In a recent issue of *The New Yorker*, Michael Specter wrote of the current surge in interest regarding the role of placebos in health care. The article described the history of placebo use, initially as a part of medical practice to supplement or replace active medications, and later in research where they typically serve as a neutral comparator. Interest in placebos has not been limited to the lay press. During the past decade, over a dozen papers have been published on the impact of placebo response in clinical trials. While most highlight the difficulties with establishing treatment benefit in the face of a high placebo response rate, others suggest a more positive role for placebos as a research tool. Among the papers are several suggesting that children and adolescents are more likely to respond to placebos than adults, making this a significant issue in the interpretation of pediatric research as well as an intriguing consideration for future study.

**Depression**

The presence of a high placebo response rate is known to be a confounding factor in antidepressant studies, particularly in those enrolling children and adolescents. In a 2005 analysis of 27 randomized placebo-controlled pediatric antidepressant studies, Bridge and colleagues found a significant benefit from treatment, but the response was less robust than anticipated. This was most evident in younger children. In the studies of children less than 12 years of age, only fluoxetine demonstrated superiority over placebo. When the individual studies were further reviewed, the most common factor among those with negative results was a high placebo response rate. In the trials showing no benefit from drug administration, the placebo response rate was approximately 60% compared to only 30 to 40% in studies showing treatment benefit. The negative studies were more often multicenter trials, causing the authors to suggest variation in practice sites as a source of inaccuracy.

A second meta-analysis by these authors, using 12 studies with a total of 2,862 children and adolescents, confirmed their findings. As in the previous paper, the single best predictor of a high placebo response rate was the number of study sites. Severity of illness at enrollment was inversely related to placebo response rate, but this effect was not significant when the number of study sites was controlled for in the model. The authors suggested that antidepressant studies conducted in the pediatric population could be improved by more careful recruitment of patients, with consideration of the number of study sites, and inclusion of more severe cases.

Cohen and colleagues performed an additional review of the literature on pediatric psychotropic drug use in 2010, focusing on predictors of placebo response. Twenty-three antidepressant trials were included, as well as ten studies of treatment for anxiety and seven for treatment of obsessive compulsive disorder (OCD). The rate of placebo response was highest in studies for OCD, followed by those for anxiety and then those for depression. As with the earlier papers, the authors observed that studies demonstrating treatment benefit were associated with lower placebo response rates. As in the 2009 Bridge study, severity of illness was negatively correlated with placebo response rate.

Many questions remain about the role of placebo controls in pediatric antidepressant trials. Some experts have suggested that controlled trials without a placebo comparator and large-scale observational studies be given more weight when assessing the risks and benefits of antidepressant use in children and adolescents. The value of these alternative study designs, however, remains controversial.
Migraines
The prevalence of migraines in children and adolescents has been estimated to range between 3 and 20%. In spite of the relative frequency of this condition and its likelihood to result in significant morbidity and impaired quality of life, there has been comparatively little research documenting safe and effective treatments in the pediatric population. A high placebo response rate, often greater than 50%, has long been known to be a confounding factor in the interpretation of these trials.\(^8\)\(^7\)

In an open-label placebo-controlled study of zolmitriptan in 850 adolescents (ages 12-18 years) published in the January 2006 issue of *Headache*, Rothner and colleagues found a similar rate of pain control in both treated and control subjects.\(^7\) The percentage of subjects experiencing pain relief at 2 hours was 54% in the 2.5 mg zolmitriptan group, 53% in the 5 mg group, 57% in the 10 mg group, and 58% in those given placebo. The findings were similar for the number of patients who were pain-free (23% in the 2.5 mg zolmitriptan group, 19% in the 5 mg group, 25% in the 10 mg group, and 20% in the controls). Addressing the high placebo response rate, the authors suggested that the shorter duration of migraines in adolescents may have rendered the 2-hour assessment period less accurate in determining response to treatment than in adults.

This difference in migraine duration has been borne out in subsequent studies. Using both adolescent and adult trial data (a total of 1,231 migraine episodes), Maas and colleagues found that response to placebo in clinical trials of sumatriptan was inversely related to subject age.\(^8\)

In the subjects receiving placebo, the mean time to achieving pain relief was 3 hours in young adolescents compared to 6 hours in subjects 30 years of age or older. Conversely, response to sumatriptan itself was not associated with age. The mean time to pain relief in those given active drug was 2 hours, regardless of age.

It has been suggested that the inverse relationship between placebo response and age may continue into adulthood. Younger adults appear to be more likely to respond to a placebo than older adults. Investigators reviewing combined data from placebo-controlled studies of rizatriptan in 5,187 adults found the treatment advantage for rizatriptan increased as age increased, implying less of a confounding effect from response to the placebo (p< 0.001 in the assessment of patients experiencing pain relief and p=0.001 for the assessment of patients who were pain-free).\(^9\)

In 2008, Fernandes and coworkers conducted a systematic review of 13 acute migraine studies enrolling 1,234 children and adolescents in an attempt to further define the significance of the placebo response.\(^10\) The pooled placebo response rate was 46% for pain relief at 2 hours, with a range from 38% to 53% demonstrating considerable variation among studies. The percentage of controls reporting being pain-free was 21% (range 17-26%). As in earlier studies of adolescents, the authors found these placebo response rates to be considerably higher than those reported in studies of adults. In their analysis, study design, number of sites, and type of pain scale used were identified as potential factors influencing outcomes.

The effects of clinical trial design were further evaluated by Evers and colleagues in their analysis of 19 placebo-controlled acute migraine trials conducted in children and adolescents.\(^11\) These authors were also interested in identifying elements of trial design that would reduce the likelihood of a placebo response and allow for a more accurate interpretation of study data. Eight cross-over trials and 11 parallel group trials were included in the assessment. Placebo response rates were lower in the trials using a cross-over design than those using a parallel design (39.4% versus 56.9% for the assessment of pain relief at 2 hours and 19.2% versus 27.1% for the assessment of patients who were pain-free at 2 hours). As in pediatric antidepressant studies, other factors associated with lower placebo response rates were use of a single-center design and smaller sample sizes.

Attention-deficit/Hyperactivity Disorder
There has been limited research into the prevalence of placebo response in the treatment of children with attention-deficit/hyperactivity disorder (ADHD). An early meta-analysis of stimulant medication trials found an average effect size of 0.32 for response to a placebo, but the results differed greatly among the studies included in the assessment.\(^12\) A recent review of the topic published in the *Journal of Developmental and Behavioral Pediatrics* confirms this rate.\(^13\) The authors concluded that, on average, most studies have found a 20% to 30% placebo response rate in young children enrolled in studies of medications for ADHD.

The placebo effect may impact caregivers as well as the patient. Several studies have found that teachers and parents rate a child with ADHD more positively when they believe the child is receiving treatment. One means of reducing the impact of observer bias on placebo response rates in ADHD trials may be the use of more objective tools for determining benefit. In a
recent pilot study, Sumner and colleagues compared the effects of low- or medium-dose medication (atomoxetine or controlled-release methylphenidate) and placebo in 30 children (ages 6 to 14 years). Response was evaluated with both a traditional ADHD Rating Scale (ADHD-RS) and the newer Quotient™ ADHD System. The Quotient™ System is a computerized tool for assessing hyperactivity, inattention, and impulsivity. Patient response was classified as having any improvement, at least 25% improvement, or at least 40% improvement in symptoms. The percentage of patients in each of these three categories was calculated using both assessment tools. During the placebo phase, the ADHD-RS scores were 80%, 47%, and 27%, respectively. In comparison the scores during the placebo phase using the Quotient™ system were significantly lower, 27%, 7%, and 0. The authors concluded that this preliminary study suggests that an objective measurement tool may improve the sensitivity of ADHD clinical trial data and reduce the numbers of patients needed to rule out type II error during analysis.

