Should Monotherapy for Epilepsy Be Reconsidered?

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Abstract

The critical goal of antiepileptic drug therapy is complete seizure control without side effects. For about half of patients, this goal is achievable with the first drug tried. Standard practice has been to switch to a second monotherapy drug if the first fails. It is time to re-think this strategy because relatively few patients achieve complete control with the second and subsequent monotherapy trials, some patients achieve complete control without intolerable side effects with combination therapy, and the new generations of drugs are easier to use in combination because they are more free of pharmacokinetic and pharmacodynamic interactions. An unanswered question is which combinations are most effective for seizure control. Not all patients are appropriate for polytherapy; some are reasonable candidates for additional monotherapy trials. However, if a polytherapy regimen is working, the wisest plan is often to continue it. Monotherapy still rules, but 'polypharmacy' as a pejorative term should be scrapped.

Keywords

Epilepsy, antiepileptic drugs, monotherapy, polytherapy

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For the past 30 years, a dogma of epilepsy treatment has been to start with monotherapy.[1] This still makes sense for several reasons: cost, lower risk of side effects, better compliance, and avoidance of pharmacokinetic (PK) and pharmacodynamic (PD) drug interactions.[2] Furthermore, data from many studies indicate that initial monotherapy produces seizure freedom in 50–70% of patients.

A secondary dogma has been to try at least one more monotherapy, possibly two or three, before embarking on adjunctive therapy trials. That is, sequential monotherapy has been preferred to adjunctive therapy if the first drug fails. This algorithm should be reconsidered because of favorable characteristics of the newer generations of antiepileptic drugs. The major reason has to do with fewer PK interactions; other reasons are fewer PD interactions, the possibility of drug combinations synergistic for efficacy, and safety considerations during the process of conversion from one drug to another. For all of these reasons, since the new drugs started to become available 15 years ago there has been renewed interest in the concept of rational polytherapy.[4]

Pharmacokinetic Interactions

PK interactions are those in which one drug affects the serum concentration, and presumably the brain concentration, of another. Older, hepatic-enzyme-inducing drugs, including barbiturates, phenytoin, and carbamazepine, are notorious for causing PK drug interactions or being the target of interactions caused by other drugs, including each other. There are many fewer pharmacokinetic drug interactions associated with most of the newer generations of antiepileptic drugs.[5] There are virtually no significant PK interactions with adjunctive gabapentin, pregabalin, levetiracetam, and lacosamide. Only one-way interactions occur with lamotrigine, topiramate, zonisamide, and oxcarbazepine; that is, their metabolism is affected by some enzyme-inducing drugs but they rarely precipitate PK-related problems themselves. Lamotrigine is also subject to an enzyme-inhibiting interaction with valproate; valproate greatly reduces lamotrigine clearance. Topiramate and oxcarbazepine can inhibit the metabolism of phenytoin when high phenytoin concentrations trigger the action of the secondary enzyme CYP2C19. With these exceptions, the new drugs as a class are much easier to combine both with each other and with older drugs because of the paucity of clinically significant PK interactions.

Pharmacodynamic Interactions

PD interactions are those in which the biological actions of one drug influence the biological actions of another. PD interactions can be additive, synergistic, or antagonistic. The classic antiepileptic drug

central nervous effects of dizziness, ataxia, and sleepiness are probably additive for most combinations. Sodium channel blockers such as phenytoin and carbamazepine often cause dizziness or diplopia in combination, even when the PK interaction works in the opposite direction to increase mutual clearance. On the other hand, a classic PD interaction that is probably synergistic is somnolence with benzodiazepines plus barbiturates, because they have complementary actions on gamma aminobutyric acid (GABA)-mediated chloride channels. Most older drugs fall into only two general categories of major mechanism of action: they are either sodium channel blockers or GABAergic agents. Because of this, there was less flexibility to avoid use of two drugs of the same class and, therefore, less chance of avoiding additive or synergistic PD adverse effects.

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The new drugs, while they certainly retain many adverse effects classically associated with older antiepileptic drugs, access newer mechanisms for seizure control. This also opens the door to a wider choice of potential side effects: choosing two drugs with different mechanisms of action will often result in a combination without additive side effects. For example, levetiracetam (a synaptic release inhibitor) rarely causes ataxia, so adding it to phenytoin (a sodium channel blocker) is unlikely to precipitate balance problems. Side effects are not always adverse. Sometimes drug side effects are offsetting. Lamotrigine (a sodium channel blocker) is usually not only non-sedating but actually stimulating, so that using it in combination with a more soporific drug such as pregabalin (a calcium current mediator) is unlikely to produce sleepiness and may actually wake the patient up.

