REVIEW

New developments in the treatment of partial-onset epilepsy

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Abstract: Although most people presenting with partial-onset seizures will achieve control with antiepileptic medication, a considerable minority will have difficult-to-treat epilepsy that is resistant to existing medication. Over the last few years, a large number of new antiepileptic drugs have been developed. Some of these have a novel mode of action. Many of the older antiepileptic drugs act through sodium channels or by enhancement of gamma amino butyric acid (GABA). Lamotrigine has sodium-channel blocking properties but also has other important modes of action, indicated by efficacy in treating not only partial-onset but also generalized seizures. Vigabatrin and tiagabine both increase GABA activity, by inhibiting GABA transaminase and limiting GABA reuptake, respectively. The main mode of action of gabapentin and pregabalin is not via GABA but through a selective inhibitory effect on voltage-gated calcium channels containing the $\alpha_2\delta$-1 subunit. Levetiracetam inhibits the recycling of SV2A (synaptic vesicle protein 2A) neurotransmitter vesicles but also has other effects, including inhibition of voltage-dependent calcium channels. Some drugs, eg, felbamate, zonisamide, and topiramate, have multiple modes of action. In many cases, although the main mode of action may have been identified, other modes of action also play a role. Two recently developed antiepileptic drugs appear to have completely novel primary modes of action; retigabine (ezogabine) and perampanel act on the potassium channel and on AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, respectively. The hope is that antiepileptic drugs with a novel mode of action will be effective where previous drugs have failed and will not have unacceptable adverse effects. However, experience with these medications is too limited to allow any conclusions to be drawn at present.

Keywords: partial-onset seizures, difficult-to-treat epilepsy, antiepileptic drugs

Introduction

One of the major challenges in the management of epilepsy is achieving control of partial-onset seizures while avoiding unacceptable adverse effects from the treatment. Although the majority of patients with new-onset epilepsy will achieve seizure control relatively easily with the first antiepileptic drug (AED) that is prescribed,[1] a large minority develop difficult-to-control seizures that are resistant to treatment.[2] After a long period in which there was almost no progress in terms of developing new drugs for the treatment of refractory epilepsy, in recent years a large number of AEDs have been marketed, mostly for the treatment of partial epilepsy. Despite these developments, many people with epilepsy continue to have uncontrolled seizures that are resistant to medication. Pharmaceutical companies acknowledge that it is necessary to provide some explanation of the mode of action of any new AED that is

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455

marketed because clinicians will be interested to know how this drug might be successful where other drugs have failed. Essential information when marketing a drug to clinicians includes not only efficacy, pharmacokinetic characteristics, and drug–drug interaction profiles, but also adverse effects, including cognitive and behavioral adverse effects,[3,4] often together with an indication of improvement on quality-of-life measures.[5,6] Although basic information on adverse effects is now often provided, it is usually inadequate at the time the drug receives a marketing license. The reasons for this are many. First, the marketing license is based on trial data, generally on only a few hundred patients who are highly selected, usually according to stringent inclusion and exclusion criteria. This implies that the numbers are inadequate to assess either subtle or unexpected adverse effects, such as the visual field defects with vigabatrin,[7] or less common but serious adverse effects, such as the hepatotoxicity and aplastic anemia with felbamate.[8,9] It also implies that often no data are available on particular groups of patients, such as women of childbearing age, patients with concomitant physical or psychiatric illness, children, and the elderly. Clinicians acknowledge that the true value of an AED is only recognized after is has been used extensively. This leads to a dilemma. On the one hand, the drive is to develop an AED with a new mode of action that might be effective where previous drugs have failed; on the other hand, if the new AED has a different mode of action it is also likely to have different adverse effects from previous AEDs, and because of this, clinicians might be very reluctant to prescribe it. The two examples of visual field defects with vigabatrin and both hepatotoxicity and aplastic anemia with felbamate have reinforced this reluctance. The experience with these two drugs underlines the importance of being both guarded and very specific when referring to the safety and tolerability of AEDs. It is irresponsible for researchers to claim, on the basis of trials involving a few hundred patients, that a drug is "safe,"[10] although many publications in the peer-reviewed literature make such statements. Again, felbamate, a drug that was initially regarded as being very safe, is a good example. In addition to the risk of potentially fatal aplastic anemia, liver damage can occur, which may require liver transplant or may also be fatal. As a result, this AED that was previously regarded as "safe" is no longer used in routine practice and is only reserved for the most refractory cases for which this level of risk might be accepted.

