Improving Outcome in Pediatric Depression

Controversy about the diagnosis and treatment of depression in children and adolescents has been ongoing for at least 30 years—prior to that, it was not thought that children could get depressed. The paper by Morrato and colleagues in this issue suggests that the controversies have focused on the wrong issues, or, at the very least, have neglected an important question: How can we improve outcome in this often chronic, recurrent disorder that causes significant morbidity and mortality?

In the 1970s and 1980s, the focus of research (and subsequent controversy) was on whether depressive disorders even occurred in the pediatric population, and if they did, whether they were the same as depressive disorders in adults. In 1973, Weinberg and colleagues (1) presented data on the diagnosis of depression in a cohort of 72 children with learning difficulties in the *Journal of Pediatrics*, and they described the treatment of 19 children with antidepressants. The journal's editor wrote, "the Editor feels it is necessary to stress extreme caution 1) in identifying any child as having a depressive illness, and 2) in prescribing any medication for such a disorder." The editor also recommended future research directions for pediatric depression, including randomized, placebo-controlled trials (1).

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Over the next 20 years, research on antidepressant treatment for pediatric depression increased, but only about 250 children were involved in randomized controlled trials. The lack of results demonstrating efficacy of tricyclic antidepressants in pediatric populations suggested that extrapolating from adult data was problematic in this population, so additional studies specific to children and adolescents with depression were needed. The first positive trial of fluoxetine in children and adolescents (ages 8–18 years) with major depressive disorder was funded by the National Institute of Mental Health (2). The pharmaceutical industry also increased its support, although to a limited extent, for pediatric research in all areas, including psychiatry. Then, in 1997, the Food and Drug Administration (FDA) Modernization Act made it mandatory that all new compounds with potential use in the pediatric population be studied in children and adolescents. The act also encouraged pediatric research on medications that were approved for use in adults and were also used in children and adolescents. This legislation was followed by the Best Pharmaceuticals for Children Act in 2002, which established a process for studying medications in pediatric populations to improve clinical trial investigations (e.g., clinical study design, weight of evidence, ethical and labeling issues, etc.).

Even with the implementation of these laws, however, there were problems with new pediatric data, including lack of research infrastructure and methodological flaws in study design; moreover, the optimal design for pediatric trials remained undetermined. Despite these limitations, such studies have provided substantial information on the use of antidepressants in the pediatric population, and the number of pediatric subjects enrolled in randomized controlled trials has increased by more than 200% in the past 10 years. The growing body of data on both pharmacological and nonpharmacological treatments resulted in the formulation of guidelines for treating depression in children and adolescents that parallel those for treating depression in adults.

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The growing pediatric data also suggested that treatment with antidepressants is associated with an increased prevalence of suicidality (suicidal behavior and ideation), with 4% of subjects on active treatment and 2% of those on placebo reporting increased suicidality. (There were no completed suicides in any of these trials.) In light of these findings, safety concerns prompted the FDA to issue a public health advisory and to mandate a black box warning for all antidepressants emphasizing close monitoring of pediatric patients after initiation of antidepressant treatment (3).

Treatment guidelines, which are based on available data and updated as new data are obtained, have been published for pediatric depression since 1998, with revisions issued as recently as 2007 (4–8). These guidelines provide not only recommendations for the assessment and treatment of youths with depression but also suggestions for methods of clinical management, such as visit frequency, monitoring of symptom improvement and adverse events, and management of difficult cases.

Morrato et al., using a large national claims database of managed care plans with data covering the period of 1998–2005, found that two-thirds of prescriptions for antidepressants for depression in children were written by nonpsychiatrists. They also found that patients were seen infrequently, even after initiation of antidepressant treatment. They further found that the FDA advisory emphasizing safety concerns did not lead to an increase in frequency of office visits and that in fact frequency of contact remains low. Less than 5% of pediatric patients had the FDA-recommended frequency of visits, and only 60% had at least three visits during the 12 weeks following prescription of an antidepressant.

The authors acknowledge limitations in their use of a managed care database. It is not clear whether treatment in the public sector or non-managed care settings would be better or worse in terms of visit frequency. Also, managed care likely identifies more primary care use than specialty care.

The paper raises several important questions. The ongoing controversy about treating depression in youths has focused discussion on which treatments are effective and safe. However, a major concern usually missed in this controversy is that less than 50% of children and adolescents with depression ever receive treatment at all. Also, among youths who do receive evidence-based treatment, as noted in the paper, they rarely receive it as recommended.

Visit frequency obviously is not equivalent to optimal treatment, but it is an important component of ensuring optimal treatment. Even before the FDA advisory on antidepressants and visit frequency, published treatment guidelines recommended frequent follow-up visits (every 1–2 weeks) after initiation of medication to monitor for side effects (8), which generally occur early in treatment.

Clearly, if patients (pediatric or adult) do not receive adequate follow-up care, the result is often poor compliance and poor outcome. Over 50% of adults with depression who are given a 30-day prescription by a primary care physician do not refill the prescription. Improving follow-up care could help limit the number of patients who do not adhere to recommended treatment.

While professional organizations, such as APA and the American Academy of Child and Adolescent Psychiatry, develop treatment guidelines, research to examine guideline implementation has been limited, despite evidence that adhering to guidelines improves outcome. In addition, there is a great need for psychiatrists to collaborate with primary care physicians to improve treatment of depression in primary care, particularly since the majority of antidepressant prescriptions are written by primary care physicians.

While there was evidence of an increased risk of suicidal behavior associated with antidepressants, the FDA advisory was also driven by personal testimony that pediatric patients receiving prescriptions for antidepressants were being inadequately monitored. The intent of the warning appears to have been to change provider practice (i.e., to increase monitoring of youths being treated with antidepressants). However, this attempt at changing provider behavior appears to have resulted instead in an overall de-

crease in antidepressant prescriptions for children and adolescents, with no apparent change in monitoring. Furthermore, the decrease in prescriptions very likely has had an adverse impact on youths who genuinely need antidepressant treatment, as suggested by the subsequent rise in suicides in this age group.

The data provided in the paper by Morrato et al. are important in identifying the fact that changes are needed to improve clinical monitoring of antidepressant treatment. Had these data been available at the time of the FDA advisory group meeting, more realistic recommendations might have been made. Hopefully, the focus will soon turn to evaluating barriers to implementing guidelines in clinical settings and articulating realistic goals for the implementation of evidence-based care, with the ultimate goal of improving outcomes for children and adolescents with depression.

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Dr. Emslie has received research support from Eli Lilly, Organon, Shire, Somerset Pharmaceuticals, BioBehavioral Diagnostics, Inc., and Forest Laboratories; has consulted for Eli Lilly, GlaxoSmithKline, Wyeth-Ayerst, Shire, and BioBehavioral Diagnostics, Inc.; and is on the speakers bureau for McNeil. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.