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CORRESPONDENCE

Letters to the Editor

Dear Sir,

In their interesting contribution to *Seizure*, Kwan and Brodie[1] reported on experiences in the Epilepsy Unit of the Western Infirmary with patients that failed on their first monotherapy drug. When failure was due to a lack of efficacy, either AED substitution or combination was undertaken. When failure was due to adverse effects the drug was substituted by alternative monotherapy. When these latter patients were not seizure free on their first tolerated drug, they also received either AED substitution or combination. The combined results of patients receiving either AED substitution or combination are reported and combination therapy appears to be an effective treatment in this category of patients. In particular, combinations of a sodium channel blocker with a drug with multiple mechanisms were associated with a favourable outcome. These observational results are in agreement with a literature review by our group[2] and merit further prospective investigation. However, their paper also raises some questions:

(1) The distinction made between patients that fail on their first monotherapy drug due to lack of efficacy and those that failed due to adverse effects is somewhat puzzling. Did the patients that failed due to a lack of efficacy do so on a maximally tolerated dose? Were the patients that failed due to adverse effects seizure free, or could this not yet be determined?

(2) In a paper by the same authors in the New England Journal of Medicine[3], a large difference was reported in the proportion of patients that eventually became seizure free between the patients that failed on their first monotherapy drug due to lack of efficacy and those that failed due to adverse effects. This difference does not seem that clear to us in the present paper.

(3) The authors report that some 'mechanistic' combinations were associated with better effectiveness than others, but did they also find that mechanisms of action should be taken into account when choosing a substitution monotherapy drug? In other words, was substitution more successful when a sodium channel blocker was substituted by a drug with multiple mechanisms of action and vice versa?

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Dear Sir,

We are grateful to Deckers and his colleagues for their interest in our outcome studies[4,5]. The aim of the project was to follow patients from their first antiepileptic drug (AED) to seizure freedom or refractoriness, and document the factors influencing the likelihood of either eventuality. The results suggested that there are two populations of patients[4]. Around 60% will be controlled on the first or second (AED) as monotherapy. The majority of the remainder will require polypharmacy or became intractable to all pharmacological manipulations. The most powerful predictor for 'refractoriness' was failure on the first AED due to lack of efficacy. By this we meant that high AED dosage was achieved without side-effects but continuing seizures. Only 11% of these patients subsequently became seizure free. Patients who tolerated the first drug poorly, i.e. developed symptoms on a modest dose and never became seizure free, did rather better long term with more than 40% subsequently being controlled on alternative medication. The Seizure paper[5] looked at the clinical course in the 248 patients in whom treatment with the first AED failed. There was a trend to better outcome with duotherapy than substitution[5]. Individual dosing data will be published in a third paper, which is currently in the hands of the reviewers[6]. These results served to generate a range of hypotheses that needs to be tested more rigorously with randomized studies.

We aim to re-evaluate our population of untreated patients 5 years on, hoping to show that a higher percentage became seizure-free patients with 'rational' combination strategies using the newer AEDs as touched upon in the Seizure paper[5]. In particular, we have seen good results combining sodium

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valproate with lamotrigine[7] and carbamazepine with topiramate[8]. The analysis plan will also look at the success or otherwise of substitution with drugs with different mechanisms of action. The original study threw up many such questions that we did not address.

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