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Future Prospects for the Drug Treatment of Epilepsy

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Abstract

Great progress has been made in the last 150 years in the pharmacological management of epilepsy, and, despite the increasing number of technological advances available, antiepileptic drugs (AEDs) remain the mainstay of treatment for the vast majority of patients with epilepsy.

This review looks at possible avenues of development in the drug treatment of epilepsy. The strengths and weaknesses of those AEDs which are currently licensed are examined, and ways in which their use may be improved are discussed (e.g. rational combinations, use of new formulations). Potentially new targets that may allow the development of effective treatments are highlighted (neuroimmunological manipulation, decreasing inherent drug resistance mecha-

nisms, and modification of adenosine neurotransmission), and a summary of the most promising AEDs currently in development is provided [e.g. carabersat, ganaxolone, harkoseride, MDL 27192, safinamide (NW 1015), pregabalin, retigabine, talampanel, valrocemide, losigamone and BIA 2093].

Epilepsy is one of the most common neurological conditions, with a lifetime prevalence of between 2[1,2] and 5%[3] of the general population, and a point prevalence of between 40 and 80 per 1000.[4] It affects an estimated 50 million people worldwide.[5]

Great progress has been made in the last 150 years in the pharmacological management of epilepsy, and antiepileptic drugs (AEDs) are still the mainstay of treatment for most patients. The last decade has seen an unprecedented expansion in the number of AEDs available for use.[4,6] Despite this, remission rates have remained essentially unchanged throughout this century.[7,8]

The likelihood of such remission varies with several factors, most notably the classification of epilepsy; seizures persist in approximately 20% of patients with generalised epilepsy and in 35% with localisation-related epilepsy.[9] It is important to note that these figures allow for the confounding factors that can lead to patients being falsely labelled as refractory to drug treatment,[10] e.g. misdiagnosis of nonepileptic phenomena and use of drugs inappropriate for the classification of epilepsy.

The first choice of AED will vary from patient to patient, being dependent on age, gender, concomitant drug therapy, fertility status, seizure type, and, when possible, the epileptic syndrome.[4,6] An adequate trial of an appropriate AED will be effective in about 70% of patients with epilepsy, and it can be argued that a lack of response to the first AED is in itself an unfavourable prognostic factor.[11] A law of diminishing returns applies; in those whose seizures continue while they are receiving a single agent, the addition of a second and third drug leads to seizure cessation in approximately 10 and 5%, respectively.[12] By implication, seizures in approximately 20% of patients with epilepsy will remain poorly controlled despite exposure to established AED polypharmacy.

While some refractory cases may be amenable to surgery, the main hope of improved seizure control for those patients with refractory seizures will come from improving the efficacy of AED treatment, whether by optimising the use of those AEDs already available, or by the introduction of new compounds. This review will expand on possible ways to enhance the success of drug treatment of epilepsy.

1. Approaches to Improving the Use of Currently Available Antiepileptic Drugs (AEDs)

Tables I and II list the currently used AEDs and their mode(s) of action.

The discovery of the first AEDs was largely dependent on chance observation of antiepileptic effects of known sedative compounds. Mining this seam of compounds meant that the earliest AEDs exerted their effect either by widespread actions on the γ-aminobutyric acid (GABA) receptor complex or by effects on sodium channels. While these drugs constituted a therapeutic advance, their wide range of actions ensured that they would have a wide range of adverse effects.[14]

Despite an improvement in the understanding of many neurobiological systems, it is ironic that a century and a half after the discovery of the antiepileptic effects of the bromide salts, currently available AEDs are limited to only four mechanisms of action: inhibition of sodium channel function, calcium channel function, the GABAergic system, and, to a much lesser extent, excitatory neurotransmission.[15] This emphasis has arguably been perpetuated by the currently used preclinical testing programme.

