AEDs is more difficult to define. All have demonstrated significant effects as adjunctive therapy in patients with refractory partial seizures but we lack head-to-head comparisons between them. Meta-analyses have not revealed conclusive evidence of differences in efficacy or tolerability between the new drugs. Direct comparisons of new and established AEDs as monotherapy in new onset epilepsy have consistently failed to demonstrate differences in efficacy, although some of the new AEDs have been better tolerated. Given the excellent response to older AEDs and the lack of difference in efficacy, these are still considered to be first choice monotherapy in new onset epilepsy. New AEDs can be considered as alternative monotherapy or add-on in case of failure on the first drugs. Future clinical trials should target specific epilepsy syndromes, rather than broad seizure types, to allow a better definition of the population that might benefit from the different new AEDs.

MONOTHERAPY with the appropriate antiepileptic drug (AED) according to the seizure type of the individual patient has been the prevailing therapeutic strategy in epilepsy since the late 1970s (ref. 1). The treatment usually starts with a low dose of the chosen AED. This dose is gradually increased to reach the anticipated first maintenance dose and then adjusted to clinical response with the aim of achieving seizure control without adverse effects. Drug selection has traditionally been based on the results of clinical trials with different seizure types and on clinical experience gained through the years. Until the beginning of the 1990s, the selection of AEDs was fairly simple because there were only few drugs available and as these AEDs had been on the market for a long time, clinical experience with each drug was extensive. Carbamazepine, and in some countries phenytoin, were established as the first line drugs for partial seizures, whereas valproate was the generally accepted drug of choice for generalized seizures.

Treatment options have increased dramatically during the last decade with the introduction of the new generation AEDs (Table 1). Although these are all different drugs that need to be evaluated individually, as a group they share some features that distinguish them from the older generation AEDs. For obvious reasons, our information on the long-term efficacy of the new drugs is limited. Likewise, the available information on long-term toxicity is insufficient, and finally we know less about rare adverse effects, efficacy and toxicity in special populations. It is the purpose of this review to briefly present data on kinetics, efficacy and tolerability of each of the newer AEDs that has reached the market and finally to discuss the role of these agents in the treatment of epilepsy at present.

The new AEDs are not only chemically and pharmacologically different, they have also been developed along different principles and strategies. Some are the result of chemical alterations of compounds with an established antiepileptic effect (oxcarbazepine). Most have been identified through screening of new compounds in appropriate animal models (felbamate, gabapentin, lamotrigine, topiramate). Only two (tiagabine, vigabatrin) are the result of rational design based on advances in knowledge of anticonvulsant mechanisms.

Clinical trials of new antiepileptic drugs

The most reliable information on efficacy and tolerability of an AED comes from randomized clinical trials

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Table 1. Selected pharmacokinetic information on new antiepileptic drugs

Drug	Bioavailability	Protein binding (%)	Half-life (h)	Elimination	Kinetic interactions
Felbamate	Almost complete	70	14–22	Renal/metabolism	+
Gabapentin	Variable	0	5–7	Renal	None
Levetiracetam	Almost compete	0	6–8	Renal/metabolism	None
Lamotrigine	Almost complete	55	8–30	Metabolism	+
Oxcarbazepine*	Almost complete	40	8–15	Metabolism	+
Tiagabine	90%	> 90	7–9	Metabolism	+
Topiramate	>80%	15	20–30	Renal/metabolism	+
Vigabatrin	Almost complete	0	5–7**	Renal	Minor
Zonisamide	Almost complete	60	50–70	Metabolism	+

*Oxcarbazepine is a pro-drug, data refer to the active monhydroxy metabolite.
**Refers to plasma half-life. Biological half-life considerably longer.

