ALL ANTIEPILEPTIC DRUGS HAVE SIMILAR EFFICACY IN NEWLY DIAGNOSED PATIENTS: YES

William H. Theodore
Chief, Clinical Epilepsy Section, National Institutes of Health, Bethesda MD, USA

It has been extraordinarily difficult to distinguish efficacy among antiepileptic drugs (AEDs) in clinical trials. Drugs sometimes differ in short-term trial retention, but this is far more often on the basis of tolerability than efficacy. Multiple studies of 'older' AEDs illustrate this conclusion. In the Veterans Administration Cooperative Study, no significant differences in efficacy, but only toxicity, were observed among PB, CBZ, PHT or primidone (Mattson et al 1985). In a study of children with partial and secondary generalized seizures, no efficacy differences were fund among PB, PHT, CBZ or VPA (de Silva et al 1996).

The multicenter Italian study of new onset epilepsy showed no effect of drug regimen including phenobarbital (PB), carbamazepine (CBZ), valproic acid (VPA) or phenytoin (PHT), on achievement of a two-year remission, even after correcting for epilepsy syndrome (Collaborative Group 1992). In the SANAD study, a large British general practice randomized but unblinded study, CBZ, gabapentin (GBP), lamotrigine (LTG), oxcarbazepine (OXC), and topiramate (TPM) were compared (Marson et al 2007). LTG had better over all effectiveness, but this was on the basis of better tolerability rather than efficacy. CBZ was slightly but significantly more effective than GBP in probability of a 12 month remission, although this might have been due to inadequate dosing of the latter. Eve here the odds ratio for failure was 0.75 for CBZ versus GBP (95% confidence interval 0.60-0.90), showing how small the differences between drugs are.

In a double-blind comparison of topiramate (TPM), CBZ and VPA, there was no difference among the drugs in seizure control (Privitera et al 2003).

A recent comparison of VPA, ethosuximide and lamotrigine (LTG) in childhood absence did find that the first two drugs had better efficacy than LTG but did not differ from each other (Glauser et al 2010).

Comparison across trials is compromised by differences in trial design, as well as placebo response, making it almost impossible to extrapolate differences in drug efficacy without a direct head-to-head study (Cramer et al 1999). Evidence reviews of 'new' AEDs for new onset seizures have found that there is not only a paucity of evidence from well-designed Class 1 randomized blinded studies for individual drug efficacy, but no data that can distinguish among them (French et al 2004 and update, Rheims et al 2011). Some studies showing differences have used inappropriate doses of one or another comparator agent. One meta-analysis found that TPM and levetiracetam were more, and GBP and tiagabine less efficacious than other AEDs, but combined a variety of trial designs, did not fully consider the effect of drug doses, and used the last observation carried forward, a measure that can overestimate treatment success, especially in short trials (Costa et al 2011, Rheims et al 2011b).

The plethora of new approved agents makes it very difficult, and even unethical, to perform placebo-controlled studies in new onset patients (Perucca 2012). In order to perform parallel studies, very large numbers of sites are needed, and among other effects this may account for the observed secular increase in placebo response rates, making data analysis even more difficult (Rheims et al 2011). Thus, data from older and more recent clinical trials are very hard to compare. Data from children and adults cannot be combined due to the much higher placebo response rates in the former (Rheims et al 2008). Another problem in comparison even within studies is the criteria to be used. An international league against epilepsy group substantially revised its criteria from 2006 to 2013, dropping a detectable non-inferiority boundary approach, making some changes to the definition of adequate comparators, and eliminating specific drug recommendations (Glauser et al 2013). Let alone being able to claim that any drug was superior to another, a surprisingly limited number of AEDs were found to have class 1 data for efficacy at all, especially when specific syndromes and age groups were considered. An examination of their suggested criteria shows how difficult it is to show that one drug has superior efficacy to another. Current clinical trial designs may need to be modified to obtain better data on comparative drug efficacy for seizure control (Perucca et al 2012).

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