But while there has been no widening of this repertoire, there has been progress of a sort; the established AEDs each possess a mixture of modes of action. The newer AEDs, in contrast, are largely

Table I. The established antiepileptic drugs

Drug	Mode of action	Spectrum of action
Barbiturates	GABA potentiation	Tonic-clonic ± absence seizures
	Sodium channel blockade	
	Depression of synaptic transmission	
	Decrease in calcium channel conductance	
	Glutamate receptor antagonism	
	Reduction in neurotransmitter release	
Phenytoin	Sodium channel blockade	Tonic-clonic ± partial seizures
	Increased Na^+/K^+ ATPase activity	
	Depression of synaptic transmission	
	Decrease in calcium channel conductance	
	Inhibition of calmodulin-related phosphorylation	
	Increase in chloride channel conductance	
Carbamazepine	Sodium channel blockade	Partial seizures ± secondary generalisation
	Reduction in calcium ion flux	
	Depression of synaptic transmission	
	Adenosine A_1 receptor antagonism	
	? NMDA receptor antagonism	
	? Benzodiazepine receptor antagonism	
Valproic acid (sodium valproate)	Increasing actions of GABA Increasing potassium ion efflux Reduction in calcium ion influx	Idiopathic generalised tonic-clonic seizures, absence, myoclonus + partial seizures ± secondary generalisation
	Reduction in EAA levels	
	? Antagonism of g-HB effects	
	? Sodium channel blockade	

ATPase = adenosine triphosphatase; **EAA** = excitatory amino acid; **g-HB** = g-hydroxybutyrate; **GABA** = γ-aminobutyric acid; **NMDA** = *N*-methyl-D-aspartate; **?** = uncertain/unknown.

more selective in their effects (table II). Such selectivity, alongside knowledge of basic epileptogenesis, should help clinicians to use these drugs in a more efficient manner.[16] While there is a great deal of work being done to look for new AEDs, is there any way that the use of existing agents can be improved?

1.1 Monotherapy: Which AED is 'Best'?

As already alluded to, the choice of 'optimal' AED will vary for each patient depending on a variety of factors. There is insufficient randomised trial evidence to predict the chances of success with each AED in any given population. In most countries, the only evidence needed to gain a licence for use is a demonstration of either efficacy superior to placebo, or some measure of equivalence with established AEDs.[17,18] Concentration on these forms of evidence has ensured that there is no data from randomised trials adequately comparing all available AEDs. A meta-analysis has been carried out in an attempt to compare the new AEDs,[19] but this has many flaws, not the least being the tendency (or necessity) to compare subtherapeutic doses of one drug with maximum tolerated doses of another. One large, publicly funded, UK-based multicentre trial (Standard and New Antiepileptic Drugs; SANAD) has begun which aims to recruit 5000 newly diagnosed patients who are receiving AED monotherapy. Any results, however, are still some way off.

In short, the choice of AED for each patient depends on a variety of individual factors rather than empirical evidence of the superiority of any particular compound.

Table II. The licensed newer antiepileptic drugs[13]

Drug	Mode of action	Efficacy in epilepsy type (mode of use)
Gabapentin	GABAergic effect	Partial (add-on)
	? Calcium channel blockade	
Lamotrigine	Sodium channel blockade	Partial/generalised (monotherapy/add-on)
	Calcium channel blockade	
Levetiracetam	? postsynaptic effects on GABA metabolism	Partial/?generalised (add-on)
Oxcarbazepine	Sodium channel blockade	Partial (add-on)
	Calcium channel blockade	
Tiagabine	GABA reuptake blockade	Partial (add-on)
Topiramate	GABAergic potentiation	Partial/generalised (add-on/? monotherapy)
	Sodium channel blockade	
	Kainate receptor blockade	
Vigabatrin	GABA-transaminase inhibition	Partial (add-on)
Zonisamide	Sodium channel blockade	Partial/? generalised (add-on/? monotherapy)
	Calcium channel blockade	
Felbamate	NMDA receptor antagonism	Partial (add-on); Lennox-Gastaut syndrome
	Sodium channel blockade	
	Calcium channel blockade	
Fosphenytoin	Prodrug of phenytoin	Status epilepticus

GABA = γ-aminobutyric acid; **NMDA** = *N*-methyl-D-aspartate; **?** = uncertain/unknown.

