The FDA Pediatric Advisories and Changes in Diagnosis and Treatment of Pediatric Depression

Pediatric depression is a national health problem that clinical, research, and public health activities aim to prevent and treat. Naturalistic longitudinal studies have shown correlations between prepubertal depression and high rates of suicidal ideation and behavior, and prepubertal depression has been found to be a predictor of both suicide attempts in adolescence and suicide in young adulthood (1–3). Moreover, the majority of pediatric suicide victims suffer from depression near the time of death (4, 5). Given the inherent relationship between depression and suicidality, close monitoring for recurrences of pediatric depression is essential.

Indirect evidence suggests that pediatric antidepressant treatment reduces the risk of suicide. Olfson et al. (6), using representative national databases to study regional changes in rates of antidepressant prescription and adolescent suicide between 1990 and 2000, found an inverse relationship between the two. Another study found that higher rates of prescription fills for selective serotonin reuptake inhibitors (SSRIs) from 1996 to 1998 were associated with lower suicide rates among 5- to 14-year-olds (7).

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The Treatment for Adolescents With Depression Study (TADS), a 12-week randomized controlled trial sponsored by the National Institute of Mental Health, compared cognitive behavior therapy alone, fluoxetine alone (the only SSRI approved in the United States for pediatric depression), combined cognitive behavior therapy and fluoxetine, and placebo in 439 youths 12–17 years of age with a diagnosis of major depressive disorder (8). Combined treatment was more effective in reducing symptoms of depression (71.0% improved) than fluoxetine alone (60.6% improved), cognitive behavior therapy alone (43.2% improved), or placebo (34.8% improved). Although the study excluded adolescents at high risk of suicide, 29% of participants had suicidal ideation at study entry. Suicidality decreased significantly in all four treatment arms. The rate of suicide attempts was low (1.6%) during the study, with no completed suicides. There were significantly more harm-related adverse events among participants who received fluoxetine than among those who did not.

Extensive debate about the safety of antidepressants for pediatric anxiety and mood disorders began when the U.K. Medicines and Healthcare Products Regulatory Agency advised on June 10, 2003, that paroxetine not be prescribed for anyone under 18 (9). On June 19, 2003, the U.S. Food and Drug Administration (FDA) issued a statement recommending that paroxetine not be used for treating pediatric depression. The FDA requested that pharmaceutical companies submit suicidality data from pediatric antidepressant clinical trials. In August 2003, Wyeth voluntarily changed labels for pediatric-use venlafaxine and issued a "Dear Health Care Provider" letter indicating that higher rates of hostility and suicidality had been reported for pediatric patients treated with venlafaxine in clinical trials. After an initial review of pediatric antidepressant clinical trials, the FDA issued a public health advisory on October 27, 2003, indicating that current data suggested an association between antidepressants and suicidality in pediatric patients treated for depression.

On February 2, 2004, at a joint open meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee, the committees agreed that the FDA should undertake an empirical evaluation of the safety of SSRIs and other newer antidepressants in pediatric clinical trials. Six weeks later, on March 22, the FDA issued another public health advisory calling for "close observation of adult and pediatric patients" treated with any of a list of 10 new-generation antidepressants.

The FDA began a reevaluation of data on 4,582 pediatric participants in 24 antidepressant trials of 4–16 weeks' duration (23 industry-sponsored trials and the TADS study) for depression (N=16), obsessive-compulsive disorder (N=4), generalized anxiety disorder (N=2), social anxiety disorder (N=1), and attention deficit hyperactivity disorder (N=1). The drugs studied were bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine. Because suicidality ratings varied, the FDA appointed researchers assembled by Columbia University to develop a reliable suicidality classification and to rerate pediatric suicidality in the various clinical trials. At a second advisory meeting, conducted September 13–14, 2004, FDA researchers presented statistical reanalyses of suicidality data indicating an increased risk of drug-induced suicidal behavior (relative risk=1.95, 95% CI=1.28–2.98) from the combined database of the clinical trials (10). Although no suicides occurred during any of the trials, the data implied that 1% to 3% of treated patients could be at risk of antidepressant-induced suicidality (10). The committee concluded that a causal link exists between antidepressant treatment and pediatric suicidality and advised that policies be implemented for pediatric use of antidepressants. On October 15, 2004, the FDA mandated that the pharmaceutical companies add a black box warning to the labeling of all antidepressants used with pediatric patients and that they include a patient medication guide.