(RCT). There are different types of RCTs that serve different purposes at the various stages of drug development. Traditionally, new compounds are first assessed in randomized double-blind placebo-controlled add-on trials in patients with partial seizures refractory to established AEDs. Such trials may provide evidence that the new AED is superior to placebo when added to existing treatment, and this is normally the basis for licensing for use as adjunctive therapy in therapy-resistant partial seizures. However, such studies are generally of a short duration, and provide little information as to long-term efficacy. For several reasons, results from add-on trials cannot be extrapolated to monotherapy. Therefore, and since monotherapy is the prevailing strategy, monotherapy trials are usually implemented when efficacy and safety have been demonstrated in adjunctive trials. There are different monotherapy trial designs that serve different purposes[2,3]. In short-term trials, patients are randomized to a high dose of the experimental drug or to placebo or a sub-optimal dose of the experimental drug or comparator. These trials are performed to satisfy requirements from regulatory bodies for licensing purposes as monotherapy. They are carried out in conjunction with seizure monitoring as part of a work-up for epilepsy surgery or alternatively as conversion to monotherapy studies. In the latter case the experimental drug is first given as add-on to patients with refractory seizures and the concomitant therapy is gradually tapered in an attempt to achieve monotherapy with a high dose of the experimental drug or the comparator (in general the experimental drug in a sub-optimal dose). These short-term regulatory trials are done under artificial conditions and the results are of little value for clinical decision-making[3]. Randomized long term comparative trials are the gold standard. In these the investigational drug should be compared with the established standard treatment under conditions resembling clinical practice, i.e. allowing individualized dosing and optimal titration rates. An increasing number of randomized trials comparing new and older AEDs are being published. However, their interpretation is hampered by methodological shortcomings such as non-flexible dosing, sub-optimal titration rates and short duration[3,4]. Furthermore, direct head-to-head comparisons of different new AEDs are missing. In summary, in terms of randomized clinical trials, there is very limited data for an evidence-based selection of AEDs, new or old.

Overview of the new antiepileptic drugs

Felbamate

Felbamate is structurally related to meprobamate. Its activity in epilepsy probably involves effects on the NMDA receptor. Felbamate is completely absorbed from the gastrointestinal tract with peak serum concentrations within 2–6 h. Binding to plasma proteins is about 25%. Felbamate is metabolized mainly through hydroxylation and conjugation. Half-life is about 20 hours, but shorter in patients treated with carbamazepine or phenytoin. Drug–drug interactions are common. Carbamazepine levels are reduced whereas concentrations of phenytoin, phenobarbital and valproate increase[5].

Felbamate monotherapy was assessed in refractory partial seizures early in its development in short-term regulatory trials (i.e. presurgery or substitution trials) of little clinical relevance[6–8]. However, efficacy has also been demonstrated in more conventional add-on trials in patients with refractory partial seizures[9,10]. Adjunctive treatment with felbamate has been shown to be more effective than placebo in reducing atonic, tonic, and tonic-clonic seizures in 73 patients with Lennox–Gastaut syndrome[11].

The most common adverse effects of felbamate are nausea, anorexia, insomnia and headache. Rash has been reported to occur in 3–4% of exposed patients. However, the major safety concern of felbamate relates to the occurrence of aplastic anemia and liver failure. Thirty-four felbamate associated aplastic anemia patients

Table 2. Summary of some clinical features of new antiepileptic drugs

	Dosing frequency doses/day	Titration rate time to target dose	Indication	Special precautions
Felbamate	2–3	2–3 weeks	Last resort refractory Lennox–Gastaut or partial seizures	Close monitoring of blood and liver function
Gabapentin	3	3–5 days	Partial seizures as add-on	
Levetiracetam	2	1–2 weeks	Partial seizures as add-on	
Lamotrigine	1–2	4–8 weeks	Partial or generalized seizures as add-on or monotherapy, Lennox–Gastaut	Monitor for skin reactions in children and with VPA combination (slow titration)
Oxcarbazepine	2–3	1–2 weeks	Partial seizures as add-on or monotherapy	
Tiagabine	3–4	3–4 weeks	Partial seizures as add-on	
Topiramate	2	6–8 weeks	Partial seizures as add-on, Lennox–Gastaut	
Vigabatrin	1	1–2 weeks	Infantile spasm or last resort refractory partial seizures	Monitor visual fields
Zonisamide	2	2 weeks	Partial seizures add-on	

have been reported, with 13 known fatalities and 18 cases with hepatic failure[5]. Because of these serious adverse effects, felbamate is considered a last resort treatment in patients with refractory Lennox–Gastaut syndrome or partial seizures unresponsive to other treatments. Use of felbamate requires close monitoring of the patient.

Gabapentin

The mode of action of gabapentin is largely unknown. It interacts with an auxiliary sub-unit of voltage-sensitive calcium channels, although the functional correlate of this binding is unclear[12]. Gabapentin has also been shown to increase GABA levels in the brain in epilepsy patients[13].

Gabapentin is rapidly absorbed from the gastrointestinal tract, and peak serum levels are attained 2 to 3 h after a single dose. The bioavailability is reduced up to 24% if antacids are taken concomitantly. The absolute bioavailability is at least 60%. Absorption kinetics are dose-dependent with decreasing bioavailability with increasing dosages. The drug is not bound to serum proteins. Gabapentin is not metabolized and is eliminated unchanged by the kidney. The elimination half-life is about 5 to 7 h after a single oral dose and is independent of the dose. Renal impairment reduces drug clearance and increases the serum levels of gabapentin[14,15]. Gabapentin is devoid of enzyme-inducing properties. Since the drug is not protein-bound and almost completely eliminated by renal excretion, gabapentin does not appear to be involved in significant pharmacokinetic interactions with other drugs.

A number of add-on trials have demonstrated efficacy of gabapentin superior to placebo in patients with refractory partial seizures[16–19]. In these studies, gabapentin doses ranged from 600 to 1800 mg/day. Subsequent experience has shown that higher doses up to and in excess of 3600 mg/day may be needed to obtain optimal effects. Gabapentin monotherapy was evaluated in a regulatory short-term presurgery trial. 3600 mg/day were found to be more effective than a pseudo-placebo dose of 300 mg/day (ref. 20). A randomized long-term (24 weeks observation) study compared gabapentin with carbamazepine[21]. Three different blinded doses of gabapentin (300, 600 or 1800 mg/day) were compared with open label carbamazepine at a fixed dose of 600 mg/day in new onset cases of partial seizures. The highest gabapentin dose was comparable with carbamazepine with respect to retention in the trial. However, the effect of gabapentin 1200 mg/day was not found to be different from placebo as adjunctive therapy against refractory generalized tonic-clonic seizures[22]. Serious or idiosyncratic adverse effects have not been reported and other side-effects have generally been mild and CNS-related, such as somnolence and dizziness.

Lamotrigine

Lamotrigine acts by blocking voltage and use-dependent sodium channels with the secondary effect of reducing the release of excitatory amino acids. Lamotrigine is readily absorbed from the gastrointestinal tract with peak serum levels within 1 to 3 h. The bioavailability is complete and serum protein binding is about 55% (ref. 23). Lamotrigine is extensively metabolized by conjugation and excreted predominantly as a glucuronide. In healthy volunteers, the elimination half-life of lamotrigine is about 25 h ranging from 14 to 50 h. There is no evidence of dose-dependent kinetics. Phenytoin, carbamazepine and barbiturates induce the metabolism of lamotrigine[24,25], and thus the half-life of lamotrigine is considerably shorter, with an average of 15 h (ref. 26). Conversely, lamotrigine metabolism is inhibited by valproate, prolonging the half-life of lamotrigine to an average of 60 h, with a range of 30 to 90 h (ref. 27). The clearance is to some extent age-dependent, being higher in children than in adults[28] and

decreased in the elderly[29]. Clearance also appears to be markedly increased during late pregnancy[30].

