

Do New Antiepileptic Drugs with Novel Mechanisms of Action Suggest Reconsideration of Rational Polypharmacy?

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Abstract

Although effective control of epilepsy can be achieved by a single antiepileptic drug (AED), the condition persists in a significant number of patients despite increasing dosages with monotherapy and polytherapy. Treatment with combinations of older AEDs has been known to cause undesirable drug–drug interactions and side effects. However, there has been renewed interest in polytherapy with the advent of newer AEDs with novel mechanisms of actions that are less likely to cause adverse effects in patients. Animal seizure models are useful for determining whether AEDs will be effective in generalised or partial seizures prior to clinical studies and isobolographic analysis may allow for a more systematic, rational approach to predicting whether a given combination of drugs will result in a greater or lesser pharmacologic effect. Since one treatment strategy does not suit all patients, studies should focus on the tolerability and safety of specific combinations of AEDs in order to provide guidance to physicians. In summary, pharmacokinetic interactions must be taken into account in studies in humans and animals with measurement of toxicity as well as efficacy.

Keywords

Epilepsy, antiepilepsy drugs (AEDs), side effects, drug–drug interactions, polytherapy, seizure models, isobologram

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Epilepsy is a common, complex, and chronic neurologic disorder affecting an estimated 0.5–1% of the global population or approximately 50 million people worldwide,^{1,2} 1.1–2.3 million of whom reside in the US.³ The ultimate goal of the treatment of epilepsy is to eliminate seizures without producing any side effects. Despite the plethora of antiepileptic drugs (AEDs) that have emerged over the past two decades, between 30 and 50% of patients continue to experience recurrent seizures.^{2,4}

Established Antiepileptic Drugs and Their Limitations

Historically, treatment options for epilepsy have been limited.³ Epilepsy is mostly managed using pharmacologic agents and major AEDs have included carbamazepine, phenobarbital, phenytoin, primidone, ethosuximide, and valproate. These older AEDs are generally effective, affordable, and familiar, but may cause hepatic dysfunction, drug interactions, and other significant side effects. This is reflected by the fact that between 1978 (when valproate was introduced) and 1993 (when felbamate received approval) no new anticonvulsants were approved by the US Food and Drug Administration (FDA).³ Figure 1 summarizes the potential targets for AED pharmacologic actions.

Many cases of newly diagnosed epilepsy can be successfully controlled with a single AED, but there are a significant number of patients in whom epilepsy persists despite receiving the highest dose of monotherapeutic AED. Polytherapy is the use of two or more medications to treat the same condition and is commonly used in the treatment of epilepsy when monotherapy fails. Since polytherapy is often unavoidable, it should be considered carefully before initiating a treatment regimen, as this carries a high risk for drug–drug interactions. Polytherapy may produce additive, antagonistic, or synergistic efficacy and toxicity.⁵ Unpredicted antagonistic effects or heightened toxicity may result from the combination of AEDs with competitive hepatic enzymatic metabolism and protein binding interactions.⁵ Many of the older AEDs have similar modes of action and therefore pharmacodynamic drug–drug interactions are common when used in combination.⁶ Historically, polytherapy has been reserved for medically intractable epilepsy due to the complexity of combining older AEDs;⁵ however, this practice should be reconsidered for earlier use in the treatment paradigm given the relatively cleaner profiles of the newer AEDs.

What Is Medically Intractable Epilepsy?

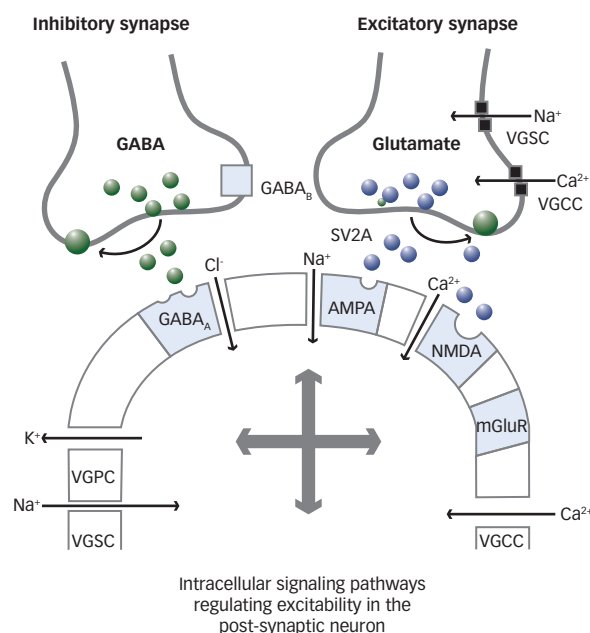
Up to 30% of epileptic patients fail to go into remission despite appropriate treatment with AEDs.^{7,8} Although the characteristics of

