Selecting Rational Drug Combinations in Epilepsy

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Abstract Monotherapy remains the standard initial therapy of epilepsy, but when the first antiepileptic drug (AED) fails, combination therapy may be considered. The choice of combination therapy should take into consideration pharmacokinetic interactions, as well as pharmacodynamic interactions related to mechanism of action. There is evidence that an AED combination with different mechanisms of action is more likely to be successful than a combination with the same mechanisms. The combination of lamotrigine and valproate has been demonstrated to be synergistic in its efficacy. However, there are limited data to support other synergistic AED combinations.

Key Points

After the first antiepileptic drug (AED) fails due to insufficient efficacy, alternative monotherapy and adjunctive therapy are equally efficacious and tolerated.

Combining AEDs with different mechanisms is more likely to be effective than combining AEDs with the same mechanism of action.

AED combinations should avoid unfavorable pharmacokinetic interactions.

The combination of valproate and lamotrigine is the only combination with proven synergy in humans.

1 Monotherapy Versus Polytherapy in the Treatment of Epilepsy

The current standard initial treatment of epilepsy is with monotherapy, using the antiepileptic drug (AED) which is most appropriate for the patient’s seizure type, as well as for the patient’s specific history and background. However, this has not always been the case. In the 1970s and early 1980s, polytherapy was the rule. Combinations of phenobarbital and phenytoin were often the initial treatment, and the two AEDs were even combined in a single pill for convenience. With the introduction of additional AEDs, primidone, carbamazepine, clonazepam, and valproic acid, combination therapies were at times associated with unfavorable interactions and toxic adverse effects. The term ‘polypharmacy’ was introduced, with negative connotations. A number of studies reviewed the potential benefits of reducing polypharmacy. For example, Shorvon and Reynolds noted that among 29 patients who were converted from polypharmacy to monotherapy, 55% had improved seizure frequency and only 17% had worsening seizure control [1]. Similarly, Schmidt reported that among 36 patients who were reduced from two AEDs to a single drug therapy, only 17% had an increase in seizure frequency. Surprisingly, 36% had an improvement in seizure control, including two patients with complete seizure control [2]. Lesser and colleagues evaluated the therapeutic efficacy and toxicity of high-dose monotherapy using carbamazepine or phenytoin in patients with previously uncontrolled seizures, and found that treatment with a single drug was equal to or better than polypharmacy, but only a few patients became free of seizures [3].

With the introduction of many new AEDs, most of which are Food and Drug Administration (FDA) approved only for adjunctive therapy, the notion of rational
Polytherapy was introduced, evaluating harmonious or synergistic AED combinations. In comparison with classical AEDs, some newer AEDs were less sedating, had an improved tolerability profile, and had a lower potential for pharmacokinetic interactions, making them suitable adjunctive agents. It was proposed that the excessive AED load rather than the number of AEDs may have played a role in poor tolerability [4, 5], and low doses of AEDs in combination may be better tolerated. Drug load was estimated as the prescribed dose divided by the defined daily dose assigned by the World Health Organization. For example, the defined adult daily dose is 1000 mg for carbamazepine, 1500 mg for valproate, and 300 mg for lamotrigine [6]. When the AED load was equal, polytherapy did not necessarily cause more toxicity than monotherapy [5]. A multicenter, double-blind, randomized clinical trial compared carbamazepine monotherapy with a combination of carbamazepine and valproate using equal drug loads in 130 adult patients with untreated generalized tonic-clonic or partial seizures. Patients received 400 mg of carbamazepine or 200 mg of carbamazepine plus 300 mg of valproate per day. No statistical differences were found between the two treatments in seizure reduction, adverse effects, or neuropsychological scores. Even though the difference did not reach significance, fewer polytherapy patients withdrew because of adverse effects (14 vs 22%) [7]. However, a large cross-sectional survey failed to find a relationship between adverse effects, number of AEDs, or drug load in 809 patients with refractory epilepsy, 627 of whom were on polytherapy [8]. The authors suggested that individual patient susceptibility, type of AED used, and physician judgment and choice of AEDs played a larger role in adverse effects than the number of drugs and the drug load [8].