The article by Libby et al. in this issue of the *Journal* highlights significant changes in aggregate rates of diagnosis and antidepressant treatment of pediatric depression within 2 years after the October 2003 FDA advisory was issued. The authors used the PharMetrics Patient-Centric Database, a national integrated claims database of more than 85 managed care plans, to analyze data on a cohort of 65,349 children 5–18 years of age who were diagnosed with depression between October 1998 and September 2005. Using time-series analyses, Libby et al. compared the observed rates of depression diagnoses and antidepressant prescription fills in the 2 years after the October 2003 FDA advisory with the expected rates based on the trend during the 5 years before the advisory. The postadvisory interval included a period of 11 months after the FDA ordered the black box warning on antidepressant-induced pediatric suicidality (October 2004), and a period of 7 months after the agency approved the language for the black box warning (February 2005).

Libby et al. suggest that although national rates of diagnosing new-onset pediatric depression increased from 3 cases to 4 cases per 1,000 from 1999 to 2004, after the FDA issued its final recommendations in February 2005, diagnosis rates dropped back to 1999 levels. Prior to the FDA's October 2003 advisory, rates of depression diagnoses made by pediatricians and nonpediatrician primary care physicians steadily increased and accounted for the majority of diagnoses of pediatric depression. After the advisory, rates of diagnosing pediatric depression significantly decreased among primary care physicians, were unchanged among pediatricians, and significantly increased among psychiatrists. Prior to the advisory, 59% of depressive episodes were associated with an SSRI prescription fill within 30 days of diagnosis, and the rate increased significantly over time. After the advisory, the percentage of SSRI prescription fills after diagnosis gradually but significantly decreased, and by 2005, SSRI prescriptions were filled for only 28% of episodes. Antidepressant prescription rates among primary care physicians were on the increase prior to the advisory, and this trend reversed significantly after the advi-

sory. The prescribing trend among psychiatrists was slightly but significantly negative prior to the advisory, and this trend also reversed after the advisory. Libby et al. found that utilization of psychotherapy, atypical antipsychotics, and anxiolytic medications did not change significantly over the study period.

The FDA's advisories had the well-meaning intent of providing information about the safety of antidepressants in pediatric use, and the agency recommended a black box warning to improve treatment safety. However, these policy actions may have had the unintended effect of discouraging the prescription of antidepressants for pediatric patients and pediatric utilization of antidepressants without compensatory increases in other specific treatments. If so, this may have resulted in the lower rates of diagnosing and treating new-onset pediatric depression seen in this study, which may well have meant that many pediatric patients received less psychiatric treatment than needed, which in turn may be a factor in the increased rates of youth suicide reported in previous epidemiological studies (6, 7).

The Libby et al. study did not evaluate possible underlying causes of shifts in rates of diagnosing depression and prescribing antidepressants. The increases in rates of diagnosis and antidepressant treatment prior to the October 2003 advisory may have been related to the pharmaceutical industry's impact on practitioners. It may be that after the FDA advisories were issued, primary care physicians became increasingly concerned about their clinical skills and the time needed for managing pediatric depression. Similarly, pediatric patients and their parents, with insufficient information about treatment options for pediatric depression, may have become reluctant to seek intervention after the FDA advisories.

The postadvisory trends might have differed substantially if professional organizations had aggressively developed new guidelines, standards, and educational programs for practitioners in diagnosing and treating pediatric depression and if advocacy groups and professional organizations had coordinated efforts to educate the public about ways to recognize pediatric depression and the imperative of seeking effective treatment. It is essential that the long-term impact of the FDA policy actions be determined empirically and that additional research be conducted on ways to enhance the effectiveness of treatments for pediatric depression.

The FDA did not recommend against use of antidepressants in pediatric treatment; its aim, rather, was to improve medical care by stimulating more extensive monitoring and collaboration among practitioners, patients, and parents and to educate consumers through an industry-provided patient medication guide describing risks and precautions for pediatric antidepressant treatment. The black box warning should not discourage practitioners from prescribing, and pediatric patients from utilizing, clinically indicated antidepressants. It should prompt providers to adhere to the FDA recommendations for close monitoring and to inform pediatric patients and their parents of the possible beneficial as well as adverse effects of antidepressants and the importance of compliance with prescribed treatment. These steps can decrease the risk of adverse outcomes. As educational information is more widely disseminated to professionals and the public, as provider skills in diagnosing and treating pediatric depression are enhanced, and as more time is allotted to consistent monitoring of pediatric antidepressant treatment, future research may well find greater pediatric treatment utilization than we saw during the period of the Libby et al. study.

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