Monotherapy versus Polytherapy in Epilepsy
A Reappraisal

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Summary

In approximately 70% of patients with newly diagnosed epilepsy, initial treat­
ment with a single antiepileptic drug leads to complete seizure control without
intolerable adverse effects. Unfortunately, monotherapy fails, even at maximal
tolerated doses, in an important minority of patients. These patients usually have
symptomatic epilepsies. For patients with refractory seizures, alternative mono­
therapy with a second-line agent is a very effective and well tolerated treatment
policy. Approximately 40% of patients with partial epilepsy that is refractory to
one agent will benefit from alternative monotherapy.

If alternative monotherapy fails, polytherapy with a combination of 2 drugs
may be helpful in a small minority of patients. However, this efficacy is usually
at the expense of added toxicity unless the daily dose of the first drug is reduced.
When 3 antiepileptic drugs fail either in sequential monotherapy or combination
therapy, diagnostic re-evaluation is required. If surgery is not suitable, mono­
therapy with the individually best tolerated drug at the lowest effective dose is
recommended until more effective antiepileptic drugs become available.
Monotherapy, i.e. the treatment of epilepsy with a single antiepileptic drug, is the universally accepted regimen of choice for patients with newly diagnosed epilepsy. However, the choice of drugs for monotherapy is up to the individual physician because large scale clinic trials have shown that the major antiepileptic drugs used for partial seizures and generalised tonic-clonic seizures are essentially equivalent, with only minor differences in terms of efficacy.\textsuperscript{1-3} Once monotherapy has failed, polytherapy (i.e. adding a second drug) is a common practice, mainly because most physicians share the view that polytherapy is superior to monotherapy for the treatment of refractory epilepsy. For example, in a recent survey, 42\% of patients in a well known epilepsy clinic were receiving polytherapy.\textsuperscript{4}

Unfortunately, no large scale, rigorously controlled clinical trials are available to provide data on the efficacy and safety of polytherapy versus monotherapy with the added drug for the treatment of refractory epilepsy.\textsuperscript{5} In addition, there has been no systematic comparative evaluation of different polytherapy combinations.\textsuperscript{6} As a consequence, the choice of drug combinations is based on rational (i.e. theoretical) pharmacological considerations\textsuperscript{7} and, more often, on clinical preference, determined from the personal experiences and knowledge of individual physicians.

In this review, we reappraise the available clinical evidence for 3 common treatment strategies, namely: (i) monotherapy in newly diagnosed epilepsy; (ii) alternative monotherapy, i.e. substitution for an unsatisfactory antiepileptic drug; and (iii) polytherapy for treatment of refractory epilepsy. Practical considerations will be offered on the rational use of monotherapy and polytherapy in the treatment of epilepsy.

1. Monotherapy for Newly Diagnosed Epilepsy

There is universal and longstanding agreement that drug treatment of patients with newly diagnosed epilepsy should begin with a single antiepileptic drug that is most appropriate for the type of seizures.\textsuperscript{8} The relative merits and limitations of this approach are outlined in table I. In general, dosage is increased at intervals until either maximum control of seizures is obtained or unpleasant or disabling adverse effects appear.

1.1 Evidence for Efficacy

In recent years, several controlled trials have documented the outstanding value of monotherapy with individual antiepileptic drugs in patients with previously untreated epilepsy.

Recent trials have carefully compared phenobarbital (phenobarbitone), phenytoin, carbamazepine and valproic acid (sodium valproate) in children and adults with newly diagnosed epilepsy with partial seizures and generalised tonic-clonic seizures.\textsuperscript{10,11} In these randomised, nonblinded parallel group studies, all 4 drugs given as monotherapy achieved similarly high degrees of seizure control, and there were no significant differences in efficacy between the drugs regardless of seizure type.

In another open, randomised trial, valproic acid and carbamazepine were compared directly when used in the routine treatment of adult patients with newly diagnosed onset epilepsy, both generalised and partial, in a hospital neurology clinic. The

<table>
<thead>
<tr>
<th>Table I. Monotherapy in the treatment of epilepsy: merits and limitations</th>
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<tbody>
<tr>
<td><strong>Merits</strong></td>
</tr>
<tr>
<td>Effective as initial treatment, although the rate of complete</td>
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<tr>
<td>seizure control depends on type of seizure and epilepsy</td>
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<tr>
<td>Sequential monotherapy is effective for refractory epilepsy</td>
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<tr>
<td>(improvement in 30 to 40% of patients with refractory partial</td>
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<tr>
<td>epilepsy\textsuperscript{9})</td>
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<tr>
<td>No drug interactions</td>
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<td>Minimum toxicity</td>
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<tr>
<td>Easy analysis of drug-induced efficacy and toxicity</td>
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<td>Pharmacological and clinical diversity, due to multiple</td>
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<td>mechanisms of action, active metabolites and efficacy in several seizure types</td>
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<tr>
<td><strong>Limitations</strong></td>
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<tr>
<td>Fails to control seizures in an important minority of patients</td>
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<td>Patients who are poor responders to any medical treatment may</td>
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<td>obscure the efficacy of single drug treatment</td>
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<td>Unexplained variation of response to individual drugs may</td>
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<td>require sequential monotherapy with several drugs</td>
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