Combination Therapy in Epilepsy: What, When, How and What Not!

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Summary

The role of combination therapy as a treatment strategy for epilepsy is undergoing reevaluation. A growing appreciation that all seizures cannot be controlled by monotherapy and the introduction of over 14 new antiepileptic drugs (AEDs) for the adjunctive treatment in refractory epilepsy in the past twenty years has triggered a renewed interest in combination therapy.

However, the experimental and clinical evidence in support of “rational polytherapy” is sparse, with only the combination of sodium valproate and lamotrigine demonstrating synergism. Robust evidence to guide clinicians on how and when to combine AEDs is lacking and current practice recommendations are largely empirical.

Introduction

Epilepsy is a common condition that occurs globally in around 50 million people (Sander 2003). Each year 40–190 per 100 000 people are newly affected, with a higher incidence in resource-poor countries. Treatment options have become plentiful as the number of available antiepileptic drugs (AEDs) has swelled worldwide over the last two decades. Appropriate pharmacological management can result in seizure freedom for 60–70% of patients (Kwan and Brodie 2000, Mohanraj 2006, Brodie 2012).

Overall, however, a substantial minority of patients fare relatively poorly, with around 30% of this population never achieving optimal seizure control (Mohanraj 2006) a figure that appears not to have significantly improved over the previous decade (Loscher 2011), despite the introduction of several new medications.

Until the early 1980s, it was accepted clinical practice to initiate treatment in patients of new onset epilepsy with more than one agent [ (Reynolds and Shorvon 1981). Some standard antiepileptic drugs were in fact, available as fixed dose combinations (eg Phenytoin and Phenobarbitone). The probable basis for this practice was the premise that low dose combination therapy was less toxic than high doses of a single drug. All AEDs available at that time, such as acetylcysteine, barbiturates, benzodiazepines, succinimides and hydantoins, were associated with considerable CNS toxicity, and mechanisms of AED action were not well elucidated.

Subsequently, concerns were raised about polytherapy including unfavourable interactions, and difficulty in evaluating individual pharmacological effects.

Older AEDs are notorious for their ability to produce pharmacokinetic interactions among themselves as well as with other medications via their effect on the hepatic cytochrome P450 (CYP) enzyme superfamily. (Pastalog and Perucca 2003). It became recognized that combining traditional agents did not necessarily improve seizure outcome and could increase the propensity for side effects (Schmidt 1982). Reynolds et al conducted a series of prospective and retrospective studies to demonstrate that many patients with newly diagnosed epilepsy could be successfully treated with a single AED (Reynolds et al 1976).

Patients reduced from polytherapy to monotherapy experienced fewer side effects and sometimes better seizure control (Shorvon and Reynolds 1979, Schmidt 1983 Albright 1985).

Thus monotherapy became the new dogma for the management of newly diagnosed epilepsy.

All the above data belongs to the era of traditional AEDs with limited and overlapping mechanisms of action. But the last two decades have seen the introduction of over fifteen new anti-seizure agents. Many of the newer agents possess broader and sometimes novel mechanisms of action, encouraging investigators to search for a pharmacomechanistic approach to combining AEDs with the goal of achieving synergism. Some newer AEDs have been shown to possess better adverse-effect profiles than their older counterparts thus raising the possibility of better tolerated drug combinations.

Both of the above factors have improved the potential for a good outcome with polytherapy regimens. Combining drugs with different mechanisms of action is a common strategy in the treatment of many medical disorders. For instance, in patients with a history of cerebrovascular disease, combination therapy with perindopril (an ACE inhibitor) and indapamide (a diuretic) produced greater risk reductions than did perindopril alone. (PROGRESS trial 2001). In infectious diseases, several antimicrobials are used simultaneously for the treatment of tuberculosis and HIV infection to reduce the risk of drug resistance. Combination therapy is the norm in cancer chemotherapy. Polytherapy is also used routinely in some neurological conditions, even at treatment initiation. Thus, in patients with Parkinson’s disease, levodopa is combined with a dopa decarboxylase inhibitor to reduce its systemic breakdown.

In epilepsy too all the newer drugs have been introduced because they demonstrated their efficacy as add-on therapy in refractory epilepsy, implying that many patients can and do benefit from polytherapy.