The question of whether the underlying cause of the epilepsy guides decisions about treatment is explored in the next section, on pathophysiology. In practice, when treating partial-onset seizures, the clinician will generally choose from one or two drugs that are well established, that are known to be effective in a high proportion of cases, and which have adverse effects that are usually mild, generally easy to manage, and only very rarely serious or life-threatening. If these well established and well known drugs are not effective or are not tolerated, then a balanced decision needs to be made with regard to the remaining options for treatment. If seizure control has not been achieved after the prescription of two drugs that are appropriate for the seizure/epilepsy type, given in adequate dose and for an adequate duration, the epilepsy is considered to be refractory. In those cases, it is advisable to follow three basic principles of management.

1. Review the diagnosis.
2. Review the AED treatment.
3. Consider epilepsy neurosurgery.

Reviewing the diagnosis is of major importance. There are now several publications[11,12] indicating that quite a high proportion of patients considered to have difficult-to-treat epilepsy do not have the condition at all and have, consequently and not surprisingly, not responded to antiepileptic medication. Conditions commonly misdiagnosed as epilepsy include syncope of various types and acute symptomatic seizures such as those following head trauma or febrile seizures in a child.[11] Antiepileptic medication in these cases would usually be inappropriate.

For partial-onset epilepsy of anterior temporal lobe origin, the outcome of anterior temporal lobectomy, in terms of seizure control, is generally good. McIntosh et al[13] carried out a systematic review and found that the median 2-year seizure-free proportion was 70%, although there was a wide range of outcomes. Wiebe et al,[14] in a randomized controlled study, reported that the cumulative proportion of 40 patients who were free of seizures impairing awareness was 58%. The proportion of seizure-free patients depends both on careful assessment for suitability and on the center performing the surgery. For patients with extratemporal focal-onset epilepsy, ie, with onset from areas of the brain other than the temporal lobe, the outcome is much less favorable.[15] Again, the possibility of cognitive and behavioral/psychiatric adverse effects arising from the treatment, in this case surgery, need to be considered carefully, with the important difference that AEDs can be stopped but resective surgery cannot be reversed. Psychiatric symptoms may improve, deteriorate or develop de novo after epilepsy surgery.[16] In some cases, the psychiatric sequelae of epilepsy surgery can be severe and

require additional psychotropic medication.[17] Although some patients can discontinue antiepileptic medication if they are rendered seizure free by epilepsy neurosurgery, a proportion of patients continue to require the AEDs if they are to remain seizure free. The result in the minority of patients who develop psychiatric symptoms is that they might need more, not less, medication, in this case psychotropic medication, after the epilepsy neurosurgery.

In recent years, one surgical procedure that can be "reversed," or at least discontinued, is vagal nerve stimulation. Some patients might view this as being an invasive procedure because some scarring is inevitable and the device has a limited battery life, although it should be noted that, on both counts, marked improvements have been made: the devices are much smaller, implying that the scarring should now be minimal and the battery lives are longer. Apart from any adverse effects on body image and some effects on the voice, usually hoarseness, which may diminish or be acceptable, this treatment appears to be relatively free of detrimental effects. There is now considerable evidence to suggest that it may improve mood, in patients with or without epilepsy.[18,19] Other surgical treatments for epilepsy, eg, deep brain stimulation, are in the experimental stage, but results so far are quite promising.[20]

Pathophysiology of partial onset epilepsy

It is interesting to note that, with very few exceptions, the underlying cause of the epilepsy is still generally not a major factor in determining which AED is chosen. On the whole, the clinician makes a decision about whether the seizures are likely to be of generalized or partial onset and decides on the choices of antiepileptic medication on this basis.

Even when acute symptomatic causes of epilepsy, such as infection (eg, meningitis, falciparum malaria), metabolic (eg, hypoglycemia, hypocalcemia), and others are excluded, the causes of partial seizures are legion. A few examples follow.