While the placebo response may make interpretation of ADHD study results difficult, the use of placebos in clinical practice may be of considerable benefit. In an intriguing study, Sandler and colleagues tested the effects of adding a known placebo to a stimulant regimen. Ninety-nine children with ADHD (6-12 years of age) were enrolled in the study. After a dose-optimization stage, patients were randomized to receive: 1) a standard (full) stimulant dose, 2) a reduced stimulant dose (50% of the full dose), or 3) a reduced dose plus a placebo. Neither the child nor the family members were blinded to the placebo. The children were taught about the role of the placebos and, although it contained no active drug, it was described as a “dose extender” to help with the stimulant dose reduction process.

At the completion of the 8-week study, the group receiving the reduced dose experienced deterioration in their ADHD scores. The group receiving the reduced dose plus placebo, however, showed results similar to those in the full dose group. Test performance was no different among the groups. The authors speculated that their results may demonstrate the positive effects of clinical trial participation or an expectation of benefit leading to behavioral changes in either the parent or child (conditioning). While this trial raises many questions about study design and assessment of response, it presents an interesting approach to the intentional use of placebos in children.

Functional Gastrointestinal Disease
There are few studies demonstrating the efficacy of drug treatment in children with functional gastrointestinal disease. To address this need, in 2009 Saps and coworkers conducted a multicenter, double-blind, placebo-controlled trial of amitriptyline in children with pain associated with a functional gastrointestinal disorder. Ninety children (ages 8-17 years) with irritable bowel syndrome, functional abdominal pain, or recurrent abdominal dyspepsia were enrolled in the 4-week trial. The children were randomized to receive amitriptyline (10 mg/day for those less than 35 kg or 20 mg/day for those 35 kg or more) or placebo. The primary outcome was pain as reported by the patient and overall sense of improvement, with secondary outcomes related to psychosocial traits and daily functioning. Improvement was noted by 63% of patients in the amitriptyline group and 57.5% of those given placebo (p = 0.63). The percentage reporting feeling worse during the study was 5% in the amitriptyline group and 2.5% in the placebo group. Logistic regression analysis revealed no difference between the groups in the numbers of subjects reporting an overall excellent, good, fair, or poor response. The only significant difference in response was a greater reduction in anxiety in the amitriptyline group (p < 0.001).

Although they found no clear benefit from amitriptyline, the authors viewed their findings as an important piece of information to add to studies on the beneficial response to placebo in children with gastrointestinal disorders. In an editorial accompanying the article, Benninga and Mayer echo the suggestion of the paper’s authors that enrollment in the study, which was likely associated with increased education about disease management, reassurance, and allocation of time to discuss the patient’s concerns, may have been the primary determinant of the strong placebo response and an indication of the importance of these factors in patient care.

Understanding the Placebo Response
In the November 2011 issue of Clinical Pharmacology and Therapeutics, Rief and colleagues published a thought-provoking article describing the mechanisms involved in both placebo and nocebo response (the positive as well as negative effects of inactive substances). The authors propose that these effects are mediated through multiple interrelated mechanisms, including the patient’s expectations of treatment benefit, the doctor-patient relationship, and associative learning or conditioning. They provide examples of the impact of placebos on psychological outcomes like perception of pain relief, as well as biologic
parameters such as pulmonary function testing in patients with asthma, and discuss the potential benefits of optimizing these effects. While some investigators have argued for elimination of placebo controls in pediatric studies or alterations in study design in order to eliminate their influence, these authors support the role of placebos and provide recommendations for further study.

Summary
High placebo response rates, as noted in these pediatric clinical trials, can lead to misinterpretation of results and a minimization of the benefits of treatment. While a positive response to a placebo may adversely affect study results, it can be of value in the clinical setting. Placebos may be useful as adjuncts for drugs with significant dose-related toxicity or in disease states where treatment options are limited. As interest in the role of placebos grows, it can be expected that new research will continue to add to our understanding of their potential use in the pediatric population.

References

Formulary Update
The following actions were taken by the Pharmacy and Therapeutics Committee at their February meeting:

1. Aflibercept (Eyelat™) was added to the Formulary for the treatment of neovascular (wet) age-related macular degeneration.

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