this group are not well-defined, prognostic factors that may cause intractability include multiple seizure types, complex febrile seizures, and symptomatic or cryptogenic epilepsy.⁹ A prospective study by Kwan and Brodie¹⁰ investigated the response to AEDs in 525 patients (nine to 93 years of age) with newly diagnosed epilepsy to identify factors associated with subsequent poor control of seizures. Patients were considered to be seizure-free if they had not experienced a seizure for ≥ 1 year. The outcomes of patients who received AED therapy are summarized in Figure 2. Although the overall rate of seizure remission was 63%, the study showed that patients with known or probable structural cerebral abnormality were 1.5 times more likely to have refractory disease than patients with idiopathic epilepsy. The authors also concluded that patients suffering multiple seizures or who were unsuccessfully treated with the initial AED were more likely to suffer from refractory epilepsy.¹⁰

Although the traditional argument against add-on therapy has been that there is a greater likelihood of toxicity with little improvement in outcome, adverse events due to pharmacokinetic and pharmacodynamic interactions between AEDs may be equally likely during the substitution phase.^{11,12} This has been demonstrated in a prospective study of patients in whom treatment with the first AED was unsuccessful, although the results did not reach statistical significance.¹³ In this study of patients with inadequate seizure control on the first well-tolerated AED, similar seizure-free rates were observed in those who received substitution monotherapy ($n=35$, 17%) and those who received combination therapy with a second add-on AED ($n=42$, 26%). Furthermore, similar incidences of intolerable side effects between the two treatment groups were observed (substitution versus add-on: 26 versus 12%.¹³

The definition of intractable or refractory epilepsy has been hotly debated.¹⁴ Recently, the International League Against Epilepsy (ILAE) proposed a consensus definition of drug-resistant epilepsy and the task force settled on the preferred term 'drug-resistant' to replace the terms medically intractable, refractory, and pharmacoresistant.¹⁵ The consensus for this choice is that drug-resistant is more consistent with the intent of the definition, namely to identify patients for whom there is sufficient information to predict that they will have a substantially poorer prognosis for seizure remission with AEDs compared with the population as a whole. The terms 'intractable' and 'refractory' imply that there is no chance at all of remission, which is never the case.¹⁵ The development of the consensus definition was driven by the growing need among medical practitioners and clinical researchers to adopt a common language in recognizing drug-resistant epilepsy, thereby facilitating comparison and meaningful generation of results across studies in the face of rapidly expanding therapeutic options.¹⁶ Furthermore, the definition could be valuable to patients and their carers, basic scientists, government regulators, legislators, healthcare administrators, insurers, educators, and employers. However, the proposed definition is not intended to be prescriptive but represents a working framework.¹⁶ The overall framework of definition comprises two levels. Level 1 provides a general scheme to categorize outcome to each therapeutic intervention (both pharmacologic and non-pharmacologic) that includes a minimum data set regarding the intervention that would be needed for such a purpose. Level 1

Figure 1: Potential Targets for Antiepileptic Drug Pharmacologic Actions



AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA = γ -aminobutyric acid; mGluR = metabotropic glutamate receptor; NMDA = N-methyl-D-aspartate receptor; SV2A = synaptic vesicle protein; VGCC = voltage-gated calcium channel; VGPC = voltage-gated potassium channel; VGSC = voltage-gated sodium channel. Adapted from Johannessen Landmark C, et al., *Drugs*, 2008;68:1925–39. Used with permission.