Genetic

In most cases, epilepsy, including epilepsy with partial-onset seizures, is idiopathic, that is, cause unknown. To the words "cause unknown," many would now add "presumed genetic," although research into specific genetic defects causing epilepsy has not been very fruitful so far. Several genes associated with epilepsy have been identified in animal models, and a few have been identified in humans.[21]

However, a single gene defect can increase the risk for several different epilepsy syndromes, and a single epilepsy syndrome can be associated with several different gene defects.

Over a decade ago, one of the current authors, in a review article, made the following comments:

We have yet to reach the stage at which every epilepsy syndrome has a known gene, perhaps coding for a known channelopathy, allowing the doctor to select the specific, scientifically-targeted antiepileptic drug to correct the ion channel defect.[22]

Although there have been considerable advances in the genetics of epilepsy, we have certainly still not reached that stage.

Autosomal nocturnal frontal lobe epilepsy was the first epilepsy syndrome for which a defect in a specific gene (coding for a subunit of the acetylcholine receptor) was identified.[23] Some further epilepsy syndromes have since been found to have a strong association with a single specific gene, including Dravet syndrome (severe myoclonic epilepsy of infancy) in which a number of defects in the sodium channel *SCN1A* gene have been found and the protocadherin 19 (*PCDH19*) gene in the X-linked infantile-onset epilepsy in girls, with or without mental retardation.[24]

Some indication that genetics might, indeed, provide a degree of guidance on therapy has been partially confirmed by the finding that seizure control in Dravet syndrome can deteriorate markedly with lamotrigine,[25] probably because this syndrome is associated with a sodium channel gene defect and lamotrigine has sodium channel blocking effects. There are very few other examples in which the underlying cause of the epilepsy guides the choice of treatment. The brain malformations (tubers) resulting from tuberous sclerosis are usually the consequence of defects in the *TSCI* (hamartin) or *TSCII* (tuberin) gene. A variety of seizure types can occur in tuberous sclerosis, including infantile spasms (West syndrome) and partial-onset seizures. For reasons that are not yet understood, infantile spasms resulting from tuberous sclerosis respond very well to the AED vigabatrin.[26]

A brief overview of some of the other causes of partial-onset seizures follows.

Brain trauma

Head injury, particularly penetrating brain injury, is an important cause of partial-onset seizures, which may present for the first time years after the injury.[27]

Brain malformations

A wide range of brain malformations ranging from microscopic cortical dysplasias to hemimegalencephaly can lead to partial seizures.[28]

Infections

In areas of the world where cysticercosis is common, this is an important cause of chronic epilepsy, often associated with calcified brain lesions. Subacute sclerosing panencephalitis, which can be a subsequent consequence of unusually early measles infection, can cause both generalized and partial-onset seizures.

Immunological/inflammatory

Systemic lupus erythematosus can cause symptomatic seizures. Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis can cause partial seizures. Potassium channel antibody encephalitis is being increasingly recognized as a cause of resistant partial-onset seizures.[29]

Tumors

A wide range of brain tumors can cause partial-onset seizures.

Degenerative diseases

Alzheimer's disease is one of many degenerative diseases that can cause partial-onset seizures.

Guidelines for the treatment of partial-onset seizures

The International League against Epilepsy Treatment guidelines, published in 2006,[30] allocated existing AEDs at that time according to six evidence levels, as follows: (1) established as efficacious or effective as initial monotherapy, (2) probably efficacious or effective as initial monotherapy, (3) possibly efficacious or effective as initial monotherapy, (4) potentially efficacious or effective as initial monotherapy, (5) no data available to assess whether effective as initial monotherapy, and (6) established as ineffective or significant risk of seizure aggravation. Their analysis of the available data for the treatment of partial seizures in adults resulted in the following findings: (1) carbamazepine and phenytoin; (2) sodium valproate; (3) gabapentin, lamotrigine, carbamazepine, phenobarbital, topiramate, and vigabatrin; (4) clobazam and primidone; (5) other AEDs available at that time; and (6) none. However, as already indicated, the rate at which AEDs have been developed over recent years implies that many AEDs

are now available that are not yet covered by the guidelines. The more recently issued (January 2012) National Institute for Health and Clinical Excellence (NICE) guideline in the UK states the following with regard to the treatment of focal seizures.[31] First-line AEDs: carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, and sodium valproate. Adjunctive AEDs: carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, and topiramate. Other AEDs that may be considered on referral to tertiary care: eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. However, this guideline also points out that more research is needed and recommends comparative prospective monotherapy trials on the newer AEDs, including eslicarbazepine acetate, lacosamide, lamotrigine, levetiracetam, pregabalin, and zonisamide, be performed.

