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Commentary

Meta-analyses of antiepileptic drugs for refractory partial (focal) epilepsy: an observation

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There are now a handful of published meta-analyses surrounding the efficacy and tolerability of, particularly, the newer antiepileptic drugs (AEDs) as adjunctive treatment for patients with refractory focal (partial) seizures [1–4]. All have included numerous published studies with largely similar designs and have come to largely similar nonspecific conclusions. These complicated and time-consuming exercises have, in the main, not contributed usefully to everyday clinical practice in helping to refine the choice of treatment for patients with drug-resistant focal epilepsies. There are two main reasons for their lack of clinical value: firstly, this patient population is notoriously pharmacoresistant; and, secondly, the vast majority of the included studies were placebo controlled and, to make matters worse, many were regulatory trials, which were designed, undertaken and completed prior to the launch of the drug under investigation.

Despite the introduction of 14 AEDs in Europe and the USA over the last two decades, the general feeling from the neurological community has been one of disappointment [5]. The main reason for this conclusion is the pattern of response in this patient population to AED therapy. There are now a number of published outcome studies in newly diagnosed epilepsy [6]. More than 50% of adult patients will become seizure free with their first drug either immediately or after a short delay to allow the diagnosis to be accepted and/or for the dosing to be optimized [7]. A further 10% will respond to their second AED or first combination. The third treatment schedule will identify a further 3% with a good outcome. Thereafter, an increasingly shrinking percentage will become seizure free with subsequent drug regimens, with only a handful being controlled on AED combinations. This last population comprises the majority of patients taking part in the studies included in these meta-analyses. After 10 years of treatment, only around 50% of this patient population will still be seizure free [7].

Outcomes after the failure of the second drug schedule are particularly disappointing in patients with focal (partial) seizures [7]. Indeed, the definition of pharmacoresistant epilepsy published by the *ad hoc* task force of the International League against Epilepsy is 'failure of adequate trial of two tolerated, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom' [8]. Patients with focal (partial) epilepsy, who are likely to be recruited into placebo-controlled trials, are almost all pharmacoresistant, and very few will subsequently become seizure free for any useful length of time.

The second major concern with these meta-analyses in patients with refractory focal (partial) seizures is the inclusion of a high percentage of placebo-controlled trials. These patients are highly selected, and the trials are subject to a broad range of exclusion criteria. Most of the studies are of short duration and employ a variety of fixed drug doses. This unpromising situation is further exacerbated by the inclusion in these analyses of a large number of placebo-controlled trials undertaken for regulatory purposes. These patient populations, in particular, are not representative of everyday clinical practice. The dose for each patient in the majority of these studies is chosen randomly and is preceded by a fixed and often overly fast titration schedule. All will already be established on high doses of other AEDs. There is little leeway for reducing the dose of the test drug if the patient does not tolerate the randomly assigned arbitrary amount, nor can the doses of existing AEDs be adjusted should side-effects develop.

Not surprisingly, very few of these patients become seizure free even for the short duration, usually 3 or 4 months, of the trial [9]. The primary end-point for these studies, therefore, is the percentage reduction in seizure numbers for the Food and Drug Administration (FDA) in the USA and responder rate (percentage of patients demonstrating a 50% or greater seizure reduction) for the European Medicines Agency (EMA), both *vs*. baseline seizure frequency. These outcomes have very little clinical relevance for epilepsy patients, whose quality of life is not improved by a percentage seizure reduction, but only by attaining sustained seizure freedom [10]. Neither does their short duration predict long-term efficacy. This trial

methodology has its drawbacks also in detecting side-effects, because recruited patients are already taking sometimes one, usually two and occasionally three other AEDs, often at high dosage.

What, therefore, can be taken from these complex, costly and time-consuming studies that is relevant for everyday clinical practice? The short answer is not very much. This brings me back to the systemic review and network meta-analysis of Pritesh Bodalia and co-workers [4]. Their first conclusion was the need for long-term comparative trials. This is obvious and arguably reasonable, if almost impossible to undertake and likely to be extremely expensive. One of the many problems with such a design is the complex and numerous pharmacokinetic and pharmacodynamic interactions among the individual AEDs that would complicate dosing, produce side-effects and interfere with honest efficacy outcomes. Their second conclusion was that conventional random-effects meta-analysis showed that all the studied AEDs were superior in efficacy to placebo, but did not permit distinctions between the drugs on the basis of efficacy and tolerability. This again is hardly surprising and not clinically useful.

If, as have other authors, Bodalia and his team had settled for these broad conclusions, all would have been well, although their paper would be rather a boring read. However, Bodalia *et al*. were tempted to apply a sophisticated Bayesian network meta-analysis comparing short-term efficacy and tolerability of the individual AEDs, which rather artificially suggested benefit for some of these drugs over others. This last analysis and its clinically naive conclusions have substantially reduced the value of the exercise. The critical letter from Gaetano Zaccara and his 11 clinical colleagues rightly points out the importance of including all studies with an appropriate design. Dosing of the AEDs needed to be relevant to everyday clinical usage. Regulatory trials that were undertaken before the drug was used in clinical practice often included higher doses than those that were subsequently found to be useful in the clinic. Lastly, Zaccara *et al*. pointed out that 'this sort of complex statistical process should always be checked against actual clinical experience'. Are they saying that poor-quality evidence is less valuable than good clinical practice? I hope so!

Competing Interests

There are no competing interests to declare.

REFERENCES

1 Beyenburg S, Stavern K, Schmidt D. Placebo-controlled efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and meta-analysis. Epilepsia 2010; 51: 7–26.

2 Costa J, Faraleira F, Ascencau R, Borges M, Sampaio C, Vaz-Carnero A. Clinical comparability of the new and epileptic drugs in refractory partial epilepsy: a systematic review and meta-analysis. Epilepsia 2011; 52: 1280–91.

3 Rheims S, Perucca E, Cucherat M, Ryvlin P. Factors determining response to antiepileptic drugs in randomized controlled trials. A systematic review and meta-analysis. Epilepsia 2011; 52: 219–33.

4 Bodalia PN, Grosso AM, Sofat R, MacAllister J, Smeeth L, Dhillon S, Casas J-P, Wonderung D, Hingorani AD. Comparative efficacy and tolerability of antiepileptic drugs for refractory focal epilepsy. Systematic review and network meta-analysis reveals the need for comparator trials. Br J Clin Pharmacol 2013; 76: 649–67.

5 Löscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. Epilepsia 2011; 52: 657–78.

6 Mohanraj R, Brodie MJ. Early predictors of outcome in newly diagnosed epilepsy. Seizure 2013; 22: 333–44.

7 Brodie MJ, Barry SJE, Bamagous GA, Norrie J, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012; 78: 1548–54.

8 Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010; 51: 1069–77.

9 Gazzola DM, Baller LJ, French JA. Seizure-free outcomes in randomized add-on trials of new antiepileptic drugs. Epilepsia 2007; 48: 1303–7.

10 Luoni C, Bisulli F, Canevini MP, De Sarro G, Fattore C, Galimberti CP, Gatti G, La Neve A, Muscas G, Specchio LM, Striano S, Perucca E, on behalf of the SOPHIE study group. Determinants of health-related quality of life in pharmacoresistant epilepsy: results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. Epilepsia 2011; 52: 2181–91.

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