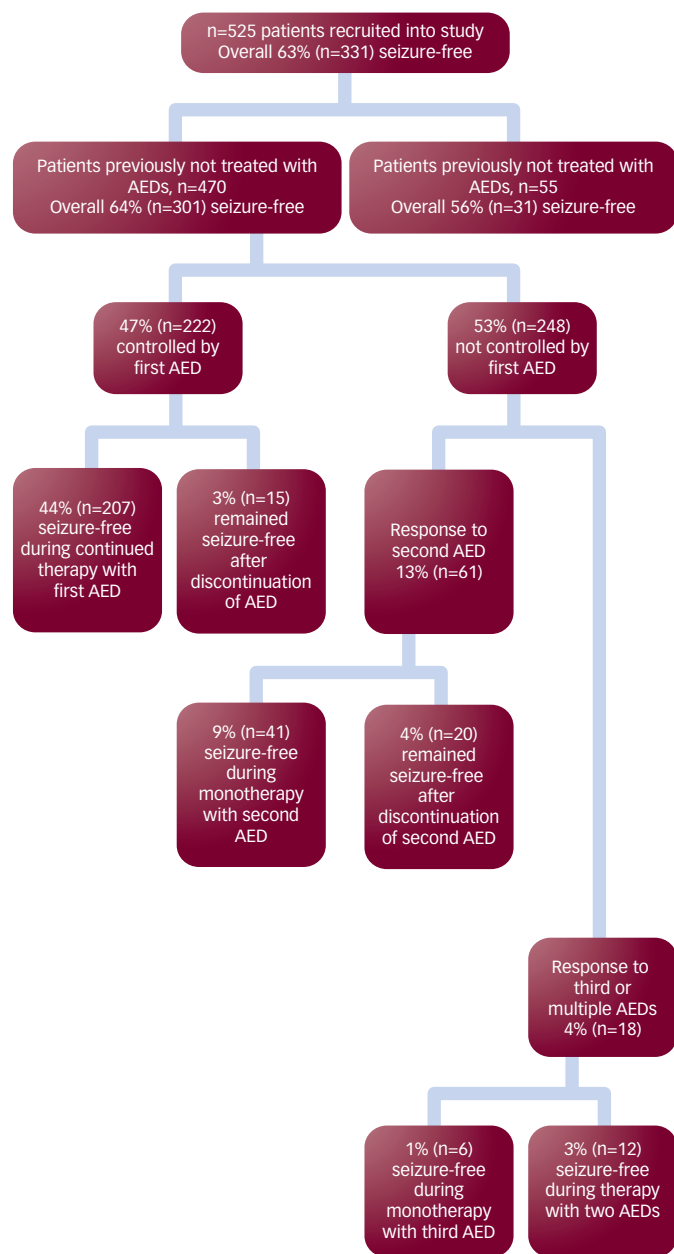
forms the basis for level 2. Level 2 provides a core definition of drug-resistant epilepsy based on the number of informative trials of AEDs that resulted in a treatment failure outcome. It is then possible to adapt, where appropriate, the core definition to specific purposes or clinical scenarios.¹⁶

Polytherapy—Rational or Irrational?

Irrational Polytherapy

Although polytherapy is implemented necessarily frequently to treat epilepsy, irrational polytherapy occurs too often. The use of multiple medications may cause adverse effects, drug–drug interactions, patient non-compliance, and medication errors. There is also the added complication of patients taking over-the-counter medications that physicians are not aware of.¹⁷ Furthermore, polytherapy has been associated with an increased incidence of mortality.¹⁸ There are several reasons irrational polytherapy occurs in the treatment of epilepsy. Poor initial diagnosis is a common reason for irrational polytherapy, with patients being prescribed an inappropriate AED in the first place. Subsequently, if a patient is not improving with the AED already prescribed, a physician may simply add further AEDs to their treatment without reassessing the drug that has already been prescribed.

Cross-titration occurs when a second drug is added. The physician may alter the dosage of drug if an immediate improvement is not achieved or, if an improvement is observed, the patient may inappropriately continue to be administered both drugs as the physician assumes that the combination is responsible for the improvement. In fact, many medication changes may not require cross-titration.

Figure 2: Outcome in 525 Patients with Epilepsy who Received Antiepileptic Drug Therapy

AED = antiepileptic drug. Adapted from Kwan and Brodie, 2000.¹⁰

Inadequate knowledge of receptor pharmacology (or a lack of attention to it) may also result in irrational polytherapy. Therefore, knowledge of AED mechanisms, as well as both experimental and clinical approaches to understanding drug effects, would seem important if clinicians are to design 'rational' therapeutic regimens.

Rational Polytherapy—How Do We Get There?