2 Initial Therapy for Epilepsy

Monotherapy continues to be the standard for initial therapy. The choice of the first AED is beyond the scope of this manuscript. In general, the first AED has to be chosen based on its efficacy against the seizure type in question, its safety, and its tolerability, taking into consideration the patient’s specific comorbidities [9]. Other factors to be considered are gender, age, cognitive function, social factors, and urgency of treatment—drugs that require a slow titration may not be appropriate when seizure severity and frequency require rapid action.

Ideally, the initial AED will have undergone a successful monotherapy clinical trial. Such trials are most available for focal epilepsy. Comparative trials have been helpful in guiding the initial AED choice. For example, large cooperative veteran administration trials demonstrated that carbamazepine and phenytoin had better tolerability than phenobarbital and primidone, and carbamazepine had advantages over valproate for the treatment of focal seizures with and without evolution to generalized tonic-clonic activity [10, 11]. Comparative trials that included newer AEDs found lamotrigine and oxcarbazepine to have better tolerability than immediate-release carbamazepine [12–15], and lamotrigine to have a better balance of tolerability and efficacy in comparison with carbamazepine, gabapentin, oxcarbazepine, and topiramate [16]. On the other hand other studies found lamotrigine, levetiracetam, zonisamide, and lacosamide to be equivalent to controlled-release carbamazepine [17–20]. In addition, eslicarbazepine acetate received approval for monotherapy use based on a withdrawal to monotherapy study in patients with drug-resistant focal seizures [21]. Less data are available to guide the initial AED choice in generalized epilepsy. In general, evidence of efficacy as adjunctive therapy may be acceptable for using an AED as initial therapy. A large trial established ethosuximide as the first drug of choice for generalized absence seizures [22]. Much evidence exists that valproate is the most effective AED in the treatment of generalized tonic-clonic seizures in idiopathic generalized epilepsy [23, 24]. However, its teratogenicity precludes its use as initial therapy in women of child-bearing potential. Lamotrigine, levetiracetam, and topiramate are often considered as first-line therapy, based on adjunctive therapy trials [25–27]; as is zonisamide, with less rigorous evidence. For generalized myoclonic seizures, valproate is known to be effective, but levetiracetam may be considered based on efficacy demonstrated in adjunctive therapy [28].

3 If the First Drug Fails, Should It be Adjunctive Therapy or Alternative Monotherapy?

Approximately 50% of patients with epilepsy become seizure free with the first AED [29, 30]. When the first AED fails due to idiosyncratic toxicity or lack of tolerability at a low dose, it is clear that it should be replaced with alternative monotherapy [31]. However, what to do after the first drug has failed due to lack of efficacy has been a matter of debate. The studies that have addressed this question have failed to find statistically significant differences between the approaches of monotherapy substitution and adjunctive therapy. In a prospective study of patients who failed the first AED due to lack of efficacy, either monotherapy substitution (35 patients) or add-on treatment was undertaken (42 patients) [32]. There was no statistically significant difference in either seizure-freedom rates (defined as no seizures for at least 1 year) or incidence of intolerable side effects, although the results were
slightly in favor of adjunctive therapy. The seizure-free rate was 17% with monotherapy substitution and 26% with adjunctive therapy; intolerable side effects occurred in 26% after substitution monotherapy and 12% after adjunctive therapy [32].

The question was again addressed in a multicenter, randomized, controlled, open-label trial in patients with partial epilepsy failing a single drug [33]. Randomization was to alternative monotherapy in 76 patients and adjunctive therapy in 81. The AED choice and dose adjustments were according to physician judgment. Patients were followed up for 12 months or until withdrawal from the allocated treatment. There was no significant difference between groups in 12-month probability of remaining on the assigned treatment (55% in patients randomized to alternative monotherapy and 65% in those randomized to adjunctive therapy), in 12-month probability of remaining seizure free (14% for alternative monotherapy and 16% for adjunctive therapy), or in the adverse effects (51% of patients treated with alternative monotherapy and 37% of those treated with adjunctive therapy).