Despite this promise of combination therapy, a robust evidence base is lacking, and controversy continues over when and how AEDs should be combined. In a randomized comparison of adjunctive therapy versus alternative monotherapy in patients with partial epilepsy taking a single AED, no difference in seizure freedom was identified between these strategies (Beghi et al 2003) Adverse events were also similar in both treatment arms. A similar observation has been reported in a handful of pragmatic studies (Kwan and Brodie 2000, Mohanraj and Brodie 2005).

There is a paucity of controlled studies investigating the question of how combination therapy can be used optimally in the management of epilepsy, particularly when to combine and what agents to use. The ideal way to test for synergism of antiepileptic drugs the clinical setting has not been agreed upon. The most scientifically valid approach to study such potential combinations is the isobolographical method (Figure 1), in which two AEDs are given in various dose proportions to identify the most effective regimen in terms of seizure control (Mawer et al 1995). This approach has been successfully applied in animal studies (Temkin 2001) but presents logistic difficulties in the
When to Consider Combination Therapy?

In current day practice, every newly diagnosed patient with epilepsy should be initiated on appropriate monotherapy, based on the seizure type and the epilepsy syndrome. This approach is reasonable because in 60% of newly diagnosed epilepsy patients, seizures are controlled on the first monotherapy (Kwan and Brodie 2005). If the first monotherapy cannot be used in full doses because of idiosyncratic side effects, alternative monotherapy should be tried.

If on the other hand, the first drug fails to achieve seizure control despite adequate doses, there is a wide variation in the strategies adopted. In a survey conducted among European physicians from different countries the percentage that adopted an add on AED strategy varied from 23% to 67% (Baldy-Moulinier et al 1998). On the other hand a survey among epileptologists in the United States, 100% of them preferred to use an alternative monotherapy after the failure of the first drug(Karceski 2005). Evidence from recent trials, are weak but suggest an insignificant trend in favour of add-on therapy over substitution, both in terms of seizure freedom and intolerable side effects (Kwan and Brodie 2000, Beghi 2003)

Among 780 newly diagnosed epilepsies, 47% became seizure free with the first monotherapy. Another 10% responded to the second monotherapy. Only 2.3% of the cohort entered remission with the third monotherapy (Mohanraj and Brodie 2006). These observations suggest that when two appropriately chosen monotherapy regimens have failed, the chance of success with the third monotherapy (Mohanraj and Brodie 2006). These second monotherapy. Only 2.3% of the cohort entered remission free with the first monotherapy. Another 10% responded to the substitution, both in terms of seizure freedom and intolerable drug(Karceski 2005). Evidence from recent trials, are weak but suggest an insignificant trend in favour of add-on therapy over substitution, both in terms of seizure freedom and intolerable side effects (Kwan and Brodie 2000, Beghi 2003)

Choosing the Next Antiepileptic Drug : What Matters?

With at least 15 AEDs available, 105 dual-therapy combinations are possible. Such an overwhelming number of options makes ‘rational polytherapy’ not only of academic interest but a practical necessity. Although a number of two-drug combinations have been tested in animals, there is a paucity of data on the comparative efficacy of different AED combinations in clinical practice.

For patients in whom substitution or addition of an AED is required, selection of the new agent depends on many factors. These include seizure type or syndrome, adverse effects, comorbidities, interactions with comedication, age, possibility of pregnancy, learning disabilities, adherence, and formulation (French et al 2004)

Rational polytherapy

The concept of rational polytherapy has evolved as a system for planning treatment (Table 1). The theory is based on what is known and believed of pharmacokinetic and pharmacodynamic properties of drugs. In epilepsy it implies selection of a combination of antiepileptic drugs that will produce optimum seizure control with minimal adverse effects. This requires extensive knowledge of drug mechanism(s) of action, clinical effects, adverse effects, drug- drug interactions and therapeutic index.

Mechanism of drug action

There is limited evidence to suggest that mechanism of action may be useful in choosing appropriate combinations (Gilliam 2004, Hakkarainen 1980).

Combination therapy with complementary mechanisms of action has generally been recommended (Table 2). There is the theoretical consideration that small effects on multiple drug targets may be more optimal than targeting a single mechanism of action (Bianchi 2009).