A number of small, fairly short, cross-over trials have reported lamotrigine responder rates (patients experiencing at least 50% reduction in seizure frequency) higher than for placebo in randomized add-on trials in partial seizures[31]. These observations have been confirmed in placebo-controlled parallel group studies of somewhat longer duration[32]. Lamotrigine has also been compared with carbamazepine in three randomized double-blind monotherapy trials in partial or primary generalized tonic-clonic seizures. None demonstrated differences in efficacy although lamotrigine was better tolerated[33–35]. Similar findings were reported from a head-to-head monotherapy comparison with phenytoin[36]. Lamotrigine monotherapy has also been shown to be more efficacious than placebo in a small study of patients with typical absences[37]. No randomized trials have been published on lamotrigine in juvenile myoclonic epilepsy although uncontrolled case series might indicate beneficial effects in this syndrome. A short randomized placebo-controlled add-on trial has demonstrated a modest effect in patients with Lennox–Gastaut syndrome[38].

The most significant tolerability concern with lamotrigine relates to rash and serious skin reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis. This has been reported to occur in the order of 1/1000 treated patients, and at a higher rate, 1/50–1/100 in paediatric patients[39]. Concomitant treatment with valproate and a too-fast dose escalation have been identified as other risk factors. The incidence of serious skin reactions appears to have decreased after adoption of slower dose escalation rates[40].

Levetiracetam

Levetiracetam is the active S-enantiomer of a racemic pyrrolodine acetamide. Its mechanism of action is unknown, and it is inactive in classic models such as pentylenetetrazol- and maximal electroshock tests. Levetiracetam is completely absorbed from the gastrointestinal tract with peak levels after one hour. It is not bound to plasma proteins. Plasma half-life is 6–8 h and levetiracetam is more than 60% eliminated unchanged in the urine[41]. There are no known pharmacokinetic interactions of levetiracetam.

The efficacy of levetiracetam as adjunctive therapy in adults with refractory partial seizures, with or without secondary generalization, has been demonstrated in double-blind, placebo-controlled trials[42–45]. Doses ranging from 1,000 to 4,000 mg/day were investigated and highest responder rates were reported at 2,000–3,000 mg/day. Although conversion to levetiracetam monotherapy has been successful in a small proportion of the patients in follow up of add-on trials[46], no formal randomized comparative long-term monotherapy studies in new onset epilepsy have been published. Likewise, results of studies in primary generalized seizures have not yet been formally reported. In general, levetiracetam has been well tolerated in add-on trials, in most cases not significantly different from placebo, and serious adverse events have not been reported.

Oxcarbazepine

Oxcarbazepine is rapidly and almost completely metabolized to 10,11-dihydro-10-hydrocarbazepine, which is responsible for the major part of the effects of the drug. Like carbamazepine, it probably acts mainly by blocking the voltage-dependent sodium channels[47]. The parent drug is readily absorbed from the gastrointestinal tract, and peak serum levels are attained within one hour following a single oral dose. They are very low and decline rapidly, the half-life being 1 to 2.5 h. Peak serum levels of the metabolite, 10,11-dihydro-10-hydrocarbazepine are attained at about eight hours. The half-life is in the order of eight to ten hours. The protein binding of oxcarbazepine is about 67%, whereas that of the metabolite is only about 38% (ref. 48) . Since the protein binding of the metabolite is only 38%, there is little risk of drug–drug interactions by displacement from binding sites. Oxcarbazepine and its major active metabolite are cleared mainly by non-oxidative processes, including ketone reduction and O-glucuronidation respectively. These processes do not depend on cytochrome P-450. Induction or inhibition of the cytochrome P-450 system will have little effect on the kinetics of oxcarbazepine and its active metabolite. In contrast to carbamazepine, oxcarbazepine does not induce its own metabolism after repeated administration[48,49].

Unlike other new AEDs, oxcarbazepine was assessed as monotherapy early in the clinical development. Oxcarbazepine was compared with carbamazepine in 235 patients with new onset partial seizures or primary generalized tonic-clonic seizures[50]. No difference in efficacy was demonstrated, whereas oxcarbazepine was better tolerated with fewer drop-outs due to adverse effects. Based on these limited results, oxcarbazepine was licensed in a few countries as early as 1990. Subsequently, randomized double-blind controlled trials have compared oxcarbazepine with valproate in new onset partial or primary generalized tonic-clonic seizures[51]; and with phenytoin in the same seizure types in adults[52]; in children[53]. None of these studies reported differences in efficacy, although oxcarbazepine was better tolerated than phenytoin.

