A Developmental Perspective on the Controversy Surrounding the Use of SSRIs to Treat Pediatric Depression

Since the 1990s, there has been at least a 3- to 5-fold increase in the prevalence of antidepressant treatment for U.S. youths aged 2–19 years (1). Although children over the age of 10 were the most likely to receive prescriptions for antidepressants, this increase has been observed across all age groups. For example, Zito et al. (2) documented that, from 1991 to 1995, preschool-age children (2–4 years old) had a 1.3- to 2.2-fold increase in antidepressant treatment. As documented by Gibbons et al. in this issue of the Journal, these dramatic increases continued until 2003–2004 when the Food and Drug Administration, as well as British and European regulators, issued public health advisories concerning the risk of suicide and self-harm associated with the use of antidepressant medication in the pediatric population. In the wake of these advisories, there has been a marked reduction in the number of prescriptions for selective serotonin reuptake inhibitors (SSRIs) in both the United States and Europe.

Is this a positive development or one that will lead to increased numbers of suicides in this vulnerable population? Gibbons et al. raise concerns about the potential for harm that may arise out of the decreased use of SSRIs in the pediatric population by pointing out an increase in suicide rates in both the United States and the Netherlands. Indeed, they offer specific predictions concerning the actual number of completed suicides should the number of prescriptions continue to decline. Unfortunately, they did not include an analysis of similar ecological data for both countries over the preceding decade, which presumably would have shown the reciprocal relationship—falling rates of suicide directly associated with the rising number of SSRIs prescriptions (3). Nor did they address the conflicting results from a recent case-control study that found in children and adolescents the risk of suicide attempts was 1.52 times higher after antidepressant drug treatment compared with no antidepressant treatment (4). Although the data presented by Gibbons et al. are largely compelling, we prefer to take a more nuanced, developmental viewpoint.

First, let us state that children and adolescents with major depression and other mental disorders associated with an increase of suicide are deserving of timely, efficacious, safe, and closely monitored treatment. Doubtless in many instances, this will involve the use of SSRIs, as it is clear, especially in short-term clinical trials, that relative to placebo the benefits of antidepressants appear to be much greater than the risks from suicidal ideation and self-harming behaviors (5). However, we hasten to point out that this comparison of benefit to risk varies as a function of age and indication. For example, in a recent meta-analysis of pediatric antidepressant treatment involving data from nearly 6,000 children and adolescents (5), the study’s authors were unable to detect a pooled-risk difference in response greater than zero in children younger than age 12 treated for major depressive disorder with SSRIs, in part due to a high rate of placebo response. Specifically, across the five trials for which age-grouped data were available, the placebo response rate was 58% for children under the age of 12 versus a 65% response rate for
EDITORIAL

those randomly assigned to active medication. Only one agent, fluoxetine, outperformed placebo in depressed children within this age group.

Second, since the choice of treatment should be the result of a collaborative discussion among the clinician, family, and patient, presentation of data concerning age-specific benefits should allow for an informed evaluation of the potential benefits and risks of these medications versus no treatment and provide a framework for their comparison with nondrug treatments.

Third, we are of the opinion that these discussions should also clearly indicate to parents that there is a paucity of data concerning the long-term effects of these agents, and what data are available are a source of concern. For example, limited data suggest that the long-term use of antidepressants may be associated with the emergence of bipolar disorder and that this risk appears to be greatest among the youngest group of children exposed (6). In one study, children exposed to antidepressants were at highest risk of conversion (number needed to harm: 10 [95% confidence interval (CI)=9–12] among 10- to 14-year-olds versus 23 [95% CI=21–25] among 15- to 29-year-olds).

It is also remarkable how few data are available concerning the long-term effects of these agents on the developing CNS. Despite the recent explosion of knowledge in the developmental neurosciences, there remains only a handful of studies that address the impact of antidepressant exposure during CNS development. More remarkably, nearly every study indicates the potential for a long-term negative impact. For example, transient inhibition of the serotonin transporter during early development with fluoxetine resulted in major reduction in exploratory activity as well as significant impairment in shock avoidance in adult mice (7). Other studies in rats have documented that early exposure to citalopram results in deficits in adult male sexual behavior and altered locomotor activity (8, 9). Early exposure to citalopram was also found to cause profound reductions both in the rate-limiting serotonin synthetic enzyme (tryptophan hydroxylase) in dorsal raphe and in serotonin transporter expression in cortex that persist into adulthood (8). More recently, LaRoche and Morgan (10) have reported that adolescent fluoxetine exposure produces enduring, sex-specific alterations of visual discrimination and attention in male rats. We conclude that the widespread use of SSRIs to treat prepubertal children with depression or anxiety may be associated with untoward outcomes for some. We may ignore the potential long-term effects of these agents on CNS development to the peril of the children and families that we serve.

In this regard, we applaud the work of John March and his Child and Adolescent Psychiatry Trials Network, which has just begun a prospective longitudinal cohort “safety registry” study of newer antidepressants in 2,420 children and adolescents with a depressive disorder, anxiety disorder, obsessive-compulsive disorder, or eating disorder. The overall goal of the study is to identify factors that predict benefit and harm in the “average patient” and also to identify those patient-specific factors that predict who should always and who should never receive a particular medication. This effort is needed and long overdue.

Fourth, the work by Melhem et al. in this issue of the Journal has clear implications for prevention. Offspring of mood-disordered parents are at increased risk for suicidal behavior, especially in the presence of mood disorder and impulsive aggression in the offspring and a history of suicide attempt and sexual abuse in the parents. Hence, those treating depressed adults must be aware of the need for careful follow-up and early intervention for their offspring (11). Conversely, those treating depressed adolescents must be alert for a history of parental depression and sexual abuse as markers for increased suicidal risk. Indeed, in studies of the familial aggregation of suicidal behavior one factor that has been repeatedly identified is impulsive aggression (12). As has been emphasized in previous studies of adults, the assessment and management of impulsive aggression are likely to be critical to the prevention of onset or recurrence of suicidal behavior impulsive aggression. In adults, psychosocial interventions that increase
emotion regulation and decrease impulsive aggression are among the only interventions that have been shown to diminish the risk of reattempt (13, 14).

References

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