Current Challenges in the Management of Epilepsy

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Epilepsy: Definition and Diagnosis

A clear definition of epilepsy is not self-evident, considering the variety of seizure manifestations and the multiple causes of seizures. The occurrence of a seizure is not, in itself, diagnostic for epilepsy, nor is the occurrence of multiple seizures necessarily diagnostic for the condition. In 2005, the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy jointly published a definition for epilepsy: "A disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition."[1] By this definition, a single seizure could be diagnostic for epilepsy, as long as it was accompanied by an alteration to the brain that conferred ongoing risk of future seizures.

The resemblance of seizures to other conditions unrelated to epilepsy makes it particularly important for other nonseizure events to be ruled out during differential diagnosis. Events that may be confused with seizures include syncope (whether possessing a cardiogenic, vasovagal, or other etiology), transient ischemic attack, sleep disorders, and psychogenic nonepileptic seizures. When the event is confirmed to be a seizure, it is necessary to determine whether the seizure is secondary to an underlying disorder, sometimes referred to as a "symptomatic" cause. Such secondary causes include sleep deprivation, hyponatremia, metabolic encephalopathy, central nervous system infection, stroke, tumor, alcohol or drug withdrawal, substance abuse, use of certain pharmacologic agents, acute traumatic seizures, and rarely, hypoglycemia.[2]

For patients with epilepsy, the initial priority is to identify the type of seizures and, if possible, the epileptic syndrome.[3] Understanding the applicable epilepsy syndrome is key for determining diagnostic details, therapeutic needs, and prognosis. Epilepsy syndromes are categorized by a variety of specific characteristics including the seizure type(s), clinical and precipitating features of the observed seizures, electroencephalographic (EEG) expression, age of seizure onset, and response to treatment.

Of the various diagnostic tools available, video EEG is particularly useful because it can help characterize both the seizure type and the epileptic syndrome, allowing for optimization of pharmacologic therapy while guiding presurgical workup.[4] Video EEG is also useful in establishing a definitive diagnosis (or, conversely, ruling out an epileptic etiology) when seizures are accompanied by an impairment

Abstract

A series of conceptual reconsiderations and therapeutic advances in recent years has resulted in meaningful changes in the classification, diagnosis, and treatment of epilepsy. The first step in evaluation of the person with epilepsy is determining whether the seizures are partial or generalized in onset; this determination will guide further evaluation and is mandatory in choosing an antiepileptic drug (AED). With 12 new AEDs and 1 device approved for use in epilepsy by the US Food and Drug Administration since 1993, the choice of AED has become more complex and it is impossible to predict whether a patient will respond favorably to a drug based on clinical features or clinical laboratory results. AEDs have many different mechanisms of action, but there does not seem to be a strong base of evidence to demonstrate that AED choice should be based on mechanism of action. Yet, a new secondary analysis of data from clinical trials of the new AED lacosamide suggests that combining this AED with another AED that has minimal or no activity at the sodium channel may lead to better tolerability and efficacy. The new AEDs have been tested in randomized controlled trials and compared with placebo; however, there are few head-to-head trials assessing the efficacy of various AEDs, and none of them provide evidence of a clear first choice drug or first add-on drug. Adverse effect profiles of the new generation of AEDs generally show better overall tolerability, but the choice of AED must be individualized (often based on comorbidities) because the adverse effect profiles of the newer AEDs differ widely. One area where the new AEDs consistently outperform the older AEDs is pharmacokinetic profile. Three new AEDs have no hepatic metabolism or protein binding, and others have minimal drug-drug interactions. Ultimately, selection of an appropriate agent involves matching a patient to a medication, or combination of medications, with the best record of efficacy while avoiding issues of tolerability and unwanted drug interactions (specifically tied to the needs of a given patient). Despite major advances in AED development, approximately one-third of people with epilepsy will have incomplete control of seizures no matter which AED is used alone or in combination, emphasizing the need for more effective AEDs. Patients with medication-resistant epilepsy may be candidates for epilepsy surgery, a highly effective treatment that is underutilized in this population.