More recent randomized placebo-controlled add-on trials have demonstrated efficacy in adults[54] and chil-

dren[55] with refractory partial seizures. There are no studies specifically targeting patients with idiopathic generalized epilepsy syndromes.

The spectrum of adverse events is similar to that of carbamazepine, but skin rashes occur less frequently according to the comparative clinical trials[50]. However, hyponatremia seems to be more common during treatment with oxcarbazepine, although this has been claimed seldom to be of clinical significance[56].

Tiagabine

Tiagabine prevents GABA reuptake from the synaptic cleft by inhibition of a GABA transporter[57]. The absorption of tiagabine is rapid after oral administration of single doses in healthy volunteers. There is no effect of food on the bioavailability, but the absorption is somewhat delayed. Peak serum levels are usually attained within one hour but considerably later when taken with food. The protein binding of tiagabine is high, 96% (ref. 57) and the drug is displaced from its binding sites by valproate, salicylates and naproxene[58]. Tiagabine is extensively metabolized, and the elimination half-life is quite variable, ranging from 4 to 13 h with an average of about 7 h. There is no evidence of dose-dependent kinetics. The half-life is even shorter in patients concurrently treated with enzyme-inducing drugs[59,60].

A double-blind randomized parallel add-on trial has compared tiagabine at three dose levels (16, 32 and 56 mg/day) with placebo in patients with refractory complex partial seizures[61]. A dose–response relationship was demonstrated with the highest responder rate at 56 mg/day. In another double-blind randomized parallel add-on trial, two tiagabine regimes (8 mg four times daily and 16 mg twice daily) were compared with placebo in refractory complex partial seizures[62]. The responder rate was significantly higher for both regimes compared with placebo. The effects of tiagabine in monotherapy were assessed in a short-term (18-week) regulatory substitution trial[63]. Patients with refractory complex partial seizures were randomized to 6 or 36 mg tiagabine daily and an attempt was made to discontinue the baseline AED. Responder rates were 18% and 31%, respectively. No trials have analysed the effect of tiagabine in idiopathic primary generalized epilepsy disorders. However, there are case-reports suggesting that tiagabine might provoke non-convulsive status epilepticus and the drug should perhaps be avoided in patients with primary generalized seizures.

The most common adverse effects are CNS-related such as dizziness, asthenia and somnolence. Because of the similarities in mechanisms with vigabatrin, there has been a concern that tiagabine would induce visual field defects, but this has not been confirmed in systematic follow-up studies[64].

Topiramate

Topiramate acts by multiple mechanisms: blocking of voltage-dependent sodium channels, enhancement of GABA receptor action, and antagonism of kainate/AMPA type glutamate receptors[65]. After oral administration of single doses, peak serum levels are attained within 2–4 h. When the drug is taken with food, the absorption is delayed. Steady-state plasma concentrations of topiramate increase linearly with the dose[66]. The binding to serum proteins is about 15%, and the elimination half-life of topiramate in healthy volunteers is 20–30 h (ref. 67). Topiramate is mainly excreted unchanged in urine but a proportion is metabolized by oxidation. Phenytoin and carbamazepine induce the metabolism of topiramate and decrease the serum levels markedly[68,69]. Valproate may also lower topiramate concentrations but to a much lesser extent[70].

