

# Virtual Mentor

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## Journal Discussion

### **Black Box Blues: Kids and Antidepressants**

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**March J, Silva S, Petrycki S, and the Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive behavioral therapy, and a combination for adolescents with depression: Treatment for adolescents with depression study (TADS) randomized controlled trial. *JAMA*. 2004;292:807-820.**

Recent warnings about antidepressants have spurred a vigorous debate over suicide risks among children and adolescents. Prevalence rates for pediatric depression of up to 3 percent in children and 8 percent in adolescents have been reported. A lifetime prevalence rate of depression for 15 to 18 year olds is estimated at 14-15 percent [1]. According to unpublished information from the CDC's Mortality Statistics branch in 1999, more than half of the children with childhood depression will eventually attempt suicide and more than 7 percent will die as a result. Children with depression, whether taking antidepressant medications or not, are at increased risk for suicidal intent. The risk is increased for those children with bipolar disorder, prior suicide attempts, and a history of substance abuse, anxiety disorders, and other comorbid psychiatric conditions. [2, 6-7]

Over the past decade, the suicide rate has decreased significantly to approximately 2000 children and adolescents per year [2]. Despite this decrease, suicide remains the third leading cause of death among children, adolescents, and young adults under 25. According to the unpublished study by the Center for Disease Control (CDC), the incidence of suicidal ideations has dropped from 1 in 4 to 1 in 6 children per year. Controversy regarding the use of antidepressant medication in the pediatric population reached a peak in June 2003 when the FDA issued a "Do Not Use Warning" for paroxetine (Paxil) due to potential risks and concerns regarding suicidal ideation in the pediatric population [3].

### **Commentary on the FDA Black Box Warning**

On October 15, 2004, the FDA announced new warnings and precautions to strengthen safeguards for children and adolescents treated with antidepressant medications. The "Black Box Warning," the strongest warning the FDA can issue, reported that "antidepressants increase the risk of suicidal thinking and behavior in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders [4]." Anyone considering the use of a medication with a black box drug warning or any other antidepressant in a child or adolescent must balance this risk of the medication with the clinical need. Patients taking antidepressants should be observed closely for clinical deterioration, suicidality, or unusual behavior changes.

Families and caregivers should be advised of the need for close observation and communication with the prescriber.

The FDA relied on a pooled analysis of 24 short-term (4-16 week) placebo controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), and other psychiatric disorders. They reported a greater risk of adverse events including suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events on medication was 4 percent, twice the placebo risk of 2 percent. No suicides occurred in these trials. It is important to note that although a black box warning was issued, none of the 4400 pediatric study subjects committed suicide. Out of the 4400 patients studied, 78 experienced suicidal thinking or suicidal behavior.

In a letter from American Academy of Child and Adolescent Psychiatry (AACAP) President Richard M. Sarles to FDA Acting Commissioner Lester M. Crawford, October 28, 2004, the AACAP expressed concern over the current FDA black box warning, reporting that the recommendation of the FDA is not consistent with current research.

The FDA black box warning will have significant impact on primary care physicians, who often attempt to refer these patients to child and adolescent psychiatrists. There are not enough child psychiatrists, even within metropolitan areas, to serve children with mental health needs. In addition, many parents may decline the use of antidepressant medication for their children as a result of the warning. Based on the clear benefit of antidepressant medication in treating depression, as seen in current research and clinical experience, there may be an increase in pediatric morbidity and mortality related to untreated depressive episodes.

It is important to understand that the current FDA warnings do not prohibit the use of antidepressants in children. However, the current warning will likely have the negative effect of frightening many people from using antidepressants.

### **Overview of TADS Study**

The TADS study is a multisite clinical effectiveness trial comparing the use of fluoxetine, cognitive behavioral therapy (CBT), a combination of the 2, or placebo, in the treatment of adolescents between the ages of 12 and 17 years of age with moderate to severe major depression [5]. The study, known as TADS (Treatment of Adolescents with Depression Study) is sponsored by the National Institute of Mental Health (NIMH).

Within this study, 20 percent of adolescents with moderate to severe depression expressed clinically significant suicidal ideation prior to treatment. Over the course of the study, 71 percent of the patients responded positively to a combination therapy with fluoxetine and CBT. The placebo response rate was 35 percent. The response rate for patients who were prescribed fluoxetine alone was 60.9 percent. The response rate for those receiving cognitive behavioral therapy alone was 43.2 percent.

Researchers from various sites using standardized clinical rating scales assessed patients at 6-week and 12-week intervals. Suicidal ideation decreased in those patients who received a combination of fluoxetine and cognitive behavioral therapy. Patients treated with fluoxetine alone and cognitive behavioral therapy alone continued to have suicidal ideation that did not differ significantly from the incidence in those receiving the placebo. A total of 5.55 percent of the patients had suicide-related events; however, there were no completed suicides in the study.

The TADS study involved 439 moderately to severely ill children and adolescents. Within this study, there were 7 suicide attempts (1.5 percent of the sample) and 24 “suicide related events” (5.5 percent). Of the 24 suicide-related events, 15 patients were on Prozac alone and 9 were receiving CBT or placebo, but no medication. There was no significant difference between these two groups.

In summary, the TADS study showed that 25 to 30 percent more of the patients receiving treatment with fluoxetine or a combination of fluoxetine and cognitive behavioral therapy had a positive response to treatment than was experienced by children and adolescents who were given placebo. Even under the best treatment circumstances, 29 percent of the adolescents did not respond to the prescribed treatment, a matter of concern. Based on the clinical results of the TADS study, however, the risk-benefit ratio was very positive for the treatment of pediatric depression with antidepressant medication and cognitive behavioral therapy.

One of the more interesting findings of the TADS study is that there appears to be a protective mechanism for adolescents who are on combined treatment with antidepressant medication and cognitive behavioral therapy. Children who are given antidepressant medication without cognitive behavioral therapy have a slightly greater increase in suicidal ideation than those who are on a combination of antidepressant medication and cognitive behavioral therapy. The latter group showed no increase in suicidal ideations.

The study is important because it shows the clinical efficacy of fluoxetine in treating pediatric depression. This study also shows the importance of the combined treatment with fluoxetine and CBT.

### **Conclusion**

The results of empirical studies accepted with no theoretical framework leaves our patients at risk. The risk of children going without appropriate treatment for their underlying depression may increase the morbidity and mortality of the pediatric population suffering from depression. Although the FDA did not contraindicate the use of antidepressants except for paroxetine, it is likely that their action will affect the treatment practice of many physicians. Treatment practices regarding depression have already changed since the FDA warning. Child and adolescent psychiatrists and other physicians are commonly using fluoxetine as a first-line treatment. Physicians are also more likely to follow current FDA suggestions regarding frequency of visits, even though there is no specific research to support the frequency of face-to-face contacts.

Treating depression requires experience, research-based clinical knowledge, and an understanding of the effect of social, familial, and cultural factors. Based on current research, the most effective treatment for depression combines cognitive behavioral therapy and antidepressant medication. Although treatment with antidepressant medication may involve risks, untreated depression may have devastating consequences. The natural course of depression will continue to place children and adults at a higher risk for suicide. Physicians must use all of their clinical expertise and knowledge of the research in their treatment of the individual and the family.

At present, we need a better independent assessment of all of the current research data. Continued funding for independent research on pediatric depression is a vital necessity. Therapeutic trials of medication and a variety of psychotherapies with children of all ages are essential to ensure the appropriate management and treatment of the pediatric population with depression.

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