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of consciousness. Ultimately, differentiating epileptic seizures from nonepileptic episodes is fundamental and constitutes the central diagnostic task. For example, an epilepsy diagnosis in a patient who does not have epilepsy could condemn that person to long-term, even lifelong, inappropriate use of antiepileptic drug (AED) therapy, with consequent adverse effects and considerable cost. At the same time, patients with epilepsy, as well as those with psychogenic nonepileptic seizures (PNES), who are misdiagnosed are subject to increased morbidity and mortality due to the untreated condition. Among patients with PNES, earlier diagnosis and treatment has been associated with better outcomes.[5]

Epilepsy may be classified as partial or generalized. Partial epilepsy is characterized by simple partial, complex partial, or secondary generalized tonic-clonic convulsions (GTC).[6] Partial epilepsy may initially develop in childhood or adulthood. Generalized epilepsy is subcategorized as idiopathic or symptomatic. Idiopathic epilepsy (also termed primary generalized epilepsy) occurs in people possessing no evident abnormalities in the structural architecture of the brain and is presumptively genetic in its etiology.[6] Myoclonic seizures, generalized tonic-clonic convulsions, and absence (formerly known as petit mal) are all seizure types seen in idiopathic epilepsy. Within the category of idiopathic epilepsy, specific syndromes, based on presenting seizures and patient age at onset, have been described. Symptomatic epilepsy (also known as secondary generalized epilepsy) is an often crippling manifestation of epilepsy typically accompanied by developmental delay.[6] Abnormalities in the structural architecture of the brain in patients with symptomatic epilepsy are either known or suspected. Lennox-Gastaut syndrome, a common syndrome associated with symptomatic epilepsy, is distinguished by the presence of cognitive impairment, multiple types of seizures, and a slow spike-wave pattern on EEG. Identification of a patient's epilepsy syndrome provides prognostic, therapeutic, and in some cases, genetic information.[7,8]

Treatment of Epilepsy

The treatment goal for a patient with epilepsy is eliminating seizures while at the same time avoiding adverse events.[4,7] The need for treatment should be individualized, and treatment selection should be guided by the particular epilepsy manifestations. AEDs constitute the mainstay of epilepsy therapy, and the broad array of available AEDs provides the opportunity for individualized treatment. AEDs may be categorized by mechanism of action (MOA). While distinction by MOA is a reasonable means of categorization, its utility is somewhat limited because a number of AEDs possess more than 1 MOA, and several AEDs appear to possess unknown MOAs (**Table 1**).[4,9] From the perspective of treatment selection, previous data from randomized controlled trials do not seem to support the consideration of MOA as a criterion for choosing an AED treatment regimen—whether it be monotherapy or combination therapy—and do not seem to demonstrate that a particular MOA improves outcomes.[10,11]

Appropriate treatment selection involves determining which agent or agents will be most effective for a patient's particular seizure type and epilepsy syndrome, as well as considering the adverse event and tolerability profiles of the AED(s). Moreover, pharmacokinetic considerations, such as possible drug interactions, must be weighed along with dosing-related issues, such as frequency of administration and AED formulation.

Efficacy

The relatively large number of available AEDs is partly explained by the heterogeneity of their efficacy and tolerability among patients. Unlike many conditions in which there is some degree of predictability of response to treatment, it is impossible to predict whether a given AED will prove to be effective in a particular patient. Moreover, efficacy comparisons of AEDs in the epilepsy population have produced no clear evidence showing an overall advantage for one therapy over another.[12] However, it is well known that some patients with epilepsy will become seizure free when switched to a different AED, despite previously failing several others. Unfortunately, however, approximately one-fourth to one-third of patients with epilepsy will not respond completely to AED therapy.[13]