Current available treatments for partial-onset seizures

The older AEDs such as phenobarbital, primidone, and phenytoin have many adverse effects. These include not only physical effects, for example skin rash or gum thickening with phenytoin, but also detrimental effects on cognition and behavior.[32] The two AEDs that became well established for many years, because they appeared to have far fewer adverse effects, are carbamazepine and sodium valproate. However, these drugs are also far from free of adverse effects: carbamazepine can be mildly sedative and has been associated with skin rashes that are sometimes accompanied by serious or even life-threatening systemic effects. Valproate has been associated with life-threatening hepatotoxicity or pancreatitis[33] in a small proportion of cases, Parkinsonian symptoms, and in offspring of mothers taking this drug during pregnancy, major fetal malformations[34] as well as impaired verbal IQ.[35,36]

After a long period of very little development in the area of antiepileptic medication to treat partial-onset seizures, since 1989 a large number of AEDs have become available. These are listed in Tables 1 and 2. AEDs are sometimes divided into the categories of first generation (phenobarbital, phenytoin, primidone, ethosuximide, carbamazepine, valproate, clonazepam, clobazam), second generation (vigabatrin, lamotrigine, gabapentin, topiramate, felbamate, tiagabine, oxcarbazepine, levetiracetam, pregabalin, zonisamide), and third generation (lacosamide, eslicarbazepine acetate, retigabine, perampanel, and others as they become available). The first-generation and second-generation AEDs will not be discussed in detail because they have been well reviewed elsewhere.

Table 1 AED introduction in the United Kingdom

AED	Year of introduction
Phenobarbital	1912
Phenytoin	1938
Primidone	1952
Ethosuximide	1960
Carbamazepine	1963
Valproate	1974
Clonazepam	1974
Clobazam	1982
Vigabatrin	1989
Lamotrigine	1991
Gabapentin	1993
Felbamate	1993
Topiramate	1995
Tiagabine	1998
Oxcarbazepine	2000
Levetiracetam	2000
Pregabalin	2004
Zonisamide	2005
Rufinamide	2007
Stiripentol	2007
Lacosamide	2008
Eslicarbazepine acetate	2009
Retigabine	2011
Perampanel	2012

Abbreviation: AED, antiepileptic drug.

Role of second-generation AEDs

A brief summary of the role of second-generation AEDs follows. Good reviews of the more recently available AEDs have also been produced, but since experience with these drugs is much more limited they will be discussed in more detail.

Zonisamide

Zonisamide is a carbonic anhydrase inhibitor, although the mode of action as an antiepileptic is thought to be through blocking of repetitive firing of voltage-sensitive sodium channels and reduction of voltage-sensitive T-type calcium currents.[37] It is effective in treating partial-onset seizures but shares the adverse effects of some of the other carbonic anhydrase inhibitors, including lethargy, loss of appetite, and kidney stones. White et al,[38] in a large study, found that psychiatric (6.9%) and cognitive (5.8%) adverse effects were frequent reasons for patients withdrawing from zonisamide.

Vigabatrin

Vigabatrin has a different mode of action from other AEDs. It is a suicidal inhibitor of gamma amino butyric acid (GABA) transaminase, the enzyme responsible for the metabolism of GABA.[39] Although initial studies showed that it was very effective in treating partial-onset seizures, concern about visual field defects has resulted in a sharp reduction in the use of this drug.[7]

Lamotrigine

Lamotrigine is a sodium-channel blocking drug, although it clearly has other modes of action since it is effective in the treatment of not only partial-onset seizures but also in the treatment of at least some types of generalized seizures.[40,41] It is well tolerated and consequently favored in clinical practice.[42] The main concern has been around the development of skin rash, which can rarely be associated with serious systemic illness.[43] Estrogen decreases lamotrigine levels, which may be problematic for women taking the oral contraceptive or during pregnancy.[44]

