Flying Almost Blind

Clinicians who treat children with bipolar disorder are in the unenviable position of having to make consequential decisions about clinical care without much data to inform them. The study by Wagner et al. in this issue of the *Journal* begins to fill this void. In a multisite trial, 116 youths 7–18 years of age with a diagnosis of bipolar I disorder, manic or mixed episode, were assigned randomly to receive 7 weeks of treatment with either oxcarbazepine or placebo; 62% of patients completed the trial. At the end of the study, among patients who had completed at least one efficacy assessment, 42% of those receiving oxcarbazepine and 26% of those receiving placebo had a reduction of 50% or more in their score on the Young Mania Rating Scale (YMRS). The difference between treatment groups on this and all other outcome measures examined was not statistically significant. When the sample was divided into children (age 7–12) and adolescents (age 13–18), the response rate to oxcarbazepine was similar across age groups, with 43% of adolescents and 41% of children responding. The response to placebo, however, was higher in adolescents (40%) than in children (17%).

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This study was a large undertaking, and it reflects a recent upsurge in interest in pediatric bipolar disorder. Interest has been fueled by the suggestion that bipolar disorder is underdiagnosed in youths as well as the related question of whether extremely irritable children with a diagnosis of attention deficit hyperactivity disorder are in fact suffering from bipolar disorder (1, 2). The increased interest in pediatric bipolar disorder also reflects a paradigm shift in which chronic adult psychopathologies such as schizophrenia and bipolar disorder are viewed increasingly from a developmental perspective, that is, as the expression of neurodevelopmental perturbations that are first manifest in childhood. Finally, research data indicate that pediatric bipolar disorder is a severe and impairing illness: affected children are ill approximately 60% of the time (3, 4); 66% have been psychiatrically hospitalized at least once, and 35% have made a suicide attempt (5).

Parents and clinicians can only be appalled by the contrast between the ample evidence documenting the severity of pediatric bipolar disorder and the paucity of controlled trials to guide its treatment; clinicians often must rely on adult clinical trials, open trials, and even case reports when deciding how to treat a child with bipolar disorder (6). In this context, the report by Wagner et al. is most welcome. The study's design represents the gold standard for clinical trials: a parallel-group, randomized, double-blind, placebo-controlled trial with a large enough sample to detect moderately large treatment effects. In contrast, the only published placebo-controlled trial of oxcarbazepine in adults with bipolar disorder included six patients, and the largest randomized trial, which compared oxcarbazepine and lithium, included 52 patients (7). Wagner et al.'s study represents a major accomplishment in this area.

Conducting a placebo-controlled, randomized treatment trial with adults with bipolar disorder is itself no easy task, and conducting one with youths presents additional challenges. For one thing, even if pediatric bipolar disorder is more common than once thought, it is still a relatively rare disorder, which means that large sample sizes can be attained only by multisite studies such as this one. Twenty sites participated in the study, presenting the investigators with multiple challenges in ensuring reliability and procedural consistency across sites. Another complicating factor with such studies is

that families and physicians alike are often understandably reluctant to enroll children in placebo-controlled trials,—especially those with an illness as severe as bipolar disorder—despite the critical importance of a placebo group in clinical trials. In this study, as the authors note, the response rate for oxcarbazepine was similar to that reported in an open trial of divalproex, lithium, and carbamazepine (8); without the placebo arm, in which 26% of patients responded, the authors might have concluded that a response rate of 42% demonstrated that oxcarbazepine is effective in treating pediatric bipolar disorder, when in fact there was no significant difference in outcome between the two treatment groups.

In the end, after a great deal of careful work, Wagner et al. found no difference between oxcarbazepine and placebo. Was this because the placebo response rate in this study was high, or the oxcarbazepine response rate low? Reviews of placebo response rates in psychopharmacological trials with youths (9) and in clinical trials with adults with mania (10) provide evidence that the rates in the Wagner et al. study are well within the range reported in other studies.

Developmental influences on placebo response merit further study. Wagner et al. report a higher placebo response rate in adolescents than in children, whereas some studies of pediatric depression find higher placebo response rates in children (11). The use of placebo run-in periods or of relatively few study sites may lower placebo response rates, but these approaches add to the challenge already inherent in studying this patient population.

Psychopharmacological trials typically rely on relatively low thresholds for defining response to medication, a practice that may have the effect of inflating placebo response rates. In this study, subjects were considered responders if they achieved a decrease of 50% or more in mania symptom severity—yet many youths with bipolar disorder would still be quite ill after a 50% decrease in symptom severity. Thus, the study's findings highlight the fact that we need pharmacological agents capable of producing full remission. With remission as the standard for defining response, it is doubtful that more than a handful of patients would "respond" to placebo.

What is the most likely research avenue from which novel treatments will emerge? If developments from other branches of medicine can be used as a guide, advances in pathophysiological research, such as recent work on intracellular signaling cascades (12), are likely to provide novel insights relevant to therapeutics. As new compounds are identified, trials using the same design as Wagner et al. will provide definitive information about the safety and efficacy of new agents.

What are clinicians to conclude about the utility of oxcarbazepine in the treatment of mania in youths? While Wagner et al. were unable to demonstrate that oxcarbazepine is significantly more effective than placebo, there was a trend toward significance on two clinical measures—percentage of subjects achieving a reduction of ≥50% in YMRS score and mean change in Clinical Global Impression scale modified for bipolar disorder. Data from studies comparing oxcarbazepine with other medications provide some support for the drug's efficacy in adults, but we must be cautious about extrapolating efficacy (and tolerability) data from adult subjects to children.

Perhaps the most important message implicit in the results of this study is that more clinical trials using the gold-standard method of evaluating therapeutics are needed for youths suffering from bipolar disorder. Several trials of treatments for pediatric bipolar disorder are under way, and their results are eagerly awaited. In the meantime, the Wagner et al. study provides clinicians with some justification, albeit relatively weak, for trying oxcarbazepine in youths with bipolar disorder; at the same time, it highlights the fact that the data on the use of this drug are limited. For now, unfortunately, clinicians, their patients, and their patients' families must continue to fly not quite blind, but in much foggier conditions than anyone would want.

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