1.2 Polytherapy: Do Rational Combinations Exist?

While there are too few comparisons between individual AEDs to inform clinical practice, randomised clinical assessment of AED combinations are even rarer. In fact, no such drug studies have been carried out in humans.[20] One recent large review assessed the published data on the use of combinations of AEDs in animal models and in humans.[20] Even allowing for clinical observations, case reports and unblinded studies, there was no firm evidence of the superiority of any particular AED combination.

Although much has been written about the use of synergy in the treatment of epilepsy, it is striking that there are no clinical data to support the manifestation of this in clinical practice. It is known, however, that the newer AEDs may be a positive benefit in the modern treatment of epilepsy. Combining older AEDs is difficult because, as a group, they tend to have multiple interactions and multiple modes of action.[21] More is known about the modes of action of the newer AEDs, and they may be far better suited to combination usage than their older counterparts. In addition, the newer AEDs have a pharmacokinetic profile much more suited to concomitant use: they have less hepatic enzyme–inducing effect, less troublesome interactions, require less hepatic metabolism, and undergo less protein binding[21] than their older counterparts.

The ideal strategy for drug combination remains uncertain. Although at first sight it may appear most logical to combine drugs that have actions on opposing systems (e.g. a GABAergic drug and a drug reducing excitation), work in animal models[22] would suggest that there may be most benefit in combining AEDs which act on the same neurobiological systems (e.g. modification of GABAergic inhibition with two different drugs). The attraction of such combinations would be the potential to gain therapeutic benefit while using lower doses of each drug, i.e. doses below the threshold for developing adverse effects.[23]

Whether certain combinations hold a specific advantage remains a vexed issue which will not be settled until there has been a direct, randomised

head-to-head comparison of the most promising AED combinations. Without clear evidence of superiority, there will be a requirement to include many treatment combinations, rendering such comparisons logistically very difficult.

1.3 Development of New Formulations

The manipulation of compounds currently in use may be a useful way of enhancing the quality of life of patients with epilepsy.

Such changes have included the development and use of sustained-release preparations, as are available for both carbamazepine[24] and valproic acid (sodium valproate).[25] Another example of innovation in formulations is the development of a buccal formulation of midazolam. This can be used as first-line acute treatment of status epilepticus, and has been shown to be as efficacious as rectal benzodiazepines in this indication.[26] Buccal administration of any drug may be more convenient, less embarrassing and less stigmatising than rectal administration.[26]

At a more sophisticated level, drug molecules may be altered to provide new, and occasionally improved, AEDs. Chemical modification of carbamazepine has given oxcarbazepine, a drug with a different metabolic profile which retains an antiepileptic effect but avoids the formation of a toxic metabolite.[27] Similarly, fosphenytoin and DP-VPA are chemical modifications which allow for easier – and, possibly in the latter case, more effective – administration of the active compound (phenytoin and valproic acid, respectively).[28,29]

2. New Developments

2.1 Novel Targets for AEDs

At present, patients who have epilepsy are almost exclusively treat with compounds that stop seizures (i.e. 'anticonvulsants'), but it may be theoretically appealing to consider developing compounds that inhibit the development of epilepsy itself (bona fide 'antiepileptic' drugs).

Studies of animal models in the prevention of epileptogenesis have shown that while drugs such as carbamazepine and topiramate are effective anticonvulsants, they do not prevent epileptogenesis. However, valproic acid, diazepam, phenobarbital (phenobarbitone), tiagabine and levetiracetam have substantial antiepileptogenetic effects in the amygdala-kindling model.[30] Clinical studies have, however, been much less encouraging. They have all been of a similar design; soon after, or occasionally before, an event that increases the risk of the development of epilepsy (e.g. traumatic brain injury), patients receive treatment or placebo. The standard AEDs have all been tested in this way and none has shown any effect in the prevention of epileptogenesis.[30] Despite some promising preclinical results none of the newer AEDs have undergone such trials. There is currently a study underway into the use of magnesium sulphate in neuroprotection and epileptogenesis.[30]

The development for truly 'antiepileptic' drugs seems some way off. Our lack of understanding of the mechanisms involved in transforming normal tissue into a hyperexcitable state makes the discovery of such drugs difficult, and seems unlikely until our knowledge of these processes improves.