Defined conceptually, rational polytherapy is an understanding that AED combinations with differing mechanisms of action are more efficacious than polytherapy with AEDs that function similarly. It is a logical concept since the pathophysiology of epilepsy is believed to be a consequence of two opposing types of neural imbalance.⁵ It is possible to divide rational

polytherapy into two categories: empiric and validated. It is generally recommended that the validated type of polytherapy be attempted before other strategies and, if possible, if monotherapy AEDs in appropriate dosages for an adequate length of time of trial have failed.¹⁷

Although monotherapy is considered to be the gold standard for drug treatment of epilepsy, there is renewed interest in polytherapy. This is due to the advent of new AEDs with novel mechanisms of action with fewer drug–drug interactions, and the recognition that most patients with refractory epilepsy are eventually treated with combinations of drugs. It is important to give careful consideration to drug additions and conversions: add-on therapy may be less risky than substitution in patients with frequent or severe seizures.¹⁹

A prospective study for substitution with lamotrigine was conducted in 54 centers across Europe.¹¹ The study recruited 347 patients with epilepsy in whom seizures were not fully controlled with monotherapies of sodium valproate (n=117), carbamazepine (n=129), phenytoin (n=92), or Phenobarbital (n=9). If upon addition of lamotrigine a $\geq 50\%$ reduction in seizures occurred, an attempt was made to withdraw the original AED and, if successful, a 12-week period of lamotrigine monotherapy followed. A total of 73% patients completed the add-on phase, of whom 47% responded to treatment (64% valproic acid, 41% carbamazepine, 38% phenytoin). The response rate was higher in patients with idiopathic tonic-clonic seizures compared with patients with partial seizures (61 versus 43%; $p < 0.01$). Furthermore, the response rate in patients with partial and idiopathic tonic-clonic seizures was higher for the valproic acid group than for those treated with phenytoin or carbamazepine. This difference was significant in patients with partial seizures ($p = 0.014$) and when all seizures were included the difference between groups was statistically significant ($p = 0.001$). In this study, synergism between lamotrigine and valproic acid was also shown.¹¹ Moreover, this study lends credence to combination therapy.

Rational choice of drug combinations is currently based more on avoidance of pharmacodynamic or pharmacokinetic side effects than evidence for supra-additive efficacy. Although indications suggest that combinations of AEDs with differing mechanisms of action are most effective, further investigation is necessary, with attention to the effects of the various combinations on both toxicity and seizure control.¹⁹

Animal Models and Isobolograms

AED therapy is primarily aimed at reducing excitability through blockage of voltage-gated Na^+ or Ca^{2+} channels, or by increasing inhibition through the enhancement of γ -aminobutyric acid (GABA) currents.²⁰ In the past AEDs were discovered by serendipity, but the most recent AEDs have been specifically designed to target one of the many receptors or neurotransmitters involved in the generation of seizures. Once identified, putative AEDs are first studied in animal models of seizures (usually in rodents) to determine whether they will be effective in generalized or partial seizures, prior to clinical studies.^{20,21} Antiseizure drug screening has not only enabled a large number of relatively safe and effective AEDs onto the market, but it has also allowed further insight into the pathophysiology of seizures. However, it should be understood that this screening of AEDs is carried out in models of seizure and not models of epilepsy. This demonstrates that the

drugs are effective for control of acute seizures, but they may be ineffective in the control of chronic epilepsy.²⁰ However, new models of hypoxia-induced seizures, febrile seizures, infantile spasms, and recurrent generalized tonic-clonic seizures have been developed that will allow for studies of new therapies.²⁰

A fundamental question that arises when considering co-prescription of two or more medications is: will this combination add more to the existing regimen or will it potentially impair or antagonize current treatment? To date, these questions are mostly answered through clinical trial and error, usually by sequential trials of different agents. One experimental technique that may allow for a more systematic, rational approach to predicting whether a given combination of drugs will result in a greater or lesser pharmacologic effect is isobolographic analysis.^{22–24} This experimental technique is based on the presumption that an individual drug displays dose-dependent increases in pharmacologic response. Once this dose–response curve is established for the individual drug, a series of drug combinations can be tested to see whether the pharmacologic response curve is changed (either enhanced or, possibly, diminished). Although inter-individual variation in the pharmacokinetics and pharmacodynamics of AEDs makes it difficult to apply such an approach in a clinical setting, isobolographic analysis has been successful in animal models.²⁵