Another multicenter, prospective, observational study recruited 124 children and 207 adults who failed the first monotherapy. The failure was due to lack of efficacy in about 73.9% and adverse effects in 26.1% [34]. There was no difference between the groups in retention time, hospital admissions, days off-work and off-school, or quality of life. Failure of therapy was noted in 27.2% of alternative monotherapy patients and 25% of adjunctive therapy patients. There was no difference between groups in reported adverse experiences (46.4% of patients on monotherapy and 40.2% on adjunctive therapy) or serious adverse experiences (9.6 vs 8.7%) [34].

The most recently published study was an open, prospective, controlled trial in patients with partial seizures that persisted despite treatment with the first AED [35]. Neurologists were randomized to prescribe either alternative monotherapy or add-on treatment. Among 264 patients evaluated there was no difference in the primary outcome of 2 months of seizure freedom after 6 months of treatment (51% in the alternative monotherapy group and 45% in the adjunctive therapy group). Similarly, there was no significant difference in the percentage of patients achieving a 50% seizure reduction at 6 months (76% in the monotherapy group and 84% in the adjunctive therapy group) or in the quality of life measures or tolerability [35].

There are common sense clinical scenarios that may favor alternative monotherapy when the first AED fails to control seizures. These include total lack of efficacy of the first AED (as opposed to partial efficacy), compliance challenges (compliance will likely be easier with monotherapy), a patient already taking multiple drugs for other indications (particularly seniors with other comorbidities), the need to limit the number of drugs due to pregnancy or pregnancy potential, and financial limitations (two prescriptions will be more costly than one).

Situations that may favor add-on therapy include partial efficacy of a first AED that was well-tolerated, or that was tolerated only at doses insufficient to produce seizure freedom, or when the add-on AED being considered does not have sufficient evidence for monotherapy efficacy. Add-on therapy may also be favored in a subject with frequent or severe seizures in whom the risk of recurrent seizures is high when the first AED is withdrawn.

Similarly to the considerations of choosing the first AED, the add on AED choice should be effective against the seizure types present, should not have the potential of seizure exacerbation, should have a favorable safety and tolerability profile, and should be appropriate considering comorbidities, age, gender, and urgency of action. In addition, the potential for favorable and unfavorable pharmacokinetic and pharmacodynamic interactions should be considered, including pharmacodynamic interactions related to mechanism of action.

4 Pharmacokinetic Antiepileptic Drug (AED) Interactions

Pharmacokinetic interactions are most often related to enzyme induction or inhibition [36]. Enzyme-inducing AEDs include phenobarbital, primidone, phenytoin, and carbamazepine (Table 1). These AEDs induce multiple P450 enzymes, increasing the clearance of drugs metabolized by these enzymes. Some newer AEDs are selective enzyme inducers. For example, oxcarbazepine and eslicarbazepine are weak inducers of CYP3A4, which metabolizes estrogen [37].

Enzyme inhibitors result in reduction of clearance and prolongation of the half-lives of AEDs metabolized by these enzymes (Table 1). Valproate inhibits the metabolism of phenobarbital, ethosuximide, carbamazepine epoxide (active carbamazepine metabolite), lamotrigine, and rufinamide, resulting in increased serum concentrations of these compounds. Felbamate inhibits the metabolism of phenytoin, valproate, and carbamazepine epoxide. New AEDs are occasionally selective weak inhibitors. For example, oxcarbazepine and topiramate are weak inhibitors of CYP2C19, which metabolizes phenytoin, and may cause an increase in phenytoin level.

Some AEDs are not metabolized (gabapentin, pregabaline, vigabatrin) or not metabolized in the liver (levetiracetam), which predicts absence of significant pharmacokinetic interactions.