While it is tempting to continue to target the four standard processes outlined in section 1, and while the therapeutic contribution of drugs that do this should be acknowledged, perhaps the continued rate of 'refractory' epilepsy should encourage a change in the currently used strategies of drug development. Are there other targets which, if hit adequately, could help achieve full control of seizures in more patients. Sections 2.1.1, 2.1.2 and 2.1.3 outline three neurobiological processes which we feel have the most potential for pharmacological intervention.

2.1.1 Immunological Aspects of Epilepsy

The hypothesis linking autoimmune dysfunction with some forms of epilepsy is an old one. Over the last 50 years, various immunological disorders have been described in patients with epilepsy, including alterations in T and B lymphocyte populations,[31,32] T lymphocyte function,[33] and serum immunoglobulin levels.[34,35]

In a few rare syndromes, there is a well established relationship between immunological dysfunction and refractory epilepsy: Rasmussen's encephalitis is usually a disorder of childhood which results in a confluent spreading encephalitis characterised by severe epilepsy, hemiplegia and intellectual decline. The role of immune mechanisms in producing this disorder is well documented; antibodies against the GluR3 subunit of the glutamate receptor have been detected in patients with Rasmussen's encephalitis,[36] and immunisation of rabbits with the GluR3 protein produced seizures and histopathological changes that mimicked the disorder.[36]

In more common patterns of epilepsy, studies have suggested associations between different seizure types and anticardiolipin antibodies;[37] temporal lobe epilepsy and antibodies to glutamic acid decarboxylase (GAD);[38] partial status epilepticus and antiglycolipid antibodies;[39] refractory partial epilepsy and antibodies to glutamate receptors;[40] and a link between cryptogenic partial epilepsy and antiganglioside antibodies.[41]

The precipitating factors for such putative immune reactions are still unknown: while viral DNA has been detected in brain specimens from patients with refractory focal epilepsy,[42] it is uncertain whether these are causative of or resultant from seizure activity. Several possible links between immunological dysfunction and seizures have been proposed, including a dysregulation of apoptosis allowing abnormal autoreactive lymphocytes to survive,[43] or the presence of specific autoantibodies against voltage-gated ion channels, GABAergic neurons or GM1 gangliosides.[41]

Immunomodulation has been shown to have activity against certain syndromes; for example, plasmapheresis can improve clinical and electroencephalographic (EEG) findings in patients with Rasmussen's syndrome,[44] and there have also been reports of clinical improvements following the use of cyclophosphamide,[45] intraventricular interferon-α[46] or intravenous immunoglobulin (IVIg) in the disorder.[47,48] Open studies have shown benefit from various regimes of IVIg in patients with symptomatic generalised epilepsies[49-51] or refractory partial epilepsy.[52-54] One blinded placebo-controlled study confirmed this in patients with refractory partial epilepsy.[55]

Given the therapeutic potential in some patient subgroups, we suggest that there may be an increasing role for immunological investigation in patients with progressive localisation-related epilepsies, particularly where there is variable or worsening neurological deficit.

2.1.2 Innate Mechanisms of Drug Resistance

It has long been recognised that expression of the multidrug resistance (MDR) gene promotes resistance to some forms of chemotherapy. The MDR gene encodes for P-glycoprotein, a pump responsible for the efflux of hydrophobic molecules from the cells. It was postulated that such genetic factors may play a role in determining AED resistance in some patients,[56] a hypothesis strengthened by the discovery that expression of MDR1 messenger RNA is present in increased quantities in some patients with intractable epilepsy.[56] Subsequent work[57] has confirmed that many AEDs are known substrates for P-glycoprotein, reinforcing the suggestion that overexpression of P-glycoprotein could have a deleterious effect on the intracellular concentration of some AEDs, and so reduce their clinical effectiveness.