Isobolographic analysis is conducted in several stages. First the anticonvulsant activity of individual AEDs is evaluated. This is followed by determination of their dose–response relationships (DRRs) by means of log-probit linear regression analysis according to Litchfield and Wilcoxon.²⁶ In general, DRR parameter values for the median effective dose (ED₅₀), slope function (S), the equation to the DRR line, and coefficient of determination (r²) are determined by log-probit analysis. Furthermore, the graphic presentation and the test for parallelism of the examined DRR lines for AEDs administered singly are particularly important for 3D isobolographic analysis.²⁷ The effective doses of AEDs are calculated directly from the respective DRR lines according to Litchfield and Wilcoxon.²⁶ In order to analyze experimental data with precision and accuracy using isobolograms, the test for parallelism between combinations of AEDs based on the log-probit analysis is implemented.²⁸

Isobolographic analysis is a valuable tool that allows precise classification of exact types of interactions between AEDs and comprehensive evaluation of their nature. Interactions may be divided into supra-additive (synergistic), sub-additive (relatively antagonistic), infra-additive (absolutely antagonistic), indifferent, or additive.²⁹ Two different types of isobolographic analysis exist: type I, which is used if all examined drugs are fully active, and type II, which is used if one of the drugs produces no effect and is considered to be virtually ineffective in an experimental model.³⁰ Three fixed ratios of AEDs are usually used: 1:3, 1:1, and 3:1.³¹ Moreover, since isobolographic analysis is based on specific presumptions, it allows exact classification of observed interactions *in vivo*. One such presumption is the parallelism of DRR curves (DRRCs) for single-drug administration.³² Occasionally, the DRRCs for AEDs are not parallel, leading to misinterpretation of results and false classification of interactions. When these situations arise, modified isobolographic analyses for different regression line

slopes according to Grabovsky and Tallarida³³ and Tallarida^{34,35} should be conducted.

Since most AEDs are approved for adjunctive therapy, it is important to know which AED combinations would be most effective and safe to use in a clinical setting. However, only a limited number of studies have been conducted to date to determine drug–drug interactions of AEDs using isobolograms. In a study by Luszczyński et al., 3D isobolographic analysis was used to determine the anticonvulsant effects of lamotrigine and clonazepam, alone and in combination, against maximal electroshock (MES)-induced seizures in mice.³⁶ Doses of fixed-ratio combinations of AEDs (1:3, 1:1, and 3:1) that elicited 16, 50, and 84% of the maximum anticonvulsant effect were determined. Furthermore, the concentrations of AEDs in the brain were determined in order to evaluate the interaction characteristics observed with 3D isobolography. 3D isobolographic analysis showed that lamotrigine interaction with clonazepam was supra-additive at fixed ratios of 3:1 and 1:1 for all anticonvulsant effects between 16 and 84% of maximum. However, the interaction was purely additive for all estimated effects in 3D isobolography at a fixed ratio of 1:3. The observed interactions were pharmacodynamic in nature since none of the AEDs altered the brain concentrations of the co-administered drug. The findings from this study suggested that the combination of lamotrigine with clonazepam could increase the efficacy of seizure control in a clinical setting.

A study was conducted by Wojda et al. to characterize the anticonvulsant effects of levetiracetam in combination with various AEDs in murine 6Hz psychomotor seizure models.³¹ Type I isobolographic analysis for parallel and non-parallel dose–response effects was used to characterize the consequent anticonvulsant interactions between the various drug combinations. The DRRC for levetiracetam administered in a single AED regimen was parallel to the DRRC for clonazepam and non-parallel to the DRRCs for oxcarbazepine, phenobarbital, tiagabine, and valproate. Type I isobolographic analysis showed that combinations of levetiracetam with clonazepam for fixed ratios of 1:3, 1:1, and 3:1 and with oxcarbazepine, tiagabine, and valproate for a fixed ratio of 1:1 were additive. Comparatively, levetiracetam administered with phenobarbital was shown to be supra-additive and identified as a potentially useful combination. Furthermore, none of the tested combinations resulted in impairment of motor co-ordination, disturbance of long-term memory, or alteration in skeletal muscular strength in the animals.