Interactions may also result from competition for protein binding. Highly protein-bound AEDs may displace each
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<th>AED</th>
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<th>Hepatic enzyme induction</th>
<th>Hepatic enzyme inhibition</th>
<th>Key interactions with other AEDs</th>
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<td>Brivaracetam</td>
<td>High</td>
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<td>May increase phenytoin and carbamazepine epoxide concentrations; Enzyme-inducing AEDs may reduce brivaracetam concentration</td>
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<td>Carbamazepine</td>
<td>High</td>
<td>+++</td>
<td>–</td>
<td>Reduces concentrations of AEDs metabolized by liver; Carbamazepine epoxide increased by valproate, felbamate</td>
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<tr>
<td>Clobazam</td>
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<td>+</td>
<td>+</td>
<td>CYP2C19 inhibitors (including cannabidiol) increase concentration of active metabolite</td>
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<tr>
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<td>–</td>
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<td>–</td>
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<td>Felbamate</td>
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<td>+</td>
<td>++</td>
<td>Increases concentration of phenytoin, valproate, phenobarbital, carbamazepine epoxide; reduces carbamazepine concentration</td>
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<td>None</td>
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<td>Valproate increases lamotrigine concentration</td>
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<td>–</td>
<td>None</td>
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<td>+++a</td>
<td>+c</td>
<td>May increase phenytoin concentration; Enzyme-inducing AEDs may reduce active metabolite concentration</td>
</tr>
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<td>–</td>
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<td>–</td>
<td>Reduces concentrations of AEDs metabolized by liver; Phenytoin concentration increased by felbamate, oxcarbazepine, eslicarbazepine, topiramate</td>
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<td>Pregabalin</td>
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<td>–</td>
<td>None</td>
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<td>–</td>
<td>Reduces concentrations of AEDs metabolized by liver; Primidone/phenobarbital ratio decreased by enzyme inducing AEDs; phenobarbital concentration increased by valproate, felbamate</td>
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<td>Rufinamide</td>
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<td>–</td>
<td>Enzyme-inducing AEDs may reduce tiagabine concentration</td>
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<tr>
<td>Topiramate</td>
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<td>+b</td>
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<tr>
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<td>–</td>
<td>+++</td>
<td>Increases concentration of phenobarbital, lamotrigine, rufinamide, ethosuximide, carbamazepine epoxide; reduces protein binding of phenytoin</td>
</tr>
<tr>
<td>Vigabatrin</td>
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<td>+</td>
<td>–</td>
<td>May reduce phenytoin concentration</td>
</tr>
<tr>
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<td>Intermediate</td>
<td>–</td>
<td>–</td>
<td>Enzyme-inducing AEDs may reduce zonisamide concentration</td>
</tr>
</tbody>
</table>

*AED* antiepileptic drug, – absent, + minimal, ++ intermediate, +++ pronounced

aHigh: > 90%; intermediate: ≥ 50 to ≤ 90%; low: < 50%
bApplies to dose ≥ 200 mg
cApplies to dose ≥ 900 mg
other from serum proteins, with a resulting increase in protein-free fractions. The protein-free fraction may also be increased in low protein states, hepatic and renal failure, pregnancy, and old age. The protein-free fraction is more clinically relevant than the total concentration for both toxicity and efficacy. The change in protein binding is of the most clinical relevance when dosing decisions are made based on total serum concentration.

AED combinations should avoid unfavorable interactions. In particular, enzyme inducers may make the adjunctive AED less effective if it is metabolized in the liver, requiring a higher dose. Some combinations cause increased levels of certain toxic metabolites. For example, the concentration of carbamazepine epoxide, responsible for some carbamazepine toxic adverse effects, may increase when using carbamazepine with valproate or with felbamate [38, 39]. In addition, the concentration of some toxic valproate metabolites and the risk of valproate-induced hyperammonemia may increase with a concomitant enzyme inducer [40, 41]. Enzyme inhibitors may be advantageous in allowing lower doses of the adjunctive affected AED. For example, a lower lamotrigine dose may be sufficient with concomitant valproate.

Some adverse interactions may involve pharmacokinetic interactions that are not totally clear. For example, valproate adverse effects are amplified by concomitant topiramate use [42], and an increased risk of hyperammonemia may result from this combination [43]. In a prospective audit of clinical practice, the combination of lacosamide with valproate was the most frequent AED combination leading to lacosamide withdrawal due to adverse effects [44].

5 Pharmacodynamic AED Interactions and AED Mechanisms of Action

Pharmacodynamic interactions are most often related to AED mechanism of action [45] (Table 2). One of the most common mechanisms is enhancement of the inactivated state of the sodium channel, thus blocking rapid repetitive firing. This is the presumed mechanism for phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine acetate, lamotrigine, rufinamide, and lacosamide. Carbamazepine and phenytoin act on the fast-inactivated state (milliseconds), while lacosamide and possibly eslicarbazepine enhance the slow inactivated state (seconds or longer) [46, 47]. Several other AEDs have multiple mechanisms that include action on the sodium channel. These include valproate, felbamate, topiramate, and zonisamide.