The primary consideration in selection of an AED is seizure type(s), because not all AEDs confer broad-spectrum efficacy; that is, efficacy for both partial and generalized-onset seizures. With the exception of rufinamide, all of the AEDs approved for use by the US Food and Drug Administration (FDA) are effective against partial seizures; however, not all approved AEDs demonstrate efficacy in generalized onset seizures. Moreover, some AEDs that are effective for partial seizures may worsen some generalized seizure types. An important example of this phenomenon occurs with carbamazepine, one of the most widely used AEDs for partial seizures; several studies suggest it increases the risk of absence, atonic, and myoclonic seizures in some patients with generalized epilepsy.[14,15,16] An increased risk of seizures has also been associated with a number of other agents, including phenytoin, gabapentin, and vigabatrin.[17,18,19] Broad-spectrum activity is an important characteristic for AEDs because many patients undergoing evaluation cannot be classified as having partial

or generalized seizures. However, there is an inherent risk of exacerbating seizures in patients who have generalized epilepsy (if this cannot be confirmed at initial diagnosis) if they are inappropriately prescribed a narrow-spectrum AED. AEDs with evidence of broad spectrum activity based on randomized controlled trials include levetiracetam, lamotrigine, topiramate, valproate, and felbamate (Table 2).[20-24] It should be noted that zonisamide is widely used as a broad spectrum agent, but its use is not supported by randomized controlled trial data. In the case of lacosamide, further study is needed to determine whether it provides broad spectrum activity.

Table 1. Mechanisms of Action of Antiepileptic Drugs[a,4,9]

Mechanism of Action	Agents
Blockers of repetitive action of sodium channel	Phenytoin Carbamazepine Oxcarbazepine Lamotrigine Topiramate
Enhancers of slow inactivation of sodium channel	Lacosamide Rufinamide
GABA-A receptor enhancers	Phenobarbital Benzodiazepines
Glutamate modulators	Topiramate Lamotrigine Felbamate
T-calcium channel blockers	Ethosuximide Valproate
N- and L-calcium channel blockers	Lamotrigine Topiramate Zonisamide Valproate
GABA reuptake inhibitors	Tiagabine
Drugs binding to unique receptors	Gabapentin and pregabalin (alpha-2-delta receptor) Levetiracetam (synaptic vesicle 2A receptor)
Carbonic anhydrase inhibitors	Topiramate Zonisamide
GABA-transaminase inhibitors	Vigabatrin

GABA indicates gamma-aminobutyric acid.
[a]Most antiepileptic drugs possess more than 1 mechanism of action.

Adverse Event Profile and Tolerability

On the whole, the tolerability of AEDs is generally comparable between agents, although there are specific differences in adverse event profiles which must be considered (Table 3).[25] Acute adverse effects are common across AEDs, although newer generation AEDs tend to be better tolerated than many of the older AEDs.[25] Longer-term adverse events are also a concern with the use of certain AEDs, and older drugs such as carbamazepine, phenytoin, and phenobarbital (all cytochrome P[CYP]450 inducers) and valproate (not a P450 inducer) are associated with long-term side effects such as decreases in bone density.[26,27]

It is, therefore, important to select an agent that matches the particular profile of each patient, especially because certain adverse events associated with AEDs can be less obvious, but very significant. For example, some agents may exacerbate underlying psychiatric disorders, and must be used with caution in patients for whom this could be a risk. At the same time, the most common adverse effects of AEDs, such as dizziness, drowsiness, ataxia, sedation, and impairment of cognitive function, provide additional grounds for personalizing treatment. For example, a 74-year-old man who experiences seizures and also suffers from an unsteady gait due to stroke should not be prescribed an AED that has ataxia or dizziness as prominent adverse effects. Similarly, when combining AEDs, it is prudent to avoid combining drugs with similar adverse effect profiles so the risk of such effects is not compounded.[25] Sedation is an important adverse effect of AEDs; however, the newer AEDs (in general) are less associated with this effect. In comparison studies, lamotrigine was associated with less sedation than carbamazepine, both in a general adult population and in a population of elderly people with epilepsy.[28,29]