A 6Hz murine model was utilized to evaluate the interaction of lacosamide with older and novel AEDs at fixed ratios of 1:3, 1:1, and 3:1 by isobolographic analysis.^{37,38} The protective action of an AED was defined as the absence of seizure. Motor side effects of AED combinations were also assessed in the rotarod test. Preliminary analysis of the data, published in abstract form, suggest that all studied AEDs produced dose-dependent anticonvulsant effects against 6Hz-induced seizures. The combinations of lacosamide with carbamazepine, lamotrigine, topiramate, gabapentin, or levetiracetam were supra-additive, revealing the synergistic anticonvulsant effects of lacosamide with both older and novel AEDs. Lacosamide in combination with phenytoin or valproate displayed additive effects with a tendency

toward supra-additivity. Furthermore, none of the combinations of AEDs induced enhanced adverse effects. The complete findings of the study are highly anticipated.

The Limitations of Polytherapy

The potential for unfavorable drug–drug interactions is a common concern, particularly the effect of older AEDs on the hepatic cytochrome P450 (CYP) enzyme superfamily.³⁹ Historically, the strongest argument against polytherapy has been the possibility of additive adverse events.^{40,41} However, it has also been argued that the efficacy and toxicity of polytherapy with AEDs is more dependent on total drug load rather than the number of drugs.⁴² Drug load is measured as the ratio of prescribed daily dose to the defined daily dose.⁴³ In one observational study,⁴⁴ the toxicity did not differ between patients on monotherapy and polytherapy when AED drug loads were equal, suggesting a purely additive effect. It may be inappropriate to quantify adverse effects, including idiosyncratic reactions, or long-term complications since drug load applies primarily to dose-related toxicity. For example, it is impossible to rule out potentially confounding pharmacokinetic interaction as the reason for adverse effects caused by administering lamotrigine and valproic acid in combination,^{45–47} since valproic acid inhibits the metabolism of lamotrigine.⁴⁸

Supra-additive effects are quite likely in polytherapy as many AED possess multiple, potentially overlapping, mechanisms of action.^{49,50} Although the supra-additive adverse effects due to pharmacodynamic interactions in polytherapy have not been well-studied in a clinical setting, there is some evidence to suggest that they are more likely to occur when AEDs share similar mechanisms of action. For example, excessive neurotoxic adverse effects have been reported in patients treated with the Na⁺ channel blockers carbamazepine or oxcarbazepine in combination with lamotrigine.^{11,51,52} However, lamotrigine and phenytoin (both voltage-gated Na⁺ channel blockers) in combination do not share the same adverse effect profile,¹¹ suggesting other factors may also be involved in this interaction.⁴⁰ Furthermore, comparatively few newer AEDs affect the metabolism of other AEDs at a clinically significant level.³⁹ Notably gabapentin, pregabalin, levetiracetam, zonisamide, lacosamide, and vigabatrin do not appear to participate in pharmacokinetic interactions with other AEDs.^{53–55}

Prescribing in Practice

Since 60% of newly diagnosed patients with epilepsy will become seizure-free with modest to moderate dosage of a single AED,^{56,57} the emphasis should be placed on the tolerability and safety of AEDs. A drug should be chosen with a spectrum of activity and adverse effect and interaction profiles that have the potential to produce freedom from seizures without intolerable toxicity or long-term sequelae for that individual. The choice should ideally be matched to the patient's seizure types(s) and/or epilepsy syndrome, age, sex, weight, psychiatric history, other disease states, concomitant medication, and lifestyle.^{40,58}

An AED should be substituted if the first drug produces an idiosyncratic reaction or adverse effects at low or moderate dosage, or fails to improve seizure control. However, if the drug is well tolerated the aim should be for complete freedom from seizures by increasing the dose

towards the limit of tolerability. If seizure control has been greatly improved but complete freedom from seizures remains elusive, another AED may be added on, particularly if there is a high density of pre-treatment seizures and demonstrable underlying pathology (e.g. cortical dysplasia and hippocampal atrophy). After adding a second AED, if a seizure-free state is achieved with no increase in toxicity, treatment with both drugs may be continued. The likelihood of success with a third monotherapy after the failure of two different monotherapies is small and, in this case, combination therapy should be considered, although further evidence is needed to support this strategy.