The effect of topiramate as adjunctive therapy to patients with refractory partial seizures, with or without secondary generalization, has been analysed in six double-blind, placebo-controlled, parallel group trials[71–76]. Doses ranging from 200 to 1000 mg/day were assessed. Increasing efficacy was observed up to a daily dose of 600 mg/day, and responder rates (proportion of patients who experience at least 50% reduction in seizure frequency) of 40–45% were reported. A significant effect in refractory partial seizures as add-on therapy has also been demonstrated in a randomized trial in 86 children[77]. Adjunctive treatment with topiramate was superior to placebo in patients with primary generalized tonic-clonic seizures in a randomized double-blind study comprising 80 children and adults[78]. The responder rate was 56% for topiramate and 20% for placebo. A small regulatory substitution monotherapy trial demonstrated that a daily dose of 1000 mg was more effective than 100 mg in patients with partial seizures[79]. Patients with new onset partial seizures were randomized to low dose (25 or 50 mg/day) or high dose (200 or 500 mg/day) topiramate monotherapy in another double-blind study[80]. Time to first seizure was significantly longer in the high-dose group, and significantly more patients on the high dose were seizure-free. Topiramate has also shown efficacy as adjunctive therapy in Lennox–Gastaut syndrome in a randomized placebo-controlled trial[81].

The most frequent adverse effects of topiramate are CNS related and include dizziness, somnolence, ataxia, parestaesia, speech disorders and abnormal thinking. With the exception of parestaesia, these adverse effects appear less frequently during monotherapy and with a slow dose-escalation. Weight loss is a rather frequent and specific dose-related adverse effect[82], and renal calculi have been reported to occur in 1–2% of patients.

Vigabatrin

Vigabatrin was the first in the new-generation AEDs. It acts by irreversible inhibition of GABA transaminase, the enzyme responsible for the degradation and inactivation of GABA, thereby increasing the CNS concentrations of this inhibitory neurotransmitter. After oral administration of vigabatrin, peak serum levels are attained within about 2 h. Vigabatrin produces dose-dependent increases in GABA concentrations in CSF. The drug is not bound to serum proteins, and no metabolites have been identified in humans. The terminal half-life is between 6 and 8 h. Vigabatrin is excreted unchanged, primarily in the urine. At clinical doses there is pharmacokinetic dose-linearity[83,84]. Administration of food does not alter the pharmacokinetic profile[85]. Due to the irreversible mode of action of the drug, the serum half-life bears practically no relationship to the duration of pharmacological effect, which will depend on resynthesis of new GABA-transaminase[84]. Hence, the antiepileptic effect of vigabatrin long outlasts its presence in serum. No drug interactions have been observed with vigabatrin and other antiepileptic drugs or other drug classes except for a moderate decrease in phenytoin serum levels in some patients. The mechanism of this interaction is unknown[86].

Several randomized placebo-controlled double-blind studies, most with fairly small numbers of patients, have demonstrated that adjunctive therapy with vigabatrin is superior to placebo in refractory partial seizures[87–91]. 40–50% of patients respond with at least 50% reduction in seizure frequency at 2–3 g/day. In another randomized add-on trial in refractory partial seizures, 1, 3, and 6 g/day of vigabatrin resulted in responder rates of 24, 45, and 54%, respectively, compared with 7% for placebo[92]. Vigabatrin has been compared with carbamazepine in four randomized monotherapy trials in patients with partial seizures[93–96]. Carbamazepine was superior in terms of efficacy in one[94] whereas no clear difference in efficacy could be demonstrated in the others. However, vigabatrin was better tolerated than carbamazepine.

Vigabatrin has been compared with hydrocortisone in the treatment of infantile spasms in a randomized trial, with a more favourable outcome in the vigabatrin group[97]. The efficacy of vigabatrin was also comparable with that of ACTH in another randomized study of infantile spasms[98]. Infants with tuberous sclerosis showed a particularly favourable response to vigabatrin.

Depression and psychosis have been reported at increased rates in patients treated with vigabatrin[99]. The most serious adverse effects, however, are persistent visual field defects. Although this may occur in 30–40% of patients exposed to vigabatrin, it took almost a decade before this association became apparent[100]. Because of this serious and frequent adverse effect, the use of vigabatrin is now restricted to selected patients with partial seizures refractory to other treatment alternatives. However, the risk–benefit equation is still considered favourable for vigabtrin in infantile spasms, in particular in relation to tuberous sclerosis, where vigabatrin may be considered as first choice.