An additional consideration when selecting an AED is that some agents may confer efficacy against other diseases and conditions, making them potentially optimal choices for patients who possess specific comorbidities. For example, gabapentin, valproate, and topiramate have all demonstrated efficacy as prophylactic agents for migraine, while pregabalin is effective in diabetic neuropathy and carbamazepine has efficacy in trigeminal neuralgia.[25] In the area of beneficial psychiatric effects, valproate, carbamazepine, and oxcarbazepine are all used as maintenance therapy for bipolar disorder (as is lamotrigine) and in acute manic or mixed episodes. Levetiracetam, on the other hand, has been associated with a higher risk of depression.[20] Valproate and lamotrigine are additionally effective for rapid cycling in bipolar disorder.[25]

AEDs may also have teratogenic effects on the fetus, and great care and counseling is needed when treating women of

Table 2. Indications for Antiepileptic Agents With Broad-Spectrum Activity[20-24]

Antiepileptic Drug	Indication
Felbamate	In patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use, felbamate may be used as: • either monotherapy or adjunctive therapy for the treatment of partial seizures, with and without generalization, in adults with epilepsy • adjunctive therapy in the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in children Patient must be advised of the risk associated with felbamate use and must provide written, informed consent.
Lamotrigine	Adjunctive therapy in patients at least 2 years of age for treatment of partial seizures, primary generalized tonic-clonic seizures, generalized seizures of Lennox-Gastaut syndrome. Conversion to monotherapy in patients at least 16 years of age with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single AED.
Levetiracetam	Adjunctive therapy in the treatment of partial onset seizures in adults and children 4 years of age and older with epilepsy. Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy. Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy.
Topiramate	Initial monotherapy in patients at least 10 years of age with partial onset or primary generalized tonic-clonic seizures. Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients at least 2 years of age with seizures associated with Lennox-Gastaut syndrome.
Valproate	Monotherapy in the treatment of patients with complex partial seizures as well as simple and complex absence seizures.[a] Adjunctive therapy in the treatment of patients with complex partial seizures, simple and complex absence seizures, and patients with multiple seizure types that include absence seizures.

AED indicates antiepileptic drug.
[a]Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

childbearing potential with AEDs. Little is known about the newer AEDs, but phenytoin, phenobarbital, carbamazepine, valproate, and topiramate have been associated with an increased risk of major malformations in children of women receiving these AEDs during pregnancy. An important new study demonstrated that even in the absence of major malformations, the use of valproate during pregnancy was associated with a significant decrease in children's intelligence quotient when tested at 3 and 4.5 years of age.[30] Among commonly used AEDs, valproate is also considered to have the highest rate of major malformations, making it an especially poor choice for women of childbearing potential. The use of folic acid supplementation during pregnancy is thought to possibly reduce the risk of malformations (especially neural tube defects), but this has never been demonstrated in a randomized controlled trial.

Pharmacokinetics

One of the most beneficial developments that accompanied the emergence of newer generations of AEDs is their generally superior pharmacokinetic profiles. Older AEDs tend to be metabolized by hepatic enzymes, with metabolism induced by other medications; often these AEDs induce the metabolism of non-AEDs. Older drugs were often used in medical school pharmacology courses as an example of a drug class with many potential drug-drug interactions. In general, newer AEDs have lower propensity to induce hepatic enzymes compared with older AEDs such as phenytoin, carbamazepine, and phenobarbital. Drug interaction is a risk associated with several AEDs, and dose adjustments may be necessary with the coadministration of drugs in which at least 1 component is primarily metabolized in the liver; for example, plasma clearance of lamotrigine is nearly doubled when coadministered

Table 3. Adverse Effect Profiles of Antiepileptic Agents[25]