In order to reduce the potential drug load, it is possible to lower the dose of the initial drug, particularly if the patient in question suffers from or develops adverse effects. However, in the event that all types of AED therapy (monotherapy and polytherapy) fail to fully control seizures, evaluation for surgery should be considered at an early stage, particularly if a structural abnormality such as mesial temporal sclerosis has been identified.^{40,59}

It is crucial to assess the likelihood of pseudo-failure or pseudo-resistance before the implementation of combination therapy as the majority of patients will respond to monotherapy. Such a situation may transpire if a patient is misdiagnosed, inappropriately treated with AED for a particular type or syndrome of seizure and epilepsy, the dose administered is not high enough, adherence to treatment is poor, or inappropriate lifestyle factors such as alcohol or recreational drug abuse are identified.⁴⁰

The existing monotherapy being used often influences the second or third AED added to combination therapy regimens. Selecting AED combinations that have potentially complementary mechanisms of action is reasonable based on the limited data available. If the patient is established on treatment with an enzyme-inducing AED (e.g. carbamazepine, phenytoin, or phenobarbital), it may be desirable to add AEDs that carry a modest or low risk of clinically relevant pharmacokinetic interactions (e.g. lacosamide, levetiracetam, topiramate, pregabalin, or zonisamide).³⁹ If a patient does not reach a seizure-free state on a two-drug regimen but suffers notably fewer and/or less severe seizures, a third AED with different pharmacologic properties can be added in small doses, concurrently reducing the dose of one or both of the initial AEDs to avoid drug overload.⁴⁰ Third-line agents including tiagabine, clobazam, and acetazolamide may be added. Vigabatrin and felbamate remain drugs of last resort because of their propensity to produce visual field defects⁶⁰ and aplastic anemia and hepatotoxicity,⁶¹ respectively. However, treatment with four or more drugs is unlikely to be successful.⁶²

Many of the newer-generation AEDs (levetiracetam, lamotrigine, topiramate, zonisamide, lacosamide, oxcarbazepine, tiagabine, pregabalin, gabapentin, and rufinamide) have multiple and, in some cases novel, mechanisms of action. Other AEDs such as vigabatrin, an analog of GABA that irreversibly inhibits GABA transaminase resulting in an increase in synaptic GABA concentration, have only one known possible mechanism of action. Levetiracetam has an unknown mechanism of action. However, it is known to bind to the

synaptic vesicle protein SV2A, which is believed to impede nerve conduction across synapses. Lacosamide, a recent addition to the AED armamentarium, is indicated in the US as adjunctive therapy for partial-onset seizures in patients ≥ 17 years of age.⁶³ It enhances slow inactivation of voltage-gated Na⁺ channels, which is novel because older AEDs affecting this pathway tend to selectively enhance fast inactivation of Na⁺ channels.^{64,65} Some of the AEDs under investigation also have mechanisms likely to affect them in adjunctive treatment. Retigabine, which is yet to be approved, potentiates GABA-evoked currents in cortical neurons through activation of GABA-A receptors containing $\beta 2$ or $\beta 3$ subunits. It blocks 4-aminopyridine-induced neosynthesis of neuroactive amino acids and stimulates *de novo* synthesis of GABA in hippocampal slices. Retigabine also activates and prolongs opening of neuronal K⁺ channels causing a hyperpolarizing shift in the K⁺ current, thereby reducing the excitability of neuronal cells. Eslicarbapazine, also yet to be approved, blocks voltage-gated Na⁺ channels by interacting with site two of the inactivated state of the channels with similar affinity to carbamazepine. Thus, it is important to have an understanding of how these different mechanisms of action may affect each other and the efficacy and safety of the various combinations of AEDs.

To summarize, not all patients are suited to one treatment strategy. It has been argued that strategies should be tailored to each patient's requirements depending on patient scenario, and this logic resonates.³⁸ If a first AED fails due to lack of efficacy but produces no side effects its dose should be increased within prescribing limits. The limit is arbitrary to an extent and it is possible to reach a point beyond which increasing the dose will not be beneficial despite the absence of side effects. Conversely, if a drug fails due to a lack of efficacy and side effects, it is possible to revert back to a lower dose that is better tolerated and to add a second AED.