It has been postulated that selection of AED combinations by mechanism of action may be useful because AEDs with similar mechanisms may have similar side effect profiles. AEDs with similar mechanisms of action may cause an excessive amount of additive side effects when used in combination. Deckers et al (1997) reviewed 39 papers on AED combination therapy with two drugs. There was a wide variability in the method of reporting with most studies focused only on seizure control. The authors conclude that it may be better to combine drugs with different mechanisms of action (Table 3). They recommend a combination of a sodium channel blocker with a GABA mimetic drug to be superior to a combination of two GABA mimetic drugs which in turn is better that two sodium channel blocker AED combination.

However, mechanisms of action have not yet provided meaningful guidelines to aid in the rational choice for polytherapy as there is insufficient evidence to determine whether identical or complementary mechanisms should be targeted. In addition, while it is convenient to conceptualise and categorise the mechanisms of action of AEDs, it is important to bear in mind that our understanding of the pathogenesis of seizure generation and propagation in the individual patient remains rudimentary. It is also likely that some AEDs possess as yet unrecognised modes of action. As we do not understand how seizures are generated and propagated in the brains of individual patients, adding molecules that possess multiple mechanisms of action, such as valproic acid, levetiracetam, topiramate and zonisamide, may be more likely to provide a beneficial pharmacological effect in the setting of refractory epilepsy. (Deckers 2004, Kwan and Brodie 2000)

Table 1: Principles of polytherapy in Epilepsy

- Rational polypharmacy in epilepsy involves combining antiepileptic drugs that
- Have different mechanisms of action
- Do not have complex pharmacokinetic interactions
- Do not have a similar adverse effect profile
- Can be combined in minimum doses to produce maximum effect

clinical setting because of the wide interindividual variation in the pharmacokinetics and pharmacodynamics of different AEDs.

<table>
<thead>
<tr>
<th>Table 2: Mechanism of action of antiepileptic drugs</th>
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</thead>
<tbody>
<tr>
<td>1. Sodium channel blockers</td>
</tr>
<tr>
<td>a. Fast-inactivated state—phenytoin, carbamazepine, lamotrigine, oxcarbazepine, eslicarbazepine</td>
</tr>
<tr>
<td>b. Slow-inactivated state—lacosamide</td>
</tr>
<tr>
<td>2. Calcium channel blockers</td>
</tr>
<tr>
<td>a. Low voltage activated channel— ethosuximide</td>
</tr>
<tr>
<td>b. High voltage activated channel— gabapentin, pregabalin</td>
</tr>
<tr>
<td>3. GABA-ergic drugs</td>
</tr>
<tr>
<td>a. Prolongs chloride channel opening— barbiturates</td>
</tr>
<tr>
<td>b. Increased frequency of chloride channel opening— benzodiazepines</td>
</tr>
<tr>
<td>c. Inhibits GABA-transaminase— vigabatrin</td>
</tr>
<tr>
<td>d. Blocks synaptic GABA reuptake— tiagabine</td>
</tr>
<tr>
<td>4. Synaptic vesicle protein 2A modulation— levetiracetam</td>
</tr>
<tr>
<td>5. Carbonic anhydrase inhibition— Acetazolamide</td>
</tr>
<tr>
<td>6. Multiple pharmacological targets— sodium valproate, felbamate, topiramate, zonisamide, rufinamide</td>
</tr>
</tbody>
</table>

Table 3: Categorization of antiepileptic drugs based on mechanism of action

- Sodium channel blockers
- Calcium channel blockers
- GABA-ergic drugs
- Non-ionic sodium channel blockers
- Synaptic vesicle protein 2A modulation
- Carbonic anhydrase inhibition
- Multiple pharmacological targets

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Thus, our understanding of seizure mechanisms and antiepileptic effect of drugs is still evolving and antiepileptic drug prescriptions can only be based on the major mechanisms of drugs that are currently known.