Adverse Effect	More Favorable	Less Favorable	Comments
Hepatic Disease	Gabapentin Levetiracetam Pregabalin	Phenytoin Phenobarbital Carbamazepine Valproate	Valproate can be hepatotoxic and cause platelet dysfunction.
Skin Rash	Valproate Gabapentin Topiramate Levetiracetam Pregabalin	Phenytoin Phenobarbital Carbamazepine Lamotrigine Oxcarbazepine	Risk of rash is lower with oxcarbazepine than with carbamazepine.
Cognition	Lamotrigine Lacosamide	Phenytoin Phenobarbital Topiramate Zonisamide	Cognitive effects are far less with topiramate 100 mg/d monotherapy. Most AEDs at high doses can adversely affect cognition.
Sedation	Lamotrigine	Phenytoin Phenobarbital Levetiracetam Gabapentin Carbamazepine Oxcarbazepine Tiagabine Topiramate Zonisamide Pregabalin	Agents are described as sedating if somnolence is one of the 5 most common adverse effects.
Weight	(Weight loss) Topiramate Zonisamide	(Weight gain) Valproate Gabapentin Pregabalin	Weight loss may not always be considered a favorable outcome.

AEDs indicates antiepileptic drugs.

with hepatic enzyme–inducing AEDs.[31] Interactions between AEDs and drugs of other classes is an area of additional concern. Important interactions with older AEDs include reduced oral contraceptive efficacy and reduced blood concentrations of some chemotherapy agents. Phenytoin was approved in the 1930s, but is still one of the most widely prescribed AEDs in the United States. Phenytoin is the prototype of the older AEDs, and it is one of the most difficult drugs to dose accurately.[32] Phenytoin is associated with numerous interactions with drugs metabolized by the liver, is highly protein-bound (thereby displacing other drugs and altering other drugs' free concentrations), and undergoes saturable metabolism within its therapeutic range, making it the most difficult AED to dose accurately.[33]

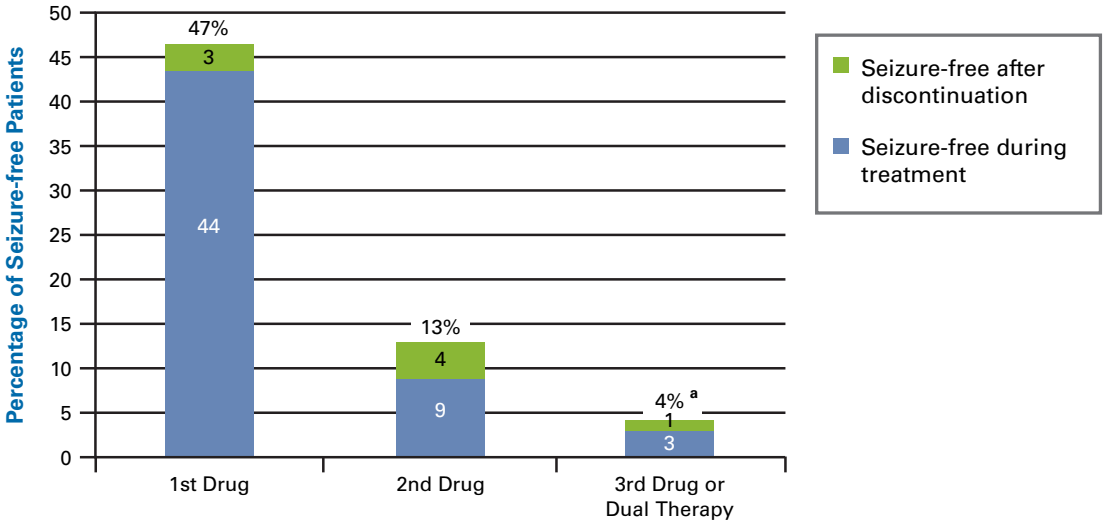
Newer AEDs can be categorized as drugs not metabolized by the liver or those that are metabolized by the liver but have a lower risk of drug-drug interactions than older AEDs. Levetiracetam, pregabalin, and gabapentin have no hepatic metabolism and no relevant protein binding, making them a good choice for patients with hepatic impairment or those receiving many concomitant drugs (as is common in the elderly). Even the newer AEDs that are metabolized by the liver are less likely to induce other medications or have relevant protein binding. Only oxcarbazepine and topiramate are associated with induction of oral contraceptives.