The next step is to prove whether MDR expression reduces the clinical effects of each particular AED. Assuming that MDR expression is pivotal to the development of refractory epilepsy, it may be possible to pharmacologically manipulate P-glycoprotein. Whether compounds active on P-glycoprotein could ever be used as monotherapy for epilepsy, or whether they need to be used in conjunction with other recognised AEDs, remains to be seen.

2.1.3 Adenosine Neurotransmission

Adenosine is an active neurotransmitter which forms part of a negative feedback loop for neurotransmission.[58,59] Activation of the presynaptic adenosine A_1 receptor decreases adenylate cyclase activity, increases potassium conductance, and thereby reduces further neurotransmitter release.[59]

The action of adenosine may be effective in stopping seizure activity: it is already known that methylxanthines, recognised antagonists of the A_1 receptor, are potent proconvulsant compounds in some animal models.[60] Loss of adenosine activity has been postulated as an *in vivo* mechanism of status epilepticus.[61] Administration of A_1 receptor agonists including cyclohexyladenosine, 2-chloroadenosine and L-phenyl isopropyladenosine has, however, been limited by major cardiovascular effects, motor depression and a tendency towards hypothermia.[62] Activation of this potent neurotransmitter will therefore necessarily be by more indirect means. Inhibition of adenosine breakdown, by inhibiting adenosine deaminase, has been recognised as having potential[62] although clinical use of such compounds is still some way off.

2.2 New Approaches to Old Targets

As discussed in section 1, several currently available AEDs act by modulating the GABAergic system. However, the profiles of different AEDs may depend on the distribution of GABA receptors which are affected by the drug; benzodiazepines have preferential effects on a single subunit of the GABA receptor and, at least during acute use, are active against most seizure types.[63] Other GABAergic drugs (e.g. vigabatrin) may promote certain seizure types in patients with idiopathic generalised epilepsy,[64] perhaps as a result of their general effects on GABAergic tone. The development of drugs that interact specifically with GABA receptor subclasses may prove beneficial, although receptor heterogeneity and multiple binding sites may make this difficult.[65] Specifically targeting any GABA receptor is a considerable challenge, and there are no such drugs as yet at an advanced stage of development.

The *N*-methyl-D-aspartate (NMDA) receptor has several modulatory sites which may be amenable to pharmacological manipulation. Some NMDA receptor antagonists have been shown to be effective in animal seizure models, but clinical testing has shown most of these to have their use limited by adverse effects.[66,67] It remains to be seen whether such intolerability is a result of the inadequate selectivity of the currently available NMDA antagonists, or whether inherent neuropsychiatric effects will prevent NMDA receptors from becoming a viable target for AEDs. The use of some of the AEDs that are in development may clarify this (see table III).

While calcium and sodium ion channels have long been targets for AEDs, other neuronal cation channels, such as the potassium channel, may be reasonable targets for drug development. Opening any of several types of potassium channels is known to promote neuronal repolarisation and hyperpolarisation.[115] Suppression of seizure development could potentially be mediated by prolonging potassium channel activation or by enhancing potassium ion buffering.[115] One of the AEDs in development (retigabine; see section 3.9) addresses this potential.

The place of disordered ion channels in the genesis of epilepsy, particularly the idiopathic generalised epilepsies, is still to be fully appraised. As knowledge of the molecular basis of disordered ion channel function increases, there may be a place for drugs specifically designed to act on the disordered parts of the malfunctioning ion channels: such bespoke prescribing for epilepsy should be the ultimate goal of further ion channel research.

3. New AEDs in Development

The development of new AEDs with improved efficacy or improved tolerability may be one way to offer hope of improved seizure control. Mass screening of candidate molecules will still be important, but as understanding of the mechanisms involved in epileptogenesis improves, a more rational approach to drug development may prove to be more efficient.