Zonisamide

Zonisamide blocks voltage-dependent sodium channels and T-type calcium channels and is a weak inhibitor of carbonic anhydrase. After oral administration, peak serum levels of zonisamide are obtained within 4 to 7 h. The absolute bioavailability is not known, but the absorption is probably almost complete[101]. The serum protein binding is 40% to 60%, and the drug is extensively accumulated in erythrocytes. Zonisamide is extensively metabolized. Analysis of urine samples in healthy volunteers revealed that zonisamide was metabolized by acetylation, and the cleavage of the isoxazole ring was followed by conjugation with glucuronic acid[101,102]. In healthy subjects the elimination half-life has been estimated to about 60 h. In patients concurrently receiving carbamazepine or phenytoin, zonisamide serum levels are decreased, and the half-life is about 36 and 27 h, respectively, suggesting that the metabolism of zonisamide is induced by other antiepileptic drugs[103,104]. In contrast, zonisamide serum levels decrease only slightly when valproate is given in addition to zonisamide[105]. In Japanese studies, serum zonisamide concentrations have been reported to increase linearly with the dose but other studies have suggested that this relationship may not always be linear at high doses[106].

Randomized double-blind add-on trials in patients with refractory partial seizures have shown zonisamide to be superior to placebo. In a US study[107], 29% of patients on zonisamide were responders, compared with 13% in the placebo group. In a European study[108], 30% responded on zonisamide and 13% on placebo. A head-to-head double-blind comparison between zonisamide and carbamazepine in 123 adults with partial seizures with or without secondary generalization revealed no difference in the decrease in seizure frequency[109]. Small studies of children with different types of generalized seizure disorders indicate that zonisamide may also be useful in these seizure types, but the studies are not conclusive[109]. Case series suggest beneficial effects in progressive myoclonus epilepsy[110] and in Lennox–Gastaut syndrome[111] but these observations need to be confirmed in randomized controlled studies.

The most common adverse effects are CNS-related, i.e. somnolence, dizziness and ataxia and anorexia and gastrointestinal complaints. Rash has been reported to occur in about 2% of patients in controlled trials[112]. Up

to 4% of patients developed renal calculi although the majority were asymptomatic[113].

Summary of efficacy and tolerability of new antiepileptic drugs

All new AEDs discussed in the present review have demonstrated significantly better efficacy than placebo as adjunctive therapy in refractory partial epilepsy. It may seem reasonable to assume that drugs with proven efficacy as add-on therapy in refractory epilepsy are also effective as monotherapy. However, results from add-on trials cannot be extrapolated to monotherapy. Vigabatrin is one example of a drug highly effective in add-on trials but with less convincing efficacy as monotherapy[94]. Furthermore, short-term regulatory monotherapy trials conducted under artificial conditions (e.g. presurgery trials) are insufficient as a basis for assessment of the clinical usefulness of new AEDs. Head-to-head comparison with established standard treatment in long-term trials is the gold standard and is necessary to determine the role of the new AEDs. Lamotrigine, oxcarbazepine, vigabatrin, and to some extent also topiramate, gabapentin and tiagabine have been evaluated in such studies. This documentation has been considered to be sufficient to grant widespread licensing for monotherapy use of lamotrigine and oxcarbazepine.

Comparative monotherapy trials of lamotrigine and oxcarbazepine have included patients with partial as well as primary generalized tonic-clonic seizures, and available data are convincing for efficacy in primary generalised tonic-clonic seizures, at least for lamotrigine. Preliminary observations suggest that topiramate, levetiracetam and zonisamide may also be effective in primary generalized seizures, but further data are needed. Vigabatrin, gabapentin and tiagabine probably have a narrower spectrum of effects, and are not suitable for primary generalized seizure disorders.

Most AED trials are still stratified for seizure type rather than for specific epilepsy syndromes, despite an increasing awareness of the need for the latter. However, there are some exceptions. Lamotrigine has been shown to be superior to placebo in childhood absence epilepsy[37], although it was not compared with standard treatments such as ethosuximide and valproate. Felbamate, lamotrigine and topiramate have also demonstrated efficacy in Lennox–Gastaut syndrome as adjunctive therapy. Finally, vigabatrin is effective in infantile spasms, particularly in conjunction with tuberous sclerosis.

Although in general, comparative monotherapy trials have failed to demonstrate differences in efficacy between the new AED and the established standard treatment, most trials have been inadequate to prove equivalence between the drugs. Furthermore, even though some of these trials have treatment periods of up to a year, this is a short time period compared with the normal treatment duration in epilepsy. Hence, they provide little information on long-term efficacy of the new AEDs. Follow-up of retention rates of patients once started on vigabatrin, lamotrigine, gabapentin or topiramate indicate that less than one fourth of patients with chronic partial epilepsy are likely to continue on therapy with the new AED beyond five years[4,114]. The data indicate that the long-term impact of new AEDs on the course of epilepsy is small. In fact only 0.6–3.5% of the patients had achieved 6 months remission by the last follow-up[114]. In accordance with this, only a few percent of patients report complete seizure control while on new AEDs during the randomized add-on trials.

While direct comparative monotherapy trials have failed to show differences in efficacy between new AEDs and standard treatment, the experimental drug is often reported to be better tolerated. However, to some extent, such differences may be due to bias in choice of dosing schemes, titration rates or formulations of the comparator[4]. Furthermore, potential advantages in immediate tolerability must be weighed against the risks associated with insufficient information concerning serious but rare adverse effects and long-term toxicity. Two examples from the experience with new AEDs underline the importance of this issue. The significant risk of aplastic anaemia associated with use of felbamate became apparent only after exposure of a sufficient number of patients after the drug reached the market. Although as many as 30–40% of those taking vigabatrin may develop visual field constrictions, this association was not revealed until nine years after the launch of the drug[100]. The latter example highlights the difficulties we may have in identifying unexpected and new types of adverse effects even if they occur frequently.

We lack direct comparisons between different new AEDs. Instead, indirect comparisons of the efficacy as adjunctive treatment in refractory partial seizures are made through meta-analysis[115,116]. However, the results of these attempts have not revealed any conclusive indication of differences in efficacy or tolerability between the new AEDs[115]. The various trials on which these analyses are based may in fact be too heterogeneous for such an approach[117].

The role of the new AEDs

The major factors that influence the selection of AEDs are data on efficacy, tolerability, safety, and pharmacokinetics as they emerge from clinical trials and experience. In addition, one cannot disregard differences in costs, in particular between drugs with similar efficacy. These differences are highly significant

for AEDs, although they may vary somewhat between countries. Mani *et al.*[118] recently reported phenytoin to be 1.6, carbamazepine 4.7, valproate 5.3, lamotrigine 16.9, gabapentin 21.4, and topiramate 25 times more expensive than phenobarbital per treatment day in India.

Considering the excellent response to the old generation AEDs in new onset epilepsy, the lack of difference in efficacy between old and new generation drugs and the differences in long term experience, it is at present difficult to argue for the new AEDs as drugs of first choice in new onset epilepsy. At that stage of treatment, the dramatic increase in number of available AEDs during the last decade has had marginal influence on therapeutic strategies. The recently published study by Mani *et al.*[118] even suggests that the oldest available AED, phenobarbital, may be an appropriate first choice for rural epilepsy care in less developed countries. The report underlines the importance of taking economic and health care resources into account in our efforts to tailor drug therapy.

Although only a few patients with refractory epilepsy will have their seizures completely controlled with new AEDs, we have much more to offer today to the patient who fails on first line therapy. This is at present the most important indication for the new AEDs.

The role of the different new AEDs might be better defined if future clinical trials would target specific epilepsy syndromes and etiologies, rather than broad seizure types as to the positive experience with vigabatrin in infantile spasm with tuberous sclerosis indeed suggests.

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