Efficacy of Two Drugs versus One

With regard to efficacy, it is still an open question whether a second monotherapy or a first adjunctive therapy is more likely to control seizures. It cannot be assumed that because two drugs have different mechanisms of action that they will have a complementary salutary effect on seizure control. This is true of both partial-onset and generalized-onset seizures, because almost no trials with this design have been carried out. A very old example is the cross-over trial of valproate versus ethosuximide for absence seizures: in this trial, about the same number of children achieved seizure control with either drug as monotherapy or with the combination, and rates of side effects did not differ.[6] No similar trials of modern drugs have been undertaken.

What do we know? We know that a second monotherapy controls seizures completely in some patients. How many? In an oft-cited trial, it was 47% for the first monotherapy but only 13% for the second.[3] In this trial, only 3% eventually achieved seizure freedom with any adjunctive combination, but apparently combinations were tried only after two or three monotherapies. We do not know how many would have been controlled if adjunctive therapy had been the second option, not the third or fourth. In the only study designed specifically to answer the question of whether adjunctive therapy or alternative therapy was best in patients who had failed only one drug, the seizure-free rates were about the same, at 14–16%.[7]

Can we ferret out the answer to this question from a meta-analysis of the many controlled trials of adjunctive therapy for partial-onset seizures? The short answer is 'no,' because most of these trials enrolled refractory patients who had already tried multiple drugs alone or in combination. The few patients enrolled after only one monotherapy are insufficient to compare with the adjunctive placebo rate in any one trial or to the results from patients who have tried several monotherapies.

We also know this: adjunctive therapy works. None of the new drugs approved in the US or Europe work only as monotherapy. In fact, they were all approved for partial-onset seizures as adjunctive therapies first, before any were approved for monotherapy. Indeed, in the US, only a few are approved as monotherapy for partial-onset seizures. These include topiramate for initial monotherapy, lamotrigine for transition to monotherapy from the older drugs only, oxcarbazepine, and felbamate. Levetiracetam, despite its popularity, is not approved for monotherapy. This means that physicians, if they choose to stay within US Food and Drug Administration (FDA)-approved indications, have many more therapeutic options for adjunctive therapies than for monotherapies. Of course, FDA-approved indications do not restrict use based on appropriate physician judgment. Less restrictive guidelines have been published by committees of national organizations,[8] but evidence-based guidelines still require controlled trials for a drug to be recommended, and there are no good controlled monotherapy trials of many of the new drugs.

To summarize, there is no clear evidence one way or the other as to whether the second-choice therapy for seizures should be polytherapy or another monotherapy, not only for efficacy, but also for side effects.[9] The only self-evident advantages of monotherapy are thus cost, ease of use, and compliance.

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What to Add? Does Rational Polytherapy Exist?

This topic has been debated among neurologists for 100 years, since phenobarbital joined bromides in 1909 as the second really effective therapeutic option.

We still do not know for sure. A few older studies suggested that the combination of phenytoin and phenobarbital is more effective than the combination of phenytoin and carbamazepine.[10] There are suggestive, but not definitive, data that the combination of valproate and lamotrigine is synergistic with regard to seizure control.[11] Furthermore, that combination presents a difficult pharmacokinetic challenge. To make matters worse, most of our drugs have multiple mechanisms of action. Nevertheless, these sparse human data provide hints that combinations of drugs with differing primary mechanisms of action are more likely to work.[5] This makes sense, but is very difficult to prove in clinical trials.

In summary, using two drugs with different major mechanisms of action makes some sense, but cannot be considered truly scientifically rational until we know more.

Animal data are thus important because of the problems of titrating two drugs to several proportions of an effective dose in an individual patient and the low numbers of patients on any one combination in a particular clinical trial. There are several published studies using the 'isobolographic' method;[12] this involves determining the ED_{50} (dose of drug that is effective in producing a given end-point in 50% of animals, such as abolition of hind limb extension in the mouse maximal electroshock seizure model), then trying various percentages of the ED_{50} of each drug in combination.

From these and other animal studies, there is some evidence that drugs with different mechanisms of action are synergistic with regard to potency. These include sodium channel blockers plus GABAergic agents, or α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA)-type glutamate receptor blockers with other agents.[12,13] However, using the same methods, two GABAergic drugs used together were found to be synergistic in some experiments,[13] so the answers remain elusive.

In summary, using two drugs with different major mechanisms of action makes some sense, but cannot be considered truly scientifically rational until we know more. However, avoiding two drugs with significant PK interactions or two drugs with similar PD side effects is a good idea, other considerations being equal. To that extent, rational polytherapy exists. If it is possible to combine two drugs at lower doses than the toxic dose of either with better efficacy, the overall 'drug load,' and thus risk of toxicity, may actually be less than with a high level of a single drug.[14]

When to Switch and When to Add Based on Efficacy

There are some good reasons to seriously consider 'adding rather than switching'—a course of action heretofore considered heretical. An earlier resort to polytherapy should be considered as a viable option.[9] However, circumstances will often determine which is best. Who should be considered for a total switch? If the first drug proves worthless (no improvement in seizures) or is intolerable, the choice is easy. It must be stopped and a second monotherapy started. Who should be considered for an additive regimen? If the first drug is almost, but not quite, completely effective, it makes sense to retain it and to gradually add a second drug to achieve the final summit of seizure control.