Drug interactions between AEDs may also be pharmacodynamic, where 2 drugs combine to produce synergistic adverse effects. For example, when oxcarbazepine is added to lamotrigine, there is an increased risk of dizziness, even though the plasma concentrations of the drugs are not altered substantially. It is further associated with the risk of other side effects. For example, dizziness can be a particular concern in elderly patients, for whom dizziness, ataxia, or drowsiness may be associated with falls and injuries. This greater vulnerability arises in part due to physiological changes that come with aging and the more frequent use of other medications due to age-related comorbidities.

Dosing

The complexity of selecting an appropriate AED for a patient with epilepsy (accounting for seizure type, seizure syndrome, safety, tolerability, and pharmacokinetic profile of AEDs) is compounded by the necessity of providing patients with a dosing regimen that is not too difficult or incon-

Figure. Response to AEDs Using Earlier Therapeutic Strategy[35]



AEDs indicates antiepileptic drugs.
[a]Subjects were given a third monotherapy (1% responded) or dual therapy (3% responded).

venient. Treatment efficacy will likely be compromised if patients have poor adherence to their therapeutic regimen.

Treatment Strategies

Standard approaches to sequential treatment strategies emphasized monotherapy over polytherapy, primarily because polytherapy caused more adverse effects and multiplied the potential for drug-drug interactions. The drawbacks of combining AEDs, however, appear to be reduced with the newer AEDs, which are associated with fewer adverse effects and demonstrate marked improvements in pharmacokinetics. One of the most widely quoted guidelines that tackled treatment strategy in epilepsy was based upon surveys of expert opinion and revolved around the treatment of 3 epilepsy syndromes: idiopathic generalized epilepsy, symptomatic localization-related epilepsy, and symptomatic generalized epilepsy. The strategies for treating these 3 syndromes were largely identical and consisted of initiating patients on AED monotherapy, and if that failed, a second monotherapy was tried. If a second monotherapy also failed, then the expert consensus was divided between trying a third monotherapy or attempting combination therapy with 2 drugs. Failure at that stage was widely agreed to require dual therapy, and if that failed, the consensus diverged.[7,34] It is important to note that these guidelines were based on expert opinion, and the experts were not asked to rank the level of evidence supporting their opinions.

The overall disappointing results with this sequential strategy were emphasized by the large retrospective review of efficacy and adverse effect data published by Kwan et al. His group evaluated the efficacy of AEDs in 525 patients with epilepsy (aged 9-93 years) by applying a treatment strategy similar to that stated above: initial monotherapy, followed by a second AED monotherapy if the first AED failed, whereupon consequent treatment failure involved treatment with either a third monotherapy or a combination therapy with 2 AEDs.[35] Of the 525 patients, 470 were AED treatment-naïve, 52% were male, median age was 29 years, and the median age at epilepsy onset was 26 years. A total of 27% of patients had idiopathic epilepsy (with a presumed genetic basis), 29% had symptomatic epilepsy (arising from a structural abnormality), and 45% had cryptogenic epilepsy (the result of an unknown underlying cause). Median follow-up was 5 years (range, 2-16 years).

Responses to the 3 stages of AED treatment, including response during treatment and after discontinuation, are depicted in the **Figure**.[35] Ultimately, slightly less than half of the patients responded well to initial monotherapy. The likelihood of success with a second monotherapy was quite poor, while third-stage dual or monotherapy therapy was even less promising.[35] Approximately 40% of patients were unresponsive to the first 2 attempts at monotherapy and possibly a third line of monotherapy or combination therapy. In light of these results, Kwan also prospectively investigated the effectiveness of earlier add-on combination therapy.[36]