There are several compounds at an advanced stage of development which may prove to be useful AEDs, some of which offer novel mechanisms of action. Outlined in sections 3.1 to 3.11 and summarised in table III (in strictly alphabetical order) are those drugs currently undergoing clinical trials

Table III. Antiepileptic drugs (AEDs) in development

Drug	Mode of action	Current clinical trial phase	Other indications under investigation
ADD 17014[68]a	Excitatory amino acid antagonist	I	None
AMP 397A[69]	AMPA receptor antagonist	I	None
AWD 131138[28,70]a	? Modulates function of GABA-sensitive ion channels	I	Anxiety disorders
BIA 2093[71]	Sodium channel blocker	II	None
Carabersat[72,73]a	Unknown. Novel stereospecific CNS binding site	II	None
CGX 1007[74]	NMDA receptor antagonist	I	Neuropathic pain
DP-VPA[28,29]	Unknown (valproic acid prodrug)	I	None
Ganaxolone[75-79]	$GABA_A$ receptor agonist	II	None
Harkoseride[80,81]	NMDA receptor antagonist (glycine subunit)	II	Neuropathic pain
HEPP[82]	? GABAergic effect	I	None
Losigamone[83,84]	Effects on GABA-A–linked chloride channels	III	None
MDL 27192[85,86]a	Unknown	II	? Neuroprotection
Milacemide[87-89]a	Glycine agonist; MAO-B inhibitor	III	Alzheimer's disease
NPS 1776[28]a	Unknown		None
Pregabalin[90-95]	Unknown; ? GABAergic effect	II	Neuropathic pain, anxiety and phobic disorders
Retigabine[96-100]	Potassium channel effects; $GABA_A$ receptor agonist	II	None
Safinamide (NW 1015)[101-104]	Calcium channel blocker; sodium channel blocker; MAO-B inhibitor	II	Parkinson's disease
Stiripentol[105-111]	? GABAergic effects; ? potentiation of other AEDs	III	None
Talampanel[112,113]	AMPA receptor antagonist	II	None
Valrocemide[114]	Unknown	II	ALS

a No data on this agent have been published recently (within the last 3 years).

ALS = amyotrophic lateral sclerosis; **AMPA** = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; **GABA** = γ-aminobutyric acid; **MAO** = monoamine oxidase; **NMDA** = *N*-methyl-D-aspartate; **?** = uncertain/unknown.

in patients with epilepsy. The current stage of development of each drug is stated, this information being based on published data. In some cases, few data have been published for some time and so the development of these compounds may not be continuing. Given the early stage of development of some of the agents outlined in table III, the eventual place of these compounds is necessarily uncertain.

3.1 BIA 2093

BIA 2093 is a carbamazepine derivative that was specifically designed to avoid the production of toxic metabolites, such as epoxides. *In vitro* studies have shown BIA 2093 to inhibit 4-aminopyridine– or veratidine-induced glutamate release from hippocampal synaptosomes. This was thought to be secondary to sodium channel inhibition.[71]

BIA 2093 is currently undergoing phase II clinical trials in Europe.

3.2 Carabersat

Carabersat is a chemically novel AED with a novel stereospecific CNS binding site, suggesting that its anticonvulsant activity may be not shared by currently available AEDs.[72] It has potent oral anticonvulsant activity in a range of rat seizure

models, with potency and efficacy equivalent to or better than carbamazepine and lamotrigine.[73] Carabersat is currently undergoing phase II clinical trials in the US and the UK in patients with refractory epilepsy.

3.3 Ganaxolone

Ganaxolone is an AED which has both a novel structure and a novel mode of action. The compound is one of a class of synthetic neurosteroids known as epalons.[75] Ganaxolone has agonist properties at a novel part of the $GABA_A$ receptor. While it has a relatively short half-life (1 to 3 hours), it has linear kinetics and exhibits no interactions with other AEDs.[75] It is currently in phase II clinical trials for the treatment of infantile spasms and paediatric epilepsy, and a phase II trial in adults with epilepsy has been completed in the US.

