Monotherapy in Epilepsy

Role of the Newer Antiepileptic Drugs

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Background: Monotherapy is the goal for pharmacological treatment of epilepsy. Well-controlled trials have established the efficacy of some of the newer antiepileptic drugs (AEDs) as monotherapy.

Objective: To review clinical data and expert opinions pertinent to the evaluation of most of the newer AEDs as monotherapy for epilepsy.

Data Sources: The MEDLINE database was searched for clinical trials using newer AEDs. Reference sections of review articles were manually searched to identify relevant studies not retrieved in MEDLINE.

Study Selection: The resulting list of references was manually reviewed to identify monotherapy studies.

Results: Lamotrigine and oxcarbazepine demonstrated efficacy in randomized active-control trials in patients with newly diagnosed epilepsy and in substitution trials in patients refractory to conventional AEDs.

Conclusion: Lamotrigine and oxcarbazepine are as effective as conventional AEDs at controlling partial seizures and are better tolerated.

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Monotherapy is preferred when treating epilepsy, although previous reports indicate that polytherapy was sometimes the standard of care and given routinely as initial treatment.1 Polytherapy began to be questioned shortly after studies showed that 50% to 75% of patients who started on monotherapy remained seizure free for at least 1 year and that monotherapy is equally or more effective, better tolerated, and associated with fewer drug interactions compared with polytherapy.2,7 Other advantages of monotherapy include better compliance, lower costs, and improved quality of life.1

The efficacy of conventional antiepileptic drugs (AEDs), including phenytoin, carbamazepine, phenobarbital, and valproate, as monotherapy is accepted.7-10 but efficacy of monotherapy with some of the newer AEDs has been established in well-controlled trials. To protect patients from the potential dangers of a noneffective agent used as monotherapy, many newer medications were initially studied as adjunctive therapy in refractory patients,4 and when efficacy and tolerability as adjunctive treatments were established, newer medications were then studied as monotherapy.11 However, felbamate and oxcarbazepine were studied as adjunctive therapy and monotherapy simultaneously.12-15 Sufficient data are now available to establish the efficacy and tolerability of some of the newer AEDs as monotherapy. This article reviews data pertinent to evaluating the role of the newer AEDs, including felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, and topiramate, as monotherapy.

EVALUATING MONOTHERAPY CLINICAL TRIALS

The long-term, randomized, double-blind, placebo-controlled clinical trial of monotherapy in epilepsy is generally untenable for new AEDs because of possible harm arising from withholding active treatment. Randomized active-control trials comparing monotherapy with a test medication and monotherapy with a reference medication (typically a conventional AED with established efficacy) in newly diagnosed patients are the next best alternative, allowing assessment of efficacy and tolerability under conditions approximating clinical use.11 Because a new drug would not be expected to surpass the
high (70%-80%) seizure remission rates achieved with established agents, demonstration of comparable efficacy of the test and reference medications is interpreted as evidence of the test medication's efficacy.

Randomized, double-blind substitution trials gradually transition refractory patients to monotherapy with either a new AED or a conventional AED as the reference medication. As with double-blind, head-to-head monotherapy trials, demonstration of comparable efficacy of the test and reference medications is interpreted as evidence of efficacy of the test medication.

While clinicians generally accept comparable efficacy of test and reference medications in double-blind comparator trials as evidence of the test medication’s efficacy, regulatory authorities considering whether to approve new medications as monotherapy may not. To be statistically powered to show equivalence between the comparator medications, these trials generally need to include a prohibitively large number of patients. If a study is underpowered, a demonstration of apparent comparable efficacy cannot exclude the possibility that test and reference medications are both ineffective. In this case, a demonstration of superior efficacy of the test medication over the reference medication provides the only incontrovertible evidence of its efficacy. This hurdle is too high for most test AEDs to overcome, although the test drug may be effective as monotherapy in the clinical setting.

Several alternative study designs compare test medication with a suboptimal treatment, which may be a nontherapeutic dose of the same drug, a different drug, or a placebo. Presurgical trials compare high doses of a test AED with placebo in patients with refractory seizures who need to discontinue their current therapy for evaluation before epilepsy surgery. These trials are of short duration because of the risks patients are exposed to in the placebo arm (ie, no AED treatment). This trial design compares the seizure frequency between the study drug and placebo, just as in other placebo-controlled trials. In open-label substitution trials, a high dosage of the test medication is compared with a suboptimal dosage of the same drug or with either a suboptimal drug or an effective dosage of a different one. When ethically feasible, a placebo group sometimes takes the place of the active comparator in substitution trials.

These alternative study designs require relatively few patients to demonstrate statistically significant effects of treatment. However, because of short duration and lack of flexibility for titrating doses to optimum levels, the practical relevance of data derived from these studies is limited.

A full discussion of all the complexities of monotherapy trial designs is beyond the scope of this article. The reader is encouraged to refer to other reviews for a more complete discussion of trial designs for monotherapy studies in epilepsy.

DATA FROM THE STUDIES

Clinical studies of the newer AEDs as monotherapy were identified through searches of the National Library of Medicine’s PubMed database, using as key words the names of the newer AEDs (ie, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide) and the term “clinical trial.” No date limits were applied. The resulting list of references was manually reviewed to identify monotherapy studies. Reference sections of review articles on AEDs were manually searched to identify relevant studies not identified in the PubMed searches. Data presented at professional meetings in abstract form are not included in this review. Because no clinical studies on zonisamide as monotherapy were identified with the methods described above, that agent is not discussed in this review.

RANDOMIZED ACTIVE-CONTROL TRIALS

Numerous active-control comparisons of new AEDs with conventional medications have been conducted in patients with newly diagnosed epilepsy, and results of several open-label comparisons are also available. Three of the studies employed a randomized, open-label design,23,28,29 1 randomized study had both an open-label and a double-blind component,19 and the other 7 were randomized, double-blind trials.20-22,24-27 Most of these studies were of sufficient duration (approximately 1 year) to allow assessment of long-term effects of the drugs on seizure control. Furthermore, many of these studies employed flexible dose-titration schedules, allowing investigators to adjust doses.

Gabapentin, lamotrigine, oxcarbazepine, and vigabatrin have been compared with conventional AEDs in patients with newly diagnosed epilepsy in randomized active-control trials. Except for vigabatrin, which compared with carbamazepine was associated with a higher percentage of discontinuations because of lack of efficacy,20 the studies show that newer agents are as effective in controlling seizures as reference AEDs including carbamazepine, phenytoin, and valproate. Seizure-free rates with both test and reference AEDs ranged from approximately 40% to 75%, consistent with rates historically observed with conventional AEDs.2,6-10

One randomized, active-control study compared 2 newer AEDs rather than a newer AED with a conventional one.20 That study, a randomized, double-blind, flexible-dose comparison of lamotrigine and gabapentin, demonstrated that both drugs were well tolerated and comparably effective in patients with newly diagnosed partial and tonic-clonic seizures, with 76% of patients in each group remaining seizure free for the last 12 weeks of monotherapy.

The newer AEDs were nearly always better tolerated, as reflected in lower frequencies of adverse events or lower rates of withdrawal from the study because of adverse events. Gabapentin (1 study), lamotrigine (3 studies), oxcarbazepine (1 study), and vigabatrin (2 studies) were each better tolerated than carbamazepine; oxcarbazepine was better tolerated than phenytoin (2 studies).20,22,24-26,29

Lamotrigine and oxcarbazepine consistently demonstrate efficacy in randomized active-control trials.20-27 Furthermore, monotherapy with these drugs is better tolerated than monotherapy with conventional AEDs. Additional study of the other newer AEDs is warranted before definitive conclusions can be drawn about them.
Gabapentin was effective vs a conventional AED in 1 active-controlled study;19; mixed results have been obtained with vigabatrin20,26; and felbamate, levetiracetam, tiagabine, and topiramate have not been assessed in published, randomized active-control studies in patients with newly diagnosed epilepsy.

PLACEBO-CONTROLLED TRIAL IN ABSENCE SEIZURES

Data from active-control studies are supplemented by a placebo-controlled trial of the efficacy of lamotrigine (median dose, 15 mg/kg per day) for absence seizures in 45 children aged 3 to 15 years with newly diagnosed epilepsy.30 A placebo control group was feasible because of the relatively benign nature of absence seizures; withholding effective treatment from the placebo group for the brief, 4-week treatment period would not endanger patients because this trial employed an escape design. When patients entered the double-blind phase, their absence seizures were fully controlled. Patients would exit the double-blind arm as soon as they were no longer seizure free. Therefore, the only patients exposed to placebo for 4 weeks were those who remained seizure free. Lamotrigine was significantly more effective than placebo, with 64% of patients receiving lamotrigine monotherapy free of absence seizures during the 4-week double-blind phase compared with 21% of placebo recipients. Lamotrigine was well tolerated, and no patient withdrew from the study because of adverse events.

SUBSTITUTION TRIALS

Several double-blind and open-label substitution trials have been conducted with the newer AEDs.13,31-38 These trials generally enrolled patients with epilepsy refractory to conventional AEDs and were initiated with add-on phases during which patients were introduced to increasing doses of the test AED while their current AED was discontinued. A period of monotherapy with the test drug ensued. Patients with worsening epilepsy (usually measured by an increase in seizure frequency, severity, or the emergence of a new seizure type) or patients who did not tolerate the test AED were withdrawn from the study.

Active-control substitution trials were conducted with felbamate (2 studies) and lamotrigine (1 study), both of which were significantly more effective as monotherapy than low-dose or a minimally effective dose of valproate.13,31-32 In the only long-term, placebo-controlled substitution trial, 3000 mg of levetiracetam was significantly more effective than placebo during 12 weeks of monotherapy.33 Substitution trials comparing low and high doses of the test AED have been carried out with oxcarbazepine (300 mg/d vs 2400 mg/d), tiagabine (6 mg/d vs 36 mg/d), and topiramate (100 mg/d vs 1000 mg/d).36-38 In all comparisons, the high dose of study medication was more effective at controlling seizures or prolonging time in the study. Generally, overall retention rates in these studies are low, and occurrence of adverse effects may be due to the high doses and rapid titration used.