Another mechanism of action relates to enhancing γ-aminobutyric acid (GABA) activity. Phenobarbital and other barbiturates prolong the GABA-mediated chloride channel openings, while benzodiazepines increase the frequency of the openings. Vigabatrin increases GABA concentrations at the synapse by irreversible inhibition of GABA transaminase, while tiagabine increases GABA concentration by inhibiting GABA reuptake. Several other AEDs enhance GABA activity in other ways. These include topiramate, valproate, and felbamate. Gabapentin and pregabalin do not interact directly with the GABA-A receptor. However, gabapentin has been demonstrated by magnetic resonance spectroscopy to increase GABA concentration in the brain [48, 49].

A few AEDs act through glutamate receptor antagonism. Perampanel is a selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist, while one of topiramate’s mechanisms of action is antagonism of the kainate- and AMPA-type receptors. It is thought that phenobarbital may also reduce AMPA/kainate receptor-mediated currents. Levetiracetam may also modulate AMPA receptors as a minor mechanism [50]. Felbamate is an N-methyl-d-aspartate (NMDA) receptor antagonist.

Several AEDs act on various calcium channels. Drugs that block the low threshold, “transient”, T-type calcium channel are generally effective against generalized absence seizures. The list includes ethosuximide, valproate, and zonisamide. AEDs that block high-voltage activated calcium channels include topiramate, lamotrigine, levetiracetam, felbamate, phenobarbital, phenytoin, and oxcarbazepine. Gabapentin and pregabalin bind to the alpha-2 delta subunit of the voltage-gated calcium channel, which decreases neuronal calcium currents.

Levetiracetam and brivaracetam bind the SV2A synaptic vesicle protein. Brivaracetam has a higher affinity and appears to be more selective in this action [51]. Although not totally clear, this SV2A binding seems to reduce neurotransmitter release.

Ezogabine/retigabine enhances the activity and prolongs the opening of neuron-specific, voltage-gated potassium channels. This AED has now been taken off the market.

The most important consequence of combining two AEDs with the same mechanism of action is that this may facilitate adverse experiences while the serum concentrations are in the “therapeutic” range. This has been best demonstrated for the combination of two traditional sodium channel blockers. For example, in a double-blind, comparative study, the combination of carbamazepine and phenytoin had a lower retention rate than the combination of carbamazepine and phenobarbital or phenytoin and phenobarbital in institutionalized subjects [52]. Combinations of carbamazepine and lamotrigine have been associated with diplopia and dizziness [53]. In a multicenter, randomized, double-blind, placebo-controlled study of oxcarbazepine add-on therapy, there was a suggestion of more premature withdrawal when the drug was added to
carbamazepine (28.1%) or phenytoin (31.8%) than when it 
was added to a different AED (16.6%) [54]. Similarly, in 
studies of eslicarbazepine acetate, adverse experiences 
were more frequently reported in treatment regimens that 
cluded carbamazepine [55]. Similar findings were noted 
in a pooled analysis of lacosamide clinical trial data [56]. 
The rate of discontinuation due to adverse effects in 
patients randomized to lacosamide was 19.3% in those 
taking an adjunctive sodium channel blocker versus 8.6% 
in those not taking a sodium channel blocker. At the 
highest dosage of 600 mg per day, the rate of discontinu-
ation due to adverse effects was 31% in those taking an 
adjunctive sodium channel blocker as compared to 6.9% in 
those who were not [56].

It was also suggested that there may be greater efficacy 
in combining AEDs with different mechanisms of action 
[31, 57, 58]. Kwan and Brodie [32, 57] found that after 
failure of the first AED, more patients treated with an 
adjunctive AED became seizure free when the combination 
involved a sodium channel blocker and a drug with mul-
tiple mechanisms of action (included in the list were val-
proate, topiramate, and gabapentin), as compared to other 
combinations (36 vs 7%; \( p = 0.05 \)). Based on a review of 
published trials, Deckers and colleagues recommended the 
combination of a sodium channel blocker with a drug 
enhancing GABAergic inhibition [59].

