Understanding Placebo Response in Pediatric Depression Trials

In spite of the evidence, it is often difficult for people to accept that clinical depression can occur in childhood. Understandably, childhood is viewed as a protected period of development during which depression "should" occur only in extraordinary circumstances (e.g., abuse, neglect, and bereavement). Even in children suffering the loss of a parent, depression (as opposed to grief reaction) has been found to be more common in those with a family history of depression (1). Caspi et al. (2) have noted an association of stressful life events and functional polymorphisms in the promoter region of the serotonin transporter (5-HTT) gene, suggesting a gene-by-environment interaction. Thus, depression in young people, as in adults, is a result of both environmental and genetic factors. While the focus of the current controversy in pediatric depression is on whether antidepressants are effective and safe, these underlying attitudes about use of medication in this population may be affecting interpretation of the data. There has been a substantial increase in clinical research on antidepressant treatment in the past 10 years. It is important for clinicians to understand the strength and limitations of the findings from this research, the limitations of the research, and, in particular, the role of placebo-controlled trials in the development of practice guidelines.

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In 1995, Hazell et al. (3) reported on a meta-analysis of all antidepressant trials (only tricyclic antidepressant studies had been conducted at that time). They identified 12 single-site randomized placebo-controlled trials over the previous 20 years, collectively comprising 336 children and adolescents (an average of 28 subjects per trial). In the six studies in which dichotomous outcomes were available, 37% of subjects had responded to placebo and 38% to tricyclics. In this issue of the *Journal*, Bridge and colleagues (4) report on a meta-analysis of 12 antidepressant trials conducted since 1995, all using second-generation antidepressants, involving a total of 2,862 children and adolescents with major depression (an average of 238 subjects per trial). In this meta-analysis, the mean response to placebo was 48%, and to active medications, 59%.

So what have we learned over the past 10 years, with an almost 10-fold increase in number of study subjects over the previous 10 years? Is bigger necessarily better? Bridge and colleagues' article focus on placebo response because, as they note, the majority of the variability between positive and negative trials is in the variability of placebo response rate. From their meta-analysis, they conclude that lower baseline illness severity and younger age (except in a single trial of fluoxetine in both children and adolescents) are associated with higher placebo response. However, the strongest predictor of the placebo response (but not response to active medication) was the number of study sites. These findings are important for methodological, clinical, and ethical reasons.

The authors suggest that the methodology of clinical trials will be improved by careful recruitment, from fewer sites, of children and adolescents with moderate to severe depression. Including only moderately to severely depressed youths will increase the probability of identifying a signal of whether a particular compound has antidepressant

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properties in the pediatric age group by decreasing the number of subjects who respond to placebo. However, the use of smaller numbers of selected sites requires substantial time for recruitment. Currently, most antidepressants trials are being conducted as a result of legislation passed during the past decade. The Food and Drug Administration (FDA) Modernization Act of 1997 made it mandatory for all new compounds with potential use in the pediatric age group to be studied in children and adolescents, and it encouraged pediatric research on already adult-approved medications that were used in children and adolescents. The Best Pharmaceuticals for Children Act of 2002 established a process for studying medications in pediatric populations to improve clinical trial investigations (e.g., clinical study design, weight of evidence, and ethical and labeling issues). Finally, in 2003, the Pediatric Research Equity Act authorized the FDA to require manufacturers of new drugs to conduct pediatric studies. These acts have led to an increase in new information about medications used in children.

However, these regulations generally result in short timelines and thus require multiple sites to recruit a large enough sample within the timeline. Furthermore, these studies are sponsored by the pharmaceutical industry, which means that antidepressants that are already available in generic formulations are not studied at all, and studies directly comparing different antidepressants are rare (there has been only one in adolescent depression).

The meta-analysis by Bridge et al. has several implications for clinicians, the most important of which is that clinicians must have a clear understanding of the evidence, both positive and negative, to adequately inform patients and parents. First, the article suggests that differences between the studies are due less to the differences in efficacy of antidepressants than to differences in response to placebo. While clinicians do not prescribe placebo, the article emphasizes the importance of a careful and extended evaluation prior to initiating medication to make sure that the depression is of sufficient severity to warrant medication treatment. Second, even when placebo-controlled studies fail to provide evidence of efficacy, clinicians should not ignore the study results, because they do provide essential information about safety. Side effects cannot be adequately evaluated in open trials, and side effects in children cannot be extrapolated from those identified in adult studies. It is important, therefore, to determine age-specific side effects using placebo-controlled trials. In this situation, clearly bigger is better in sample size, particularly for less common side effects. For example, increased suicidality with antidepressants was evident only when data from all available trials were combined (5).

The key ethical dilemma in placebo-controlled trials lies in avoiding exposing children to unnecessary risk versus meeting the need for adequate information to guide clinical care. It is important to minimize the chances of including children in a failed trial (i.e., a trial that does not provide conclusive evidence of efficacy or lack thereof). High placebo response is a frequent cause of failed clinical trials. As Bridge et al. note, identifying methods to reduce placebo response is important when developing these trials. The alternative is to avoid conducting placebo-controlled trials in this age group. Obviously, the problem with this approach is that placebo-controlled trials are the only way to establish age-specific information on efficacy and safety. Furthermore, as noted in the article, there may also be differences between children and adolescents in terms of response, so it is important for younger children to be included in clinical trials.

The study has several limitations, as the authors point out. These are primarily due to the level of the data that are available for meta-analysis. For example, it would be very informative to have week-by-week data on the timing of response to examine whether placebo response tends to occur earlier than true drug response, a possibility proposed by Quitkin et al. (6). Also, with only a general measure of illness severity, there are insufficient data to examine the clinical characteristics and symptom changes in placebo responders. Finally, it is difficult to compare results across trials because of different

methodologies, including outcome measures that vary between trials. Despite these limitations, the information provided is an important first step. While the results of many of the studies have not been definitive, they still provide important information, and the experience gained through these trials is helping to refine future research.

The high rate of response to placebo in multisite clinical trials should not be misinterpreted to mean that childhood depression is not a valid clinical entity or that it does not require vigorous treatment, including use of antidepressant drugs where appropriate. To that end, the Bridge et al. study is an important step toward clarifying issues of trial design that should be modified to increase the likelihood that these important trials identify the children who are most likely to be in need of treatment.

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