**Drug Interactions during combination therapy**

The potential for pharmacokinetic and pharmacodynamic interactions is an important consideration when substituting or combining AEDs. Several older AEDs produce pharmacokinetic interactions via their influence on the hepatic cytochrome P450 and other enzyme systems, affecting the clearance of other AEDs and comedications (Table 3)(Kwan 2006). In particular, phenobarbital, primidone, phenytoin, and carbamazepine induce the metabolism of many lipid-soluble drugs including oral contraceptives, cytotoxic agents, antiretrovirals, cardiac antiarrhythmics, immunosuppressants, and warfarin.

Enzyme induction can also contribute to the development of chronic adverse effects, such as reduced bone density, sexual dysfunction, and potentially deleterious changes in cholesterol concentrations and other markers of vascular risk (Perucca 2005).

Valproic acid is a weak enzyme inhibitor, and as such, can slow the clearance of other AEDs such as phenytoin and lamotrigine (Stephen 2003). (Table 3). The newer drugs are less likely to induce hepatic metabolism Interactions of newer AEDs with CYP enzymes is minimal and they are generally less likely to affect the metabolism of other AEDs to a clinically significant extent (Pastalos and Perucca 2003). Levetiracetam and gabapentin are notable for their lack of drug interactions, a clear advantage in combination AED therapy and with other medication. However, oxcarbazepine, eslicarbazepine, felbamate, rufinamide, and topiramate (at daily doses above 200 mg) can all selectively induce the breakdown of the oestrogenic component of the oral contraceptive pill (Burakgazi 2009). Consideration of these potential interactions must be taken into account when treating patients with drug-resistant epilepsy.

**The Valproate Lamotrigine Combination therapy**

The best evidence in favour of a synergism with a particular AED combination is for sodium valproate with lamotrigine (Brodie and Yuen 1997). During a trial in 347 patients designed to

### Table 3: Pharmacokinetics and drug interactions of anti-epileptic drugs (Kwan 2006)

<table>
<thead>
<tr>
<th>AED</th>
<th>Undergoes hepatic metabolism</th>
<th>Affects hepatic cytochrome P450 enzymes</th>
<th>Affects metabolism of other AEDs</th>
<th>Metabolism affected by other AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older AEDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Primidone</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Newer AEDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Effect modes, see section 1.2.*

The best evidence in favour of a synergism with a particular AED combination is for sodium valproate with lamotrigine (Brodie and Yuen 1997). During a trial in 347 patients designed to assess the efficacy of lamotrigine in patients failing monotherapy with sodium valproate, carbamazepine, or phenytoin, a better response was demonstrated for the valproate/lamotrigine combination with 64% patients reporting a 50% or greater seizure reduction, compared with 41% taking carbamazepine/ lamotrigine and 38% on phenytoin/lamotrigine, despite similar circulating lamotrigine concentrations. Supportive data for a synergistic interaction came from a study (Pisani 1999) which reported that seizure freedom can be achieved with lower median doses of valproate and lamotrigine.

Add retrospective study by Poolos in Neurology about VPA/LTG combination 2011

**Other combination therapies**

Other small studies and case studies have made claims for pairing sodium valproate with ethosuximide for absence seizures (Rowan 1983), Phenobarbital with phenytoin for tonic–clonic seizures (Cereghino 1975), vigabatrin with tiagabine for refractory epilepsy (Leach 1994), lamotrigine with topiramate for a range of seizure types (Stephen 1998) and carbamazepine with valproate or vigabatrin for focal seizures (Brodie and Mumford 1999). Although observational at best, these combinations do all involve drugs with different modes of action (Brodie and Sills 2011).

The best studied antagonistic combination is LTG and CBZ. Although it was initially proposed to be a pharmacokinetic effect due to the increase in the toxic epoxy residue of CBZ as a result of LTG administration [56], further studies have found this unfavorable combination is more likely due to a pharmacodynamic effect(Besag 1998, Gidal 1997)

**Polytherapy in special groups**

**Pregnancy : Risk of teratogenicity**

Studies have confirmed higher birth defect rates than expected among children of mothers with epilepsy. Commonly quoted figures are 3–6% for women with epilepsy compared with 2–3% in the general population (Morrow 2006).

