

ANTIDEPRESSANTS AND THE RISK OF SUICIDAL BEHAVIOR

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Introduction

Research indicates that, at any one time, as many as 8% of adolescents experience depression (Lock, Walker, Rickert & Katzman, 2005). Because mood disorders, such as depression, substantially increase the risk of suicide, much attention has been placed on measuring the effectiveness of treatments for depression. This is particularly true for adolescents because depression in that age group is a strong indicator of suicidal behavior (Treatment for Adolescents with Depression Study [TADS], 2004; Miller, Rathus & Linehan, 2007). Given the serious nature of depression among adolescents, it is imperative that the most effective treatment be made available while minimizing any risks associated with these treatments are minimized (Lock, Walker, Rickert & Katzman).

Different treatments have been shown to be effective for children and adolescents diagnosed with depression. Certain antidepressant medications, selective serotonin reuptake inhibitors (SSRIs), have been shown to be effective (National Institute of Mental Health [NIMH], n.d.) However, research has also revealed a possible relationship between suicidal thoughts or actions, known as suicidality, and the use of SSRIs in children and adolescents with depression. This section will review the current literature on the benefits and risks associated with antidepressant use in children and adolescents with depression. Additional information about effective treatments for youth with depression is located in the “Depression and Dysthymia” section of the *Collection*.

Food and Drug Administration Advisory Statement

The first accounts of the use of selective serotonin reuptake inhibitors (SSRIs) in youth with depression was presented to the Food and Drug Administration (FDA) in 2003 (Hammad, Laughren & Racoosin, 2006). The report suggested the possibility that youth diagnosed with major depressive disorder (MDD) being treated with paroxetine, a type of SSRI, experienced increased risk of suicidal thoughts and behaviors (Hammad, Laughren & Racoosin). In response, the FDA reviewed data from the 24 placebo-controlled clinical trials conducted on the use of antidepressants for youth (23 of which were conducted by antidepressant drug manufacturers), specifically looking for the effects of the medication on suicide-related adverse events. The review, as cited by Hammad, Laughren & Racoosin, indicated that:

- 167 events were classified as suicide-related events, although no completed suicides took place in any of the trials;
- 1 to 3% of youth taking antidepressants may experience the onset of suicidal thoughts or behaviors or the worsening of suicidal thoughts and behaviors beyond what would be expected from the underlying psychopathology alone, resulting in a doubling of the number of youth experiencing suicidal thoughts or behaviors.

In 2004, the FDA released a statement based on the recommendations of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Drugs Advisory Committee regarding the possibility that increased suicidal thinking and behavior was associated with antidepressant use in pediatric patients (Wolf, 2005). The Advisory Committees' statement reflected the findings from controlled pediatric antidepressant trials, which found that antidepressant use in pediatric patients presented an increased risk of suicidality (Wolf).

The FDA then directed manufacturers to add a black-box warning to the health professional label on antidepressants which describes the increased risk of suicidal thoughts and behavior in children and adolescents (2004). The following points were to be included:

- Antidepressants increase the risk of suicidal thinking and behavior in children and adolescents with MDD and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- A statement regarding whether the particular drug is approved for any pediatric indication(s) and, if so, which one(s).

Sources: FDA, 2004; Wolf, 2005.

The FDA warning instructs clinicians prescribing antidepressants to children to inform parents and custodial adults of the black-box warning. While an advisory statement was issued, the Advisory Committees did have a split decision (15 yes; eight no) regarding recommendations for a black-box warning for the increased risk of suicidality (Wolf, 2005). In response to the black-box warning, some practitioners have ceased prescribing antidepressants to children and have begun to refer patients to child and adolescent psychiatrists (Virginia Joint Commission on Health Care, 2005).

Effectiveness of Selective Serotonin Reuptake Inhibitors (SSRIs) and the Risk of Suicidality

In evaluating the risk-benefit ratio of using antidepressants, particularly SSRIs, for children and adolescents diagnosed with depression, it is important to have an understanding of the evidence supporting the use of these medicines. Much of what is known about the benefits of antidepressants in treating youth with depression comes from the Treatment for Adolescents with Depression Study (TADS, 2004). TADS was conducted spring 2000 through spring 2003 across 13 clinics throughout the United States. TADS examined the short and long-term effectiveness of one SSRI, fluoxetine, and evaluated its effectiveness, both alone and in combination with psychotherapy, for treating depression in adolescents ages 12 to 17.

TADS compared four different treatment conditions for adolescents with depression: Cognitive Behavioral Therapy (CBT), fluoxetine, combined CBT and SSRI therapy, and a placebo (TADS, 2004). TADS' data indicated that there was an increase in harm-related events among the adolescents who received fluoxetine as part of treatment. Specifically, adolescents treated with fluoxetine alone were twice as likely to experience a suicidal event compared with those treated with combination therapy or CBT.

The study team also concluded, after accounting for benefit and risk, the combination of fluoxetine and CBT was more effective than either treatment alone. Additionally, the SSRI treatment alone was shown to be more effective than the placebo (TADS, 2004). In fact, 61% of the youth treated with fluoxetine experienced a reduction in their depressive symptoms, compared to 35% for the placebo (Lock, Walker, Rickert & Katzman, 2005).

The study's primary conclusion was that fluoxetine treatment for depression in youth is effective, but with some risks, whereas combining CBT with fluoxetine can improve outcomes and reduce the risks associated with fluoxetine (TADS). Overall, fluoxetine has demonstrated the largest effect difference between active drug and placebo (American Academy of Child & Adolescent Psychiatry [AACAP], 2007). It is unclear why other SSRIs have not consistently demonstrated effectiveness over placebo, but possibilities include little effect and poor study design, too-low doses and insufficient duration of treatment (AACAP).

Researchers have also looked at the trends in suicide since SSRIs became more commonly used. Olfson, Shaffer, Marcus and Greenberg (2003) examined the trend in the number of suicides occurring from 1990 to 2000 and compared those to the number of youth prescribed antidepressants during that period. This study found an inverse relationship between youth suicide and use of antidepressants and noted that the increased rate of antidepressant use in children and adolescents from 1990 to 2000 was associated with a decrease in suicide rates (Olfson et al.). Further, analysis indicated that SSRI use was associated with an even more notable decrease in the suