Efficacy of antiepileptic drugs in adults vs children

Does one size fit all?

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Neurology® 2012;79:1420–1421

During the past 25 years, our armamentarium of antiepileptic drugs has grown, and there continue to be new drugs in the pipeline. As premarketing studies are often limited to adult cohorts, the great majority of these new drugs were initially marketed with an indication for the treatment of partial-onset and secondarily generalized seizures in adults. Given the multiple challenges of performing pediatric studies,[1] trials in children have been carried out either after marketing or not at all.[2] For only 3 of the new drugs (felbamate,[3] rufinamide,[4] and clobazam[5]) did the initial submission to the regulatory agency allow for a pediatric indication for the treatment of seizures associated with Lennox-Gastaut syndrome, a form of epilepsy invariably diagnosed during childhood.

The lack of pediatric efficacy data when a new drug is introduced leaves those who treat children with epilepsy with the unfortunate choice of not using available treatments—which some do—or using them off-label—which most do. In the absence of these data, an important question is whether the trials performed in adults are predictive of efficacy in children.

In this issue of *Neurology*®, Pellock et al.[6] report on a systematic review, funded by UCB Pharma, that was designed to address this question. An analysis of 30 clinical trials of adjunctive therapy for the treatment of partial-onset seizures allowed them to conclude that for this seizure type the efficacy of adjunctive antiepileptic therapy in adults is predictive of adjunctive antiepileptic therapy in children 2–18 years of age. The authors undertook a search of 3 databases (Medline/PubMed, Embase, and the Cochrane Library) for clinical antiepileptic efficacy trials (monotherapy and adjunctive therapy) of partial-onset seizures and primarily generalized tonic-clonic seizures in adult cohorts and children <2 years and 2–18 years; this yielded >3,000 hits, the vast majority of which were excluded based on stringent inclusion criteria set by the authors. The insufficient number of eligible trials did not permit an analysis of comparative efficacy in children <2 years, in monotherapy trials for the treatment of partial-onset seizures in children 2–18 years, and in any therapy in primarily generalized tonic-clonic seizures in children 2–18 years.

Overall, the efficacy data for adjunctive therapy for partial-onset seizures for children 2–18 years fell within the ranges reported in adults for lamotrigine, levetiracetam, oxcarbazepine, and topiramate. Eslicarbazepine and lacosamide were not included in this analysis due to the absence of published clinical trials in children. The data are less convincing for gabapentin, for which the median percent reduction values (figure 3), and more dramatically the responder rates (figure 4), are lower in children than in any trials in adults. This difference may be due to nonequivalent dosing.

An important additional demonstration of this systematic review is that for clinical trials of adjunctive therapy for the treatment of partial-onset seizures, there was no instance in which a drug that was found to be superior to placebo for partial-onset seizures in several trials in adults failed to exhibit superiority to placebo in 1 or 2 trials in children >2 years. Given this finding, the authors' conclusion is justified, as these trials were all superiority/inferiority studies with significant differences. However, based on limitations acknowledged by the authors, such as different trial designs and dosages, the conclusion drawn from their analysis should be viewed as qualitative, not quantitative, in the sense that one cannot exclude the possibility that any of the antiepileptic drugs could be less effective in children than in adults at any dose.

A notable caveat in this comparative study is that there are seizures in children that never occur in adults, such as partial-onset seizures associated with the benign focal epilepsies (e.g., benign focal epilepsy with centrotemporal spikes and Panayiotopoulos syndromes). It is possible that these seizures may have a different mechanism than partial-onset sei-

See page 1482

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zures in adults. Therefore, the conclusion that data on the antiepileptic drug efficacy obtained in adults can be extrapolated to children may only be permissible if one specifically excludes the benign focal epilepsies of childhood.

Finally, the study by Pellock et al. addresses efficacy only. It is imperative to keep in mind that safety, adverse effects, and pharmacokinetics in children cannot be predicted from studies in adults.

This article by Pellock et al. provides new and robust answers to an old and practically important question: Can efficacy data from antiepileptic drug trials in adults be extrapolated to children? The evidence presented indicates that this extrapolation is possible in the case of several antiepileptic drugs effective as adjunctive therapy against partial-onset seizures. The finding should provide some reassurance and support to all pediatric neurologists who, for decades, have had no other choice but to prescribe antiepileptic drugs off-label in order to do what they thought was best for their patients. However, given the limitations of this study and the available data, the answer to the question of whether one size fits all remains incomplete. Therefore, there is a continued need for randomized controlled studies in children to be performed either prior to initial marketing or soon thereafter.

DISCLOSURE

B. Bourgeois has served as a consultant to Upsher-Smith Pharmaceuticals and has received support from Lundbeck Pharmaceuticals for a multicenter trial of clobazam in Lennox-Gastaut syndrome. H.P. Goodkin reports no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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