The notion that combinations of AEDs with different 
mechanisms are superior to those of AEDs with a similar 
mechanism was tested in the analysis of a large commercial 
claims database [60]. The study identified 8615 adults with 
a recent partial-onset seizure diagnosis and concomitant 
use of two AEDs, and categorized the patients by AED 
mechanism of action. The mechanism of action categories 
were sodium channel blockers, GABA analogs, SV2A 
binding, and multiple mechanisms. The success of the 
AED combination was assessed by measuring treatment

<table>
<thead>
<tr>
<th>AED</th>
<th>Traditional sodium channel blocking</th>
<th>Multiple mechanisms including blocking sodium channels</th>
<th>Enhancing GABA</th>
<th>Glutamate antagonism</th>
<th>HVA Ca channels</th>
<th>T Ca channels</th>
<th>α2β Ca channel subunit</th>
<th>Binding SV2A</th>
<th>K channel opening</th>
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AED antiepileptic drug, GABA \( \gamma \)-aminobutyric acid, HVA high-voltage activated, SV2A synaptic vesicle glycoprotein 2A

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persistence from the start to the end of the AED combination as well as health care resource use during the combination. Combinations with the same mechanism of action (two sodium channel drugs or two GABA analogs) had the shortest persistence and a greater hazard of discontinuation compared with combinations that had different mechanisms of action. In addition, combinations using two drugs acting on the sodium channel had a higher risk for emergency department visits compared with combinations that included a sodium channel drug and a drug with a different mechanism. Combinations that included two GABA analogs had a higher risk for inpatient admission than the combination of a GABA analog and a drug with a different mechanism [60]. With the recent marketing of brivaracetam, two SV2A analogs are now available. Their combination seems to be unfavorable as well. In the brivaracetam clinical trials, adjunctive levetiracetam use was associated with decreased brivaracetam efficacy [61–63].

6 Synergistic and Antagonistic Combinations of AEDs and Other Seizure Therapies

There has been a great interest in the notion that particular AED combinations may be advantageous, but there are only limited human data in support of specific combinations [64, 65]. The ideal synergistic combination has supra-additive efficacy and infra-additive side effects. However, either of these properties alone would be advantageous [66]. The effectiveness of specific AED combinations has been best studied in animal models, using the method of isobolography [67, 68]. This involves administering two AEDs in various proportions and identifying the doses required to produce a specific effect. The combination is supra-additive when the two drugs combined produce a greater effect than the sum of the individual AEDs and infra-additive if the two drugs combined produce a lesser effect than the sum of the individual AEDs. This method, used mainly to investigate efficacy of AED combinations, has supported a large number of combinations as being synergistic. However, solid human data exist only for one combination, that of valproate and lamotrigine. The synergy between valproate and lamotrigine was first noted in a study of conversion to lamotrigine monotherapy [69]. The study enrolled patients who were not fully controlled with valproate, carbamazepine, phenytoin, or phenobarbital monotherapy. After the baseline phase, patients entered a 16-week add-on phase during which the original AED dose remained unchanged, followed by an attempt to withdraw the original AED to achieve lamotrigine monotherapy. During the add-on phase, there was a significantly greater responder rate among patients taking valproate (64%) than those taking carbamazepine (41%) or phenytoin (38%). The findings were confirmed in a prospective study of 20 adults with refractory complex partial seizures not previously exposed to valproate or lamotrigine, who were scheduled to receive consecutive add-on treatments with valproate, lamotrigine, or the valproate and lamotrigine combination [70]. Each treatment period consisted of a dose optimization phase followed by a 3-month evaluation phase at stabilized serum concentrations. Only patients not responding to one treatment proceeded to the next. A 50% or greater reduction in seizure frequency was observed with valproate in three out of 20 patients and with lamotrigine in four of the remaining 17 patients. Among the remaining 13 patients who did not respond to either valproate alone or lamotrigine alone, eight responded to the combination, and four of these were seizure free. The improved response was not due to the known pharmacokinetic interaction between valproate and lamotrigine, as the peak serum concentrations of both valproate and lamotrigine were lower than during separate administration [70]. The synergistic interaction of valproate and lamotrigine was further demonstrated in institutionalized developmentally disabled adults with refractory epilepsy [71]. Monthly convulsive seizures and AED regimen were charted over 30 years, allowing the comparison of AED regimens in their effect on seizure frequency. The study found that dual therapy provided better efficacy than monotherapy, while combination of three AEDs had no advantage over two AEDs. The combination of lamotrigine and valproate provided significantly better efficacy than other combinations, particularly in patients with focal epileptiform abnormalities. The superiority of this combination was not explained by pharmacokinetic interaction [71]. The findings were again confirmed in a follow-up study with an expanded database [72].