In that study, 248 patients newly diagnosed with epilepsy experienced failure of initial monotherapy.[36] Patients were then placed into 1 of 2 groups based on treatment: 1) "switch" to another monotherapy, or 2) "add-on" combination therapy. If treatment failure was due to adverse events, patients were switched to another monotherapy agent; if treatment failure was due to lack of efficacy, patients were either switched to another monotherapy agent or another agent was added to the original treatment (add-on combination therapy).[36] Of patients who received add-on combination therapy, 26% (11 of 42 patients) became seizure-free; of patients who switched to a different agent, 17% (6 of 35 patients) became seizure-free.[36] These observations support the use of add-on combination therapy when initial monotherapy is unsuccessful.[36]

In a 2010 consensus document, the ILAE defined drug-resistant epilepsy as "failure of adequate trials of 2 tolerated and appropriately chosen and used AED schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom."[37] The ILAE task force on therapeutics strategies that arrived at this definition further noted that patients who are designated as drug-resistant may be candidates for surgical assessment or comprehensive evaluation at an epilepsy center.[37] The ILAE task force observed that responsiveness to a given regimen can fluctuate at least partly as a consequence of pathophysiologic changes in the underlying disease, and that designating epilepsy as drug resistant does not preclude the possibility that such a designation may change in response to therapeutic adjustments or other factors.[37]

Another publication by Kwan et al casts doubt on the traditional view that AED polytherapy is typically associated with marked increases in adverse effects. Patients whose second step of therapy was an AED combination, typically including a newer generation AED, were less likely to discontinue therapy due to adverse effects than those whose second step was an alternative monotherapy.[35] Although these data were not from a prospective, randomized, double-blind trial, the rates of discontinuation due to adverse events were much lower than the rates observed in combination studies with older AEDs.

Although comparative data are limited, newer strategies for treating epilepsy must account for the significant expansion in the therapeutic armamentarium. Most AED trials conducted to procure drug approval from the FDA are geared toward achieving end points that are valued by the FDA but are not often clinically useful. For example, most pivotal trials are placebo-controlled and attempt to determine superiority over no treatment. Moreover, dosing in such trials may be higher than the doses that are finally recommended, making extrapolation to the real world difficult. Finally, in studies that involve conversion from one monotherapy to another, end points are typically aimed at proving less deterioration in patient status rather than improvement.[6] Despite these significant caveats, clinical trial data suggest a similar likelihood of achieving seizure control with newer generations of AEDs compared with older AEDs, and generally with fewer serious adverse effects and drug interactions.[38]

Combination Therapy and Rational Polypharmacy

The use of combination therapy in epilepsy provides the potential to achieve efficacy and tolerability that may not be achieved with monotherapy. As with monotherapy, selection of combination therapy must be individualized, and must factor in the adverse event and pharmacokinetic profiles of available agents.[39] In theory, the MOAs of AEDs should be particularly important in combination therapy because of the opportunity for synergistic effects in efficacy.[39,40] The ongoing emergence of new AEDs multiplies the potential for such synergistic uses, and the concept of rational polypharmacy has taken on greater importance for the treatment of epilepsy in recent years, particularly with regard to treatment-refractory manifestations of the disease. Clinical trial evidence has been scant, but a recent example of the benefits of synergistic MOAs was observed in trials with lacosamide, a new sodium-channel blocker that unlike "traditional" sodium-channel blockers selectively enhances slow inactivation of sodium channels.[41] A pooled analysis of data from 3 phase 2/3 trials, which included approximately 1300 difficult-to-treat patients with partial-onset seizures (with or without secondary generalization) who were receiving concomitant treatment with 1 to 3 AEDs, showed that the addition of lacosamide significantly increased treatment response compared with the addition of placebo.[41] A second pooled analysis of data from phase 2/3 clinical trials assessed the efficacy of adjunctive lacosamide when added to existing therapy that did nor did not include at least 1 "traditional" sodium-channel blocker (ie, carbamazepine, lamotrigine, oxcarbazepine, or phenytoin). The authors observed that seizure reduction was significantly greater with lacosamide compared with placebo when added to existing regimens, regardless of whether it included a "traditional" sodium-channel blocker.[42] Although the efficacy data are often difficult to interpret independently of adverse effect data, these data underscore the potential utility for rational polypharmacy through synergistic uses of AEDs with different MOAs, particularly when applied to patients who have demonstrated nonresponsiveness to other approaches to AED therapy.

