ONLINE FIRST

No Evidence of Efficacy or Evidence of No Efficacy

HEADACHE IS AN ALMOST UNIVERSAL COMplaint. In any given month, nearly 49% of children will report headaches, with 4.2% of those having headaches on 10 or more days per month.[1] Affecting nearly 8% of children and adolescents, migraine is the most important cause of pediatric consultations due to headaches.[2]

The clinical presentation of migraine varies as a function of age,[3] and this has diagnostic and therapeutic importance.[4] Indeed, the diagnosis and treatment of migraine in children and adolescents resembles a kaleidoscope with many facets of striking peculiarities—in young children, the attacks may be very short and sometimes headaches are not present, such as in the associated periodic syndromes (eg, cyclical vomiting and abdominal migraine). More frequently than adults, children seem to respond to treatment with simple analgesics, and this may probably reflect their exacerbated placebo response. When measured in the context of clinical trials, nearly 55% of children receiving placebo prophylaxis achieve the primary end point and the rate approaches 70% with acute therapy. In adults, rates are close to 35% and 45%, respectively.[5] Factors that explain the high placebo rate in children include regression to the mean (short duration of attacks), inadequate study designs, and beliefs and perceptions that are inherent to the age group.[6]

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Of relevance is also the fact that although pediatricians often treat children with migraine using medications that were tested in the adult population, good-quality evidence tailored to the pediatric population is yet scarce, at least for the prophylactic treatment of migraine.

Two studies published in the current issue of the journal shed light on the subject, focusing on acute and prophylactic treatment of migraine in children. Sun et al[7] focused on the acute treatment of migraine. They conducted a systematic review of trial data submitted to the Federal Food and Drug Administration between 1999 and 2011 to identify predictors of outcome (failure or success in dealing with the placebo effect) among children treating their attacks with triptans. Among the several strategies aimed at reducing the placebo response, the authors found that double randomization is probably the best design. As the name implies, in this design, randomization initially selects patients to receive placebo or medication at different randomization rates. Typically, most children will receive placebo and only a minority will receive active treatment. Those with a high placebo rate are then excluded, and the remaining participants are re-randomized and the study is conducted as a typical parallel-design clinical trial. This innovative strategy was recently applied in a very large registration trial that granted Federal Food and Drug Administration approval for pediatric use of a triptan.[8] Other strategies traditionally considered to be helpful were not found to be so including (1) enrolling older children (adolescents) with migraine attacks lasting more than 4 hours, (2) adopting an end point of pain relief at 1 hour (rather than pain free at 2 hours), and (3) excluding patients who did not experience any headache attack during a run-in period.

The second article by El-Chammas et al[9] focused on trial-design issues when testing the preventive treatment of migraine. Their meta-analysis included 13 placebo-controlled trials and 11 trials with an active comparator (3 of which also included placebo arms) within a universe of 2918 studies. One of the indirect conclusions of the study was that good-quality evidence on the preventive treatment of migraine is urgently needed. The recommended approach for future studies suggested that they should (1) be randomized and placebo controlled, with sample size calculations to account for the placebo response; (2) include patient-recorded outcomes; (3) have headache frequency as a primary outcome; and (4) have dichotomous outcomes based on at least 50% improvement (as recommended by the International Headache Society guidelines).[10] The authors stated that firm conclusions are impossible based on the paucity of data. Limited evidence merely supports the efficacy and safety of topiramate and trazodone for the prophylaxis of migraine in children and adolescents, while recommendations regarding other commonly used drugs, such as clonidine, flunarizine, pizotifen, propranolol, and valproate, cannot be made.

Based on the results of the 2 studies, what is the take-home message?

First, both studies force us to remember that "no evidence of efficacy does not mean the evidence of no efficacy."[11] Many of the medications used for migraine prophylaxis in children are routinely prescribed off label, and they seem to be efficient and safe. Are they effective or are clinicians observing the placebo effect? This is impossible to answer other than by proposing another question: Does it matter? Although placebo is the enemy of great clinical trials, it is likely the best friend of good clinicians. I am not advocating that clinicians should ig-

nore or not demand evidence. Indeed, the acute treatment of migraine in children can be solidly conducted within label because medications including ibuprofen, acetaminophen, almotriptan, and rizatriptan are approved by the Federal Food and Drug Administration for use in children. I am just acknowledging that, in many circumstances mainly involving the preventive treatment of migraine, pediatricians need to make best use of the little available evidence.

Second, advances in clinical trial design have not kept pace with the significant advances observed in the last decade in our understanding of the diagnosis, epidemiology, and impact of migraine in children and adolescents. The mismatch becomes more frustrating in the face of recent evidence that unequivocally demonstrates the impact of migraine on children's quality of life,[12] mental health,[13] and school attendance and performance,[14] as well as on their families.[15] Therefore, I advocate that lack of evidence should not be translated into paralysis, with clinicians passively ignoring children's suffering.

What should we do? (1) Keep in mind the incredible burden of migraine to affected children; (2) when possible, treat within label by giving preference to approved drugs; and (3) when no evidence is available, or when first-line therapies have failed, select a drug based on plausibility, proved efficacy in studies with adults, and proved safety of the drug in children. Lack of evidence associated with lack of good reasoning to navigate the lack of evidence is likely an ominous combination to children with migraine.

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