Overall, substitution trials are consistent with randomized active-control trials in demonstrating efficacy of newer AEDs. The data for felbamate, lamotrigine, and levetiracetam are most robust because they were obtained from studies using an active comparator or a placebo control group.13,31,32,35 The other studies, which either were open-label and did not include a comparator or compared low and high doses of the test AED, should be interpreted cautiously because of the lack of a reference treatment.33,34,36-38

Substitution trials extend the data from the trials in patients with newly diagnosed epilepsy by showing that seizures can be controlled with the newer medications in many patients refractory to conventional AEDs. The findings should be generalized to clinical practice carefully because these treatment-resistant patients may not be representative of typical clinical populations of patients with epilepsy.

PRESURGICAL TRIALS

Presurgical trials have been conducted with felbamate, gabapentin, oxcarbazepine, and tiagabine.15,37,39,40 In 3 placebo-controlled studies (felbamate, oxcarbazepine, and tiagabine), the test AED was more effective than placebo at reducing seizure frequency or prolonging time in the study.13,37,38 In the fourth comparison, a higher daily dose of gabapentin (3600 mg) was more effective than a lower dose (300 mg) in prolonging time in the study.40 Presurgical trials, while having the benefit of a placebo group, provide limited information because their design does not mimic clinical practice. These trials are of short duration (ie, 8-10 days), the inpatient setting is more controlled (ie, supervised) than an outpatient setting, study medication is administered via unorthodox conditions (ie, with rapid-dose escalation after abrupt withdrawal of the patient’s usual AED), and AED doses cannot be titrated as they would be in clinical practice.

OTHER FACTORS TO CONSIDER IN EVALUATING MONOTHERAPY

Because currently available AEDs are generally not distinguishable on the basis of efficacy data from clinical trials, factors such as mechanism of action, spectrum of activity, neuropsychiatric profile, sedative burden, long-term adverse effects, and ease of dosing need to be considered in choosing AEDs for monotherapy.6 Many of these features are not directly assessed in clinical trials. Taking into account these features and others, the newer AEDs lamotrigine, gabapentin, oxcarbazepine, and vigabatrin are considered to have better profiles as AED monotherapies than the conventional AEDs phenobarbital, phenytoin, carbamazepine, and valproate. Specific advantages of the newer AEDs include better tolerability, predictable kinetics, and broad-spectrum efficacy or well-defined spectrum of efficacy.

In addition to these characteristics of AEDs, medication effects in special patient populations warrant consideration.6 It is important to be aware that some AEDs (phenobarbital, phenytoin, carbamazepine, oxcarbaz-
epine, felbamate, and topiramate) increase the metabolism of hormonal contraceptives, while others (valproic acid, vigabatrin, lamotrigine, gabapentin, tiagabine, and levetiracetam) do not interact with hormonal contraceptives. Drugs with cognitive adverse effects should be avoided in elderly patients, who may be particularly susceptible to central nervous system toxicity.

Finally, there is evidence to suggest that the majority of patients who achieve seizure freedom with AEDs do so with monotherapy. The results of a prospective study evaluating AED response in patients with newly diagnosed epilepsy suggest that, regardless of the drug, only a relatively small percentage of patients who do not achieve seizure control with monotherapy will achieve control with polytherapy. Of the 64% of patients naive to AEDs before the start of the study who became seizure free, 61% achieved seizure freedom with monotherapy, while the remaining 3% were seizure free with a 2-drug regimen. The finding that only 3% of the 64% of patients who were seizure free required polytherapy suggests that, for most patients who are responsive to pharmacotherapy, monotherapy is an effective treatment regimen.

Leaders in the field of epilepsy recommend valproate and lamotrigine as first-line monotherapy for generalized tonic-clonic seizures; valproate, ethosuximide, and lamotrigine for absence seizures; valproate and lamotrigine for myoclonic seizures. Lamotrigine was recommended as first-line treatment for idiopathic generalized epilepsy among women of reproductive age, including those who are pregnant or breastfeeding; elderly patients; and those with intellectual impairment. Oxcarbazepine is currently approved by the Food and Drug Administration as monotherapy for partial seizures in adults, and lamotrigine is FDA-approved for conversion to monotherapy in adults with partial seizures.

COMMENT

Long-term, randomized, double-blind, placebo-controlled trials are not appropriate to evaluate monotherapy because of the risks involved in withholding active treatment from a patient. Therefore, several alternative designs are generally used. It is important to keep the strengths and weaknesses of these trial designs in mind when interpreting results and evaluating options for monotherapy.

Results of several clinical trials demonstrate that the newer AEDs can be as effective as monotherapy for epilepsy. Efficacy is particularly well established for lamotrigine and oxcarbazepine, and compared with conventional AEDs such as carbamazepine, phenytoin, and valproate, both are equally effective at controlling seizures and are better tolerated. Data for the other newer AEDs are less voluminous and less consistent than those for lamotrigine and oxcarbazepine, and additional clinical study is warranted before the place of these medications can be established.

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REFERENCES


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