Two open-label add-on trials in a total of 64 paediatric patients with refractory partial and generalised epilepsy have shown approximately a 33% responder rate,[76,77] and the drug appears to be particular useful in infantile spasms.[76,77] In a double-blind, add-on trial in candidates for surgical treatment of refractory partial epilepsy, 52 patients received ganaxolone or placebo for up to 8 days. Withdrawal from the trial was at the time of the first seizure. 50% of the ganaxolone-treated group remained in the trial up to day 8, compared with 25% of the placebo-treated group.[78]

3.4 Harkoseride

Harkoseride is currently at the phase II stage of development in the US. It is an antagonist of the glycine binding site within the NMDA receptor. The drug has potent activity against maximal electroshock seizures in rodents.[116] It has a plasma half-life of about 12 hours, <1% protein binding, and a near 100% bioavailability. The drug and its metabolites are excreted predominantly by the kidneys.[80] Preliminary data suggest no interaction between harkoseride and the standard AEDs carbamazepine, phenytoin and valproic acid.[85]

The only clinical data available on harkoseride are from a study of 13 patients with refractory partial epilepsy. They received add-on harkoseride therapy titrated in weekly 100mg increments up to a maximum of 600mg twice daily. There was a reduction in mean weekly seizure frequency from 9.9 to 5.3 after 3 weeks. The most frequent adverse events were dizziness, ataxia and headache, but none required cessation of the drug.[81]

3.5 Losigamone

Losigamone is a novel compound structurally related to β-methoxybutenolides that is currently undergoing phase III clinical trials in patients with refractory partial epilepsy.

Pharmacolgical studies indicate that losigamone is a broad-spectrum anticonvulsant, with activity on $GABA_A$ receptor–linked chloride channels, presynaptic sites and neuronal membranes.[83,84] Losigamone has linear pharmacokinetics with a half-life of about 4 hours.[117]

In an open-label add-on study in adults with refractory partial epilepsy, 19 patients received losigamone for up to 6 months. There was a responder rate of 37% (7/19), with a further seven patients showing some improvement.[118] In another open study in adults with partial epilepsy, there was a median reduction in seizure frequency of 39% in the nine patients studied.[119]

A randomised, placebo-controlled trial of losigamone in 203 patients with drug refractory partial epilepsy[120] showed a significant median seizure reduction in the losigamone group compared with placebo (14.9 *vs* 6.9%). A greater proportion in the treatment group had a 50% reduction in seizure frequency (22.3 *vs* 14.6%), but this was not statistically significant. Losigamone was generally well tolerated with the most common adverse effect being dizziness.

3.6 MDL 27192

MDL 27192 is an AED with an uncertain mechanism of action. It has been shown in animal studies to have a broad anticonvulsant profile, and to

have neuroprotective properties.[85,86] It is currently in the phase II of development in the US.

3.7 Pregabalin

Pregabalin is an analogue of GABA which has anticonvulsant activity in a variety of animal models of epilepsy.[90] Its mechanism of action is unknown but appears to be different from that of other AEDs. It may have some GABAergic effects, since pregabalin increases neuronal GABA content and displaces gabapentin from its binding site. It also enhances GAD activity in a concentration-dependent manner.[91]

Pregabalin has an oral bioavailability of approximately 90%, is excreted largely unchanged in the urine,[121] and has a plasma half-life of 5.8 hours.[91]

In multicentre double-blind, placebo-controlled, add-on studies in a total of 1053 patients with drug-refractory partial epilepsy, pregabalin induced a significant reduction in seizure frequency compared with placebo, with an effective dosage range of 150 to 600 mg/day.[92-94]

93 patients with partial epilepsy were randomised to receive monotherapy with either pregabalin or gabapentin. 57% of the pregabalin-treated patients completed the 8-day treatment period, compared with 23.5% of those who received gabapentin.[95]

Dose-dependent, CNS-related adverse effects were most common (dizziness, somnolence and ataxia).