Other combinations have much weaker evidence for synergy. A small case series suggested that the combination of ethosuximide and valproate may be effective for generalized absence seizures when each AED alone has failed [73]. One study found that the concomitant use of lamotrigine predicted favorable response to levetiracetam [74]. When lacosamide is used in conjunction with a non-sodium channel blocking AED, there was not only a suggestion of better tolerability, but also better efficacy than when used in conjunction with a sodium channel blocker [56, 75]. In a post hoc pooled clinical trial data analysis, the median percent seizure reduction at 400 and 600 mg per day was 39% and 42.7% in patients taking a concomitant sodium channel blocker versus 62.5 and 79% when the concomitant AEDs did not include a traditional sodium channel blocker. Similarly, the 50% responder rate at 400 and 600 mg per day was 39.9 and 42.4% with a traditional sodium channel blocker, and 62.3 and 79.2% in
the absence of a traditional sodium channel blocker [56]. In a post hoc pooled analysis of eslicarbazepine acetate clinical trial data, patients taking concomitant carbamazepine had less marked improvements in efficacy outcomes than those taking other concomitant AEDs, although the differences in outcome did not reach statistical significance [76]. Patients taking concomitant carbamazepine also had higher placebo-adjusted rates of dizziness, diplopia, vomiting, and nausea than those not taking carbamazepine [76].

With most AED trials it was not possible to demonstrate superior efficacy with any specific adjunctive AED or AED mechanism of action. For example, a pooled analysis of ezogabine/retigabine placebo-controlled trials failed to show a difference depending on whether the AED regimen included an adjunctive sodium channel blocker or not [77]. A post hoc analysis was also conducted to assess the impact of concomitant AEDs on perampanel efficacy and tolerability. As expected, efficacy was less in the presence of an enzyme-inducing AED. However, efficacy was not affected by the presence or absence of a non-enzyme-inducing sodium channel blocker. Efficacy was reduced in the presence of multiple AEDs, possibly reflecting more drug resistance rather than a pharmacodynamic interaction. Tolerability was not affected by concomitant AED mechanism or AED number [78].

Some synergistic interactions were demonstrated in the efficacy of combined AED and non-AED therapies. In children treated with the ketogenic diet for drug-resistant epilepsy, a > 50% seizure reduction was significantly less likely in combination with phenobarbital, and more likely in combination with zonisamide [79]. In addition, there seemed to be a synergistic interaction in the combination of the ketogenic diet with vagus nerve stimulation [80]. In patients who underwent temporal lobe epilepsy surgery for drug-resistant epilepsy, the perioperative use of levetiracetam predicted a favorable outcome as early as 4 months after surgery, with increasing advantage by 5 years after surgery [81].

7 Conclusion

The most important principle governing rational drug combinations lies in the avoidance of unfavorable pharmacokinetic and pharmacodynamic interactions. In addition, it is best if the combination includes AEDs with different mechanisms of action. The combination of two traditional sodium channel blockers should be avoided, mainly because of toxicity. There is only limited evidence for specific synergistic AED combinations, except for the combination of lamotrigine and valproate. Synergistic AED combinations that appear exceptional in animal models should be tested in well-designed clinical trials to help guide clinical practice. In addition, a better understanding of epilepsy pathophysiology in individual patients should help refine the science of AED rational drug combinations.

Compliance with Ethical Standards

Funding None.

Conflict of interest Bassel Abou-Khalil declares no conflict of interest.

References


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