The cause is probably multifactorial, but antiepileptic drugs (AEDs) are the main reason for the increased risk. Fetal risks associated with maternal seizures are less well delineated, but
generalised tonic-clonic seizures can induce fetal lactic acidosis and hypoxia and status epilepticus can cause fetal death. Frequent tonic-clonic seizures during pregnancy have been associated with poor cognitive performance in childhood. The challenge for clinicians is to balance these risks and to select a treatment that is effective in preventing major seizures while minimising adverse fetal drug effects. Clarifying the teratogenic potential of a new drug takes a long time, and data comparing the safety of different treatment options have only begun to be available. The past decade has seen intensified clinical research on the subject, with several pregnancy registries reporting pregnancy outcomes after maternal use of AEDs (Meador 2008). This meta-analyses and other studies have demonstrated a greater risk of teratogenicity with polytherapy compared to monotherapy. The risk of teratogenicity increases with the doses and number of AEDs taken (Holmes 2001). Polytherapy is associated with greater risk than monotherapy for both MCMs and cognitive outcome (Harden 2008). Recent findings from prospective pregnancy registers suggest a higher risk of foetal malformation in patients taking valproic acid compared to those receiving lamotrigine alone. (Cunnington 2005, Morrow 2006)

The risks of teratogenicity weigh against the use of polytherapy and current recommendations dissuade the use of polytherapy in pregnancy (Harden CL 2009). A few recent studies suggest that the fetal hazard of AED polytherapy relative to monotherapy may depend more on the degree of exposure to valproate than on the fact of polytherapy per se (Vajda 2010, Holmes 2011).

Where pregnancy is a possibility, and the first AED fails, it would seem sensible to substitute rather than combine antiepileptic drugs, and aim for a low dose without compromising seizure control as far as possible.

**Practice Recommendations**

**Start with Monotherapy**

- Choose AED appropriate for seizure type and epilepsy syndrome, emphasise on safety and tolerability. More than 50% of patients respond to the first appropriately chosen drug in moderate doses. Dose escalation should always be steady and gradual to avoid poor tolerance.
- If the first drug produces idiosyncratic adverse effects or side effects at low doses, substitute with a suitable alternative drug.

**Combination Therapy: When and How**

- If first drug reduces seizures, dose should be escalated to the maximum tolerated dose. If seizure freedom is elusive despite full doses of the first AED, a second drug may be added. The second drug should have a different mechanism of action and should not have an overlapping side effect profile. Drugs with similar mechanisms of action should preferably not be combined. (Refer to Table for mechanisms of action for various AEDs)
- Combination therapy should also be tried after two monotherapy regimens fail, as chances of seizure control on third monotherapy are slim.
- Before considering AED change or combination for lack of effective seizure control, the diagnosis of epilepsy, seizure type and syndrome should be reviewed and compliance of the patient with AEDs should also be confirmed.
- If seizure freedom is achieved on the combination therapy, dose of the first drug may be reduced gradually, if necessary, to avoid drug overload.
- If seizure control is good on the combination, but seizure freedom is still elusive a third drug with a different mechanism of action may be tried in small doses. However adding a fourth or a fifth drug is unlikely to be successful.
- Three drug regimen are generally avoided if possible. Indeed, the vast majority of patients reaching seizure freedom do so with two AEDs, and virtually no one achieves seizure freedom with four AEDs. If a patient is on four or more AEDs, a concerted attempt should be made to reduce the regimen to two or three AEDs.
- Treatment for each patient is individualised based on seizure type, syndrome, age, gender, co-morbid conditions and comorbidities.
- When two monotherapies fail or a combination of two AEDs fails to achieve seizure freedom, the patient qualifies to have drug resistant epilepsy. Such patients should be evaluated for alternative therapeutic strategies such as epilepsy surgery.

**Combination Therapy: When Not**

- Women who are likely to become pregnant should be maintained on monotherapy in moderate doses as far as possible. Suboptimal control of seizures other than tonic clonic seizures during this period may be an acceptable trade off, to reduce the risk of teratogenicity from polytherapy or high drug load. Risk of teratogenicity is highest soon after conception and in the first trimester, hence AED therapy has to be rationalized before conception. High dose valproate either alone or in combination therapy is best avoided throughout pregnancy.

**References**

13. PROGRESS Collaborative Group. Randomised trial of perindopril-based blood pressure lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet*