Further studies on efficacy and adverse effect synergy based on MOA are needed.

Monitoring

Monitoring AED blood concentrations can provide valuable information related to treatment efficacy and tolerability. In terms of efficacy, monitoring can help identify whether poor response is a result of suboptimal dosing (ie, low serum concentrations) and may also help identify patients who are not adherent to therapy.[43] Evaluating drug concentrations can help determine whether there may be a pharmacokinetic explanation for uncontrolled seizures or side effects. It can also be used to track pharmacokinetic changes in patients who have hepatic, renal, or gastrointestinal disease, or those who are pregnant (all conditions which may affect drug absorption or concentration). Children and the elderly, who are likely to absorb drugs at different rates than the general adult population, are also appropriate targets for drug concentration monitoring.[43] Also, monitoring can help refine the use of drugs with narrow reference ranges and to evaluate drug interactions and rates of elimination in combination therapy. It may help elucidate whether the use of more than 1 drug is contributing to improved efficacy in a given patient.[43]

Surgery and Vagus Nerve Stimulation

For patients who experience epilepsy that is refractory to AED therapy, surgical intervention to remove the part of the brain where seizures originate can be highly effective in stopping seizures. A clinical trial of 80 patients randomized to receive temporal lobe surgery or AED treatment showed a dramatic superiority of surgery after 1 year of follow-up.[44] It should be noted that epilepsy surgery involves an extensive evaluation process, including video EEG monitoring and other tests of structural and functional brain integrity. Nevertheless, the outstanding effectiveness of surgical intervention for cases of drug-resistant epilepsy make it an important alternative for all patients who fail AED treatment. Vagus nerve stimulation is another alternative for patients with drug-resistant epilepsy. Although it has not demonstrated superiority to AED treatment, vagus nerve stimulation does provide an effective adjunctive treatment for patients in whom AEDs are ineffective or poorly tolerated.[45]

Conclusions

The management of epilepsy is currently undergoing a broad transformation that includes changes in classification, diagnostic criteria, and treatment. It is clear that no universal treatment for epilepsy exists and that therapy selection must be tailored to each individual, with considerations of the patient's medical history, presenting signs, and symptoms. Other important considerations include matching the predicted adverse effect profile to the patient and matching pharmacokinetic properties of the AED to the patient's comorbidities and concomitant drugs. Although AEDs may be categorized by MOA, treatment selection based on MOA is not supported by clinical evidence and segmentation of AEDs based on MOA cannot predict clinical efficacy. The most important criterion for choosing an AED is whether the patient presents with partial, generalized, or an undetermined seizure type, as some AEDs may be ineffective for, or exacerbate, generalized onset seizures. Unfortunately, no constellation of signs, symptoms, and test results can predict which patient will respond to which AED.

Numerous therapeutic agents are available for the management of epilepsy. Monotherapy is preferable for compliance and minimization of adverse events, while combination therapy has an important role for those who do not respond to monotherapy. The emerging prominence of rational polypharmacy, based on the potential for synergistic application of AEDs with differing MOAs, constitutes an arena in which significant advances in therapeutic efficacy may be, and to some extent are being, achieved. Further clinical trials are needed to establish an evidence base that can be used to guide rational polytherapy. For now, rational polypharmacy depends on an assessment of complementary pharmacokinetic and adverse effect profiles. Successfully managing drug therapy in any given patient requires an understanding of the pharmacokinetic properties of AEDs to make appropriate medication choices, minimize adverse drug reactions, and avoid drug-drug interactions, thereby improving outcomes in patients with epilepsy.

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