Table 1 summarizes other scenarios for which add-on or substitution therapies may be beneficial. In conclusion, polytherapy is a rational and effective maneuver for many patients. Furthermore, polytherapy will be established on a much firmer foundation by studies comparing various combinations in a rigorous manner for specific seizure types and patients. As for all situations in a medical setting, following a blind strategy without consideration of individual circumstances is never in the best interest of the patient.¹⁹

The Future of Antiepileptic Drugs and Emerging Novel Therapies

Failure of the newer AEDs to produce significant improvements in seizure control for the majority of patients refractory to older AEDs continues to provide impetus for the development of more effective treatments.⁶⁶ The limited success with newer AEDs might be attributed to the strategies by which they were developed, which mainly relied on random screening in relatively crude animal seizure models, structural alteration of existing agents, or rational drug design based on a limited understanding of the pathophysiology of seizures.⁶⁷ Conversely, the surprising ability of these albeit unsophisticated approaches to identify compounds with unique pharmacologic profiles has been highlighted, including novel mechanisms of action, broader efficacy spectra, or improved pharmacokinetics.⁶⁸

Table 1: Patient Scenarios that May Favor Sequential Monotherapy (Substitution) versus Polytherapy (Add-on)

Add-on	Substitution
Inadequate control with two sequential monotherapies	Patient failed a single monotherapy at adequate doses
First AED appropriate, provided partial control	First AED has disadvantages (e.g. frequent monitoring, high cost, known teratogenicity in woman of childbearing age), or pregnancy is anticipated
No anticipated drug interactions	Drug interactions expected
Patient risk-averse or consequences of seizure exacerbation are high	Seizure exacerbation unlikely
Patient tolerating first AED	Patient not tolerating first AED

AED = antiepileptic drug. Adapted from French and Faught, 2009.¹⁹

It is likely that future improvements in outcome will be incremental rather than transformative.⁶⁸ Regardless, there is a more focused approach with the development of compounds boasting novel mechanisms of actions that act on molecular targets derived from advances in the knowledge of seizure pathogenesis.⁶⁹ Time will tell whether these pharmacologic improvements will translate into superior effectiveness over the existing agents in clinical practice. Notably, many of these emerging compounds are concurrently being developed for the treatment of other neurological or psychiatric conditions, some of which may co-exist with epilepsy. These wider choices will provide a welcome expansion of the pharmacological armamentarium for the treatment of drug-resistant epilepsy and will potentially allow drug selection to be more individualized.⁷⁰

However, drugs developed under current strategies and administered systematically are unlikely to provide the answer to the challenges of drug-resistant epilepsy. They are failing because of limited approaches to drug development and intrinsic patient factors, including possible genetic differences and impaired access of AEDs to the seizure focus,⁶⁶ that have not been addressed adequately. To overcome these problems, novel drug-delivery techniques (e.g. polymers) aiming to bypass the systematic circulation to allow drugs to reach the epileptogenic focus directly are being investigated.⁷¹ Furthermore, animal models of chronic epilepsy instead of acute seizures should be better used for pre-clinical screening of compounds.⁷⁰

It is critical to decipher the pathogenesis of pharmacoresistance. One method to achieve this is to study ways to identify patients who would or would not respond to particular AEDs with known mechanisms of action. Pharmacogenomics holds the potential to inform prescription of existing drugs or develop novel compounds based on the individual genetic profiles of patients, but conceptual and technical hurdles remain to be overcome before its clinical impact can be anticipated. However, the ultimate challenge in epilepsy therapeutics is to identify pharmacologic approaches that will prevent the development and progression of epilepsy in high-risk patients. Cell transplantation and gene therapy are examples of such methods and are in early pre-clinical stages of evaluation.⁶⁶ Furthermore, larger and better randomized controlled studies are needed to determine the optimal time and method to combine AEDs.⁴⁰

Conclusions

It will not be possible to determine which polytherapy regimens are most effective with the least toxicity for different seizure types unless more information becomes available. It is known that certain types of polytherapy are effective and well-tolerated in certain patients, but physicians need guidance on which specific regimens to select, particularly which add-on AED would be best to combine with specific monotherapy drugs. Although this can already be predicted to some extent based on adverse event profiles, it cannot be predicted satisfactorily based upon efficacy. The solution to this dilemma is to conduct well-controlled studies of specific combinations. As it is not possible to test all the different pairs of drugs and our knowledge of drug mechanisms is fragmentary, shrewd selection of AEDs for polytherapy studies should be based on what 'ought' to be a rational combination (based on presumed major mechanism of action) and more

based on the empiric results from animal studies. Experiments, whether human or animal, must take into account pharmacokinetic interactions and must measure toxicity, not just efficacy.¹⁹ ■



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