Oxcarbazepine

Oxcarbazepine is chemically related to carbamazepine and also acts by blocking sodium channels,[45] but it does not have the potentially toxic epoxide metabolite. Clinically it appears to have a similar spectrum of action to carbamazepine but is reported to be associated with an increased risk of hyponatremia.[46]

Felbamate

Felbamate is a broad-spectrum AED with efficacy in treating both partial-onset and generalized seizures. It apparently has multiple modes of action, including possible effects on both GABA and NMDA receptors.[47] The serious adverse effects of hepatotoxicity and aplastic anemia have greatly limited the use of this drug.[8]

Gabapentin

Gabapentin appears to be less effective in treating partial-onset seizures than other available AEDs, although some authors have questioned whether this might be because the doses that are usually given are too small. The mode of action is through binding to the $\alpha2$-δ subunit of a voltage-dependent calcium channel.[48] It is very well tolerated, and safety has become well established because of very extensive use as an analgesic drug for neuropathic pain. Because of this extensive safety and tolerability data, some clinicians would still have advocated gabapentin as a first-line AED for partial-onset seizures before the advent of pregabalin (see later).

Topiramate

Topiramate, which has multiple mechanisms of action, including blockade of sodium channels and kainate/AMPA

(α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, enhancement of GABAergic transmission and inhibition of carbonic anhydrase,[49] is established as a very effective AED for partial-onset seizures but is associated with some significant adverse effects, including renal stones and word-finding difficulties.[50]

Tiagabine
Tiagabine excited considerable interest as a treatment of partial-onset seizures when it was first introduced because it was one of the few drugs with a well understood specific antiepileptic mode of action; it is a GABA reuptake inhibitor.[49] However, it has been very little used in practice because of limited efficacy.

Levetiracetam
Levetiracetam is effective in treating partial-onset seizures. It has a broad spectrum of activity which may be due to its novel mechanism of action: it inhibits the recycling of SV2A neurotransmitter vesicles, but levetiracetam has other effects; for example, it inhibits voltage-dependent calcium channels, which may also contribute in part to its mechanism of action.[51] There have been no major safety or tolerability concerns, although some patients may become lethargic if the dose is escalated too rapidly.

Newer AEDs
Newer AEDs for partial-onset seizures available from 2004 include the following.

Pregabalin
Pregabalin, like gabapentin, binds to the α2-δ protein subunit of voltage-gated calcium channels.[52] It is effective in treating partial-onset seizures and is generally well tolerated. It has effectively superseded gabapentin, being a more potent drug with a similar mode of action.

Rufinamide
Rufinamide, which acts by modulating the frequency of sodium-dependent neuronal action potentials (although the mechanism has not yet been fully determined),[53] has primarily been used in treating the Lennox-Gastaut syndrome, for which it has an orphan drug license, but it has also been shown to be effective in treating partial seizures.[54]

Stiripentol
Stiripentol, which acts by increasing brain GABA levels by inhibition of synaptic GABA uptake and/or inhibition of GABA

transaminase,[55] has an orphan drug license for the treatment of seizures in Dravet syndrome (severe myoclonic epilepsy of infancy), which includes partial-onset seizures. It increases the blood levels of clobazam and its pharmacologically active metabolite, N-desmethylclobazam, twofold and threefold higher respectively, although it is claimed that stiripentol itself has antiepileptic properties and that the efficacy is not due to increasing clobazam and N-desmethylclobazam blood levels alone.[56]

Most recent AEDs
Eslicarbazepine acetate, lacosamide and retigabine are among the most recently licensed AEDs and will be discussed in more detail, although reviews on these drugs are available.[57,58]

Eslicarbazepine acetate
Eslicarbazepine acetate might be described as the least novel of the recently licensed AEDs. It is a pro-drug of eslicarbazepine and shares a chemical pathway with oxcarbazepine. It has a similar affinity to carbamazepine for the inactivated state of the sodium channel but a threefold lower affinity for the resting state of the channel. Efficacy has been proven in three double-blind, multicenter, parallel-group, placebo-controlled, randomized, adjunctive-therapy trials in patients with refractory partial-onset seizures.[59–61] The pooled, intention-to-treat efficacy analysis of the 1050 patients in these three trials revealed a statistically significant decrease in seizure frequency at doses of 800 and 1200 mg/day compared with placebo. There was no statistically significant difference in efficacy between 400 mg/day and placebo. The mean responder rates ($\geq$50% seizure reduction) were 19.9% at 400 mg, 36.2% at 800 mg and 39.3% at 1200 mg/day compared with 18.5% on placebo. The prominent treatment-emergent adverse events included dizziness, somnolence, headache, nausea or vomiting, visual disturbance, and incoordination. Most events were dose related.