The more difficult scenario is when there is a modest effect of the first drug. In that circumstance, a common past practice has been to try to switch over completely to a second monotherapy. However, suppose that the two drugs are synergistic? It is even theoretically possible for a drug to be completely ineffective as monotherapy, but to contribute to efficacy as a component of a combination. There is probably not such a drug but, based on animal studies, there is good evidence that many drug combinations are synergistic; that is, that lower doses of each drug in combination may work as well as full doses of either. If such a combination happens to be chosen in this scenario, it might be more effective to use lower doses of both drugs; switching completely could be the wrong course of action.

Two things are clear: there is some risk of more seizures during a switch from one monotherapy to another, and it is a tricky process. It can be done safely, and has been done in several clinical trials,[15] but care and vigilance on the part of the physician is necessary. Gradually reducing the first drug while gradually increasing the second is complicated, and more seizures may occur because it is impossible to guess the equivalent proportions of each drug as the transition is made. Holding the first drug at full dose while ramping up the second drug to full dose is safer, but more likely to produce side effects.

Nevertheless, if this process is chosen, the new drugs still make it easier because one must consider only the PD properties of the drugs—relative efficacy and side effects—not usually the PK interactions. For example, in switching from monotherapy phenytoin to monotherapy valproate, one must worry about how long the phenytoin-caused induction of hepatic metabolism will last. For a time, which is hard to estimate, valproate will be metabolized fast, then, as the hepatic induction wanes, it will be metabolized more slowly. Translating this into a titration schedule for a patient so that therapeutic levels of some drug are always maintained is challenging indeed. On the other hand, transitioning from lamotrigine to oxcarbazepine monotherapy requires only an estimation of what are equivalent efficacy dosages of each medication. That is still not easy;

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it requires assumptions about the relative potency of each drug milligram for milligram, and as discussed above this is not clear even from animal studies.

The answer to the question posed in the title is 'yes'… However, this must be a qualified 'yes,' because there are categories of patients for whom serial monotherapy remains a better strategy.

When to Switch and When to Add—Patient-related Considerations

Our primary job is to prevent seizures. If a so-called 'breakthrough' seizure is more likely with a simultaneous switch of drugs, rather than with addition of a new drug to a full dose of the old one, which is almost certainly true, why would we ever do this?

There are some patients for whom it is appropriate: those who are having significant side effects from the first drug; those with new-onset or very infrequent seizures, for whom the likelihood of a breakthrough seizure is low and for whom it is important to avoid side effects; and those with 'mild' seizures—such as simple partial events—for whom a breakthrough seizure would not be disastrous.

Other than these patients, then, it is a better strategy to hold the first drug at a therapeutic dose, or at least at the patient's currently tolerated dose, and to add the second drug gradually to a 'full target dose.' The full target dose may or may not be the dose recommended by the manufacturer for adjunctive therapy; it is often less because with experience physicians often find that lower doses are effective and better tolerated.

Once the second drug reaches the target dose, the next question arises: should the first drug be tapered off and stopped? What if the patient is doing fine, with no seizures and no side effects on the combination? It is then not unreasonable then to accept this regimen and to make no further changes. Go with it for a while to see if this happy state of affairs persists. Of course, this is not always the only reasonable course; the same categories of patients for whom a simultaneous switch may be appropriate are those for whom a later discontinuation of the second drug may be the right plan. Patient preferences, as well as the clinical situations, must be considered.[16]

Conclusions

The answer to the question posed in the title is 'yes': we should reconsider the practice of second or third monotherapy treatment sequences for epilepsy because early polytherapy is often effective and well-tolerated with the new generation of drugs. However, this must be a qualified 'yes,' because there are categories of patients for whom serial monotherapy remains a better strategy. We certainly need more research on this issue.[17]

In our actual practice at our epilepsy center, 66% of patients are taking two or more antiepileptic drugs. However, this is a refractory patient population and it must be emphasized that most patients in community neurology practice can and should be treated with monotherapy.[2] For most of these, though, this monotherapy will be the very first drug tried, or at least the very first drug tolerated. Not many will be on a monotherapy agent after failure of two or more drugs because of lack of efficacy.[3,18] These patients tend to be refractory, and most will end up on combination therapy. This is not such a bad thing, and does not signify physician failure. The new drugs combine more easily for several reasons, so 'polypharmacy' should not be such a pejorative term. More often heard today is the term 'polytherapy,' and rightly so. ■

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