Additional studies are planned to assess use as monotherapy and in paediatric patients.

3.8 Retigabine

Retigabine has a novel mechanism of action, as a potent potassium channel opener with selectivity for neuronal cells. It also potentiates GABA-induced chloride currents and, at higher concentrations, has weak sodium and calcium channel blocking effects.[96-99] It has a broad spectrum of anticonvulsant activity in animal models.[99] A study in genetically epilepsy-prone rats suggested efficacy against generalised seizures.[100]

Retigabine undergoes hepatic acetylation and it exhibits a linear relationship between dose and peak plasma concentration, independent of acetylator status. It has a mean half-life of about 9 hours.[28]

Two open-label phase IIa add-on trials in patients with refractory partial epilepsy were primarily concerned with assessing the safety, tolerability and pharmacokinetics of retigabine.[28] In the 46 patients treated there was a responder rate of 26%, with an effective dosage range of 600 to 1200 mg/day.[28] Retigabine would appear to be well tolerated, with somnolence, vertigo, blurred vision and ataxia being the most commonly reported adverse events.[28]

3.9 Safinamide

Safinamide (NW 1015) is a structurally novel compound with a broad spectrum of anticonvulsant activity.[101-103] It is likely that sodium and calcium channel blockade underlie its anticonvulsant activity but inhibition of MAO-B may also play a role.[104] It is currently in phase II development in Italy and Switzerland.

Human studies have shown safinamide to have linear kinetics and a half-life of 21 to 23 hours.[28]

3.10 Talampanel

Talampanel is a noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor antagonist currently undergoing phase II clinical trials in the US. Animal studies have shown it to have a broad spectrum of anticonvulsant activity.[112] Plasma concentrations are affected by acetylator status, protein binding ranges from 67 to 88%, and the mean plasma half-life is about 7 hours.[28] It is an irreversible inhibitor of CYP3A and so may increase concentrations of concomitantly administered carbamazepine.[113]

A double-blind, placebo-controlled add-on trial in 49 patients with refractory partial epilepsy showed a mean seizure reduction of 21% compared with placebo. Dizziness and ataxia were the most common adverse effects.[28]

3.11 Valrocemide

Valrocemide was developed from a series of *N*-valproyl derivatives of GABA and glycine, but its exact mechanism of action is unknown.[114]

Animal studies have shown it to have a broad spectrum of anticonvulsant activity.[122] The drug has a half-life of 7.2 to 8.5 hours, and an estimated 4 to 6% is metabolised to valproic acid.[123] Valrocemide metabolism is increased by enzyme-inducing comedication.[28]

A safety study showed no serious adverse events in 22 patients with epilepsy who were given valrocemide, the most common adverse effects being CNS- and gastrointestinal-related.[28]

4. Conclusion

During the last 15 years, huge strides have been made in the treatment of epilepsy. The stranglehold of the nonspecific, sodium channel–blocking AEDs has been broken, and, in the UK at least, there have been seven novel drugs introduced for use in epilepsy. While these new drugs have not directly been shown to have superior efficacy when compared with the established AEDs, they are generally better tolerated, with an improved pharmacokinetic profile. It is reasonable to assume that they will form a new generation of established AEDs.

Further developments in the treatment of epilepsy, however, are equally exciting. While such developments may provide huge benefits for patients with refractory epilepsy, the current status of AED treatment should be kept in perspective: while complacency is to be avoided, it should be noted that the majority of newly diagnosed patients with epilepsy do well with AED monotherapy. For such patients, there remains a pressing need, not for so-called 'super AEDs', but for accurate diagnosis and classification of their epilepsy, and for the provision of evidence-based advice regarding fertility, pregnancy, life normalisation and drug withdrawal. Such challenges will not be met simply by introducing more and more new drugs, but instead will require committed medical and nursing input, with appropriate support from colleagues with expertise in EEG and scanning. New treatments are only part (albeit an important part) of the optimal regimen for patients with epilepsy.

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