Lacosamide
Lacosamide is a sodium-channel blocking drug, but the mechanism is different from other sodium-channel blocking AEDs because it enhances the slow inactivation of voltage-gated sodium channels with no apparent effect on fast inactivation.[62] It has been shown to be effective in the treatment of partial-onset seizures in three double-blind, multicentre, parallel-group, placebo-controlled randomized adjunctive-therapy trials in patients with refractory partial-onset seizures. Pooled, intention-to-treat analysis of these

three trials on a total of 1294 patients revealed a statistically significant decrease in seizure frequency compared with placebo at all three doses, with responder rates of 34.1% at 200 mg/day, 39.7% at 400 mg/day, and 39.6% at 600 mg/day, compared with 22.6% on placebo. The prominent treatment-emergent adverse events were dizziness, headache, nausea, and diplopia, all of which, apart from headache, were dose related. Other adverse events that occurred at the highest dose of 600 mg/day were vomiting, fatigue, ataxia, blurred vision, tremor, and nystagmus.[63,64]

Retigabine

Retigabine is a first-in-class drug with an entirely different mode of action from other current AEDs. Unlike many other AEDs that have mechanisms affecting sodium channels, the primary action of retigabine is to enhance neuronal-specific M-type potassium currents mediated by Kv7 channels[65–67] resulting in decreased neuronal excitability, although this is probably not the sole mode of action. Efficacy in partial-onset seizures has been shown in three double-blind, multicenter, parallel-group, placebo-controlled, randomized adjunctive-therapy trials in adults.[68–70] The pooled intention-to-treat data on 1244 patients showed a statistically significant decrease in seizure frequency at 900 and 1200 mg/day compared with placebo. The mean responder rates were 27.5% at 600 mg/day, 35.5% at 900 mg/day, and 38.5% at 1200 mg/day, compared with 17% on placebo. The 900 and 1200 mg/day doses were statistically significantly superior to placebo. The most frequently reported adverse events that were dose-dependent were dizziness and somnolence. Fatigue and confusional states were also reported.

Perampanel

Perampanel is the newest AED to be licensed for the treatment of partial seizures, and because it represents a new mode of action, namely it acts via AMPA receptors, the following section will discuss AMPA receptors and the role of perampanel.

AMPA receptors and the role of perampanel

Normal brain activity depends on a balance between excitatory and inhibitory neurotransmission; an imbalance between these two systems can result in abnormal, epileptiform activity. This principle has led to endeavors to produce AEDs that act specifically either by increasing inhibition or decreasing excitation. Glutamate is the most important excitatory neurotransmitter in the brain. Attempts have been

made to produce AEDs that inhibit the action of glutamate at specific receptors. Rogawski[71] has provided a good overview of this work, which started in the 1940s when glutamate was first recognized as an excitatory chemical in the brain that could lead to seizures. Various ionotropic glutamate receptors were subsequently identified. These include NMDA receptors, kainate receptors, and AMPA receptors. Kainate receptors are the least prevalent of the ionotropic glutamate receptors, but they do contribute to excitatory transmission to some extent. Unlike the NMDA and AMPA receptors, which are mostly postsynaptic, kainate receptors are presynaptic at both excitatory and inhibitory synapses. Rogawski[71] has stated that the role of kainate receptors in the pathophysiology of seizures is still incompletely understood but they could contribute to seizure generation in some circumstances.

Attempts to produce AEDs that act on NMDA receptors have been disappointing.[72] Instead of improving seizure control, in trials the seizure control deteriorated in some patients. It was subsequently concluded that AEDs targeting NMDA receptors were unlikely to be of value. Rogawski[71] has pointed out that AMPA receptor antagonists have a broader spectrum of anticonvulsant activity than NMDA receptor antagonists and do not appear to produce the same adverse effects. In animal models AMPA receptor antagonists appear to have a wide range of anti-seizure activity apart from lacking efficacy in genetic models of absence epilepsy. There is also a suggestion that AMPA receptor antagonists might be beneficial in treating status epilepticus.[73,74] Both competitive and noncompetitive AMPA receptor antagonists have been shown to be effective in animal seizure models but the noncompetitive antagonists seem to have better antiseizure activity, perhaps because they are effective even in the presence of high glutamate levels. Because AMPA receptors are widely distributed, adverse effects from AMPA receptor antagonists might be expected. However, Rogawski[75] has drawn attention to the finding that, unlike NMDA receptor antagonists, AMPA receptor antagonists do not seem to cause PCP (phencyclidine)-like behavioral effects or psychoticomimetic effects in humans. The previous AMPA receptor antagonist, talampanel was shown to be effective in the treatment of partial-onset seizures,[76] but drowsiness was a problem, and it is subject to pharmacokinetic interactions: plasma concentrations of this drug are greatly reduced by enzyme-inducing AEDs. Trial results were not sufficiently favorable, and the drug has not been developed further. Another AMPA receptor antagonist, perampanel, has been found to be active in the mouse MES (maximal electroshock) test, the mouse audiogenic seizure model, PTZ (pentylenetetrazol)-induced clonic seizures, and the psychomotor seizure test. It is

Table 2 Principal identified mechanisms of neuronal action of AEDs

AED	Excitation decreased					Inhibition increased	
	Na⁺	Ca²⁺	Glutamate	SV2A	AMPA	Cl⁻ (GABA)	K⁺ (KCNQ)
First generation							
Carbamazepine	√						
Phenobarbital		√	√			√	
Phenytoin	√						
Primidone		√	√			√	
Valproate						√	
Second generation							
Felbamate			√			√	
Gabapentin		√					
Lamotrigine	√						
Levetiracetam				√			
Oxcarbazepine	√						
Pregabalin		√					
Tiagabine						√	
Topiramate	√		√			√	
Vigabatrin						√	
Zonisamide	√	√					
Third generation							
Eslicarbazepine acetate	√						
Lacosamide	√						
Retigabine							√
Perampanel					√		

Notes: Also see text. The mode of action has not always been fully elucidated and drugs may have multiple modes of action.
Abbreviations: AED, antiepileptic drug; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid. GABA, gamma amino butyric acid.

also effective in amygdala-kindled rats, but as expected, had no effect on a rat genetic model of absence epilepsy. In summary, in vitro, perampanel is a potent, highly selective, noncompetitive AMPA receptor antagonist which reduces neuronal excitability[77] and that does not appear to be associated with the adverse characteristics of talampanel, nor has it been associated with the behavioral adverse effects and lack of efficacy of NMDA receptor antagonists. In Phase II studies, perampanel was well tolerated up to 12 mg/day in patients with refractory partial-onset seizures,[78] whilst in Phase III randomized, double-blind, placebo-controlled trials, perampanel once-daily, at doses of up to 12 mg/day significantly decreased seizure frequency.[79,80] It appears to be a promising drug that has a very different mode of action from other available AEDs and consequently might be effective in controlling seizures that have been resistant to previously available treatments. Although current data suggest that it might be quite well tolerated and no major safety concerns have emerged, insufficient numbers of patients have been treated to allow a definitive statement to be made with regard to safety.

Conclusion

The treatment of partial-onset seizures remains challenging. Although the majority of patients will achieve seizure freedom with the first AED, a large proportion will continue to have uncontrolled seizures. Some who have drug-resistant epilepsy will be suitable candidates for epilepsy surgery, but for those for whom surgery is not an option, the development of newer AEDs with different modes of action from current treatments and with freedom from unacceptable adverse effects is worthwhile. Two current drugs, retigabine (ezogabine), which acts on potassium channels, and perampanel, which acts through inhibition of AMPA receptors, together with other drugs in development, appear to fall into this category and offer fresh promise to individuals who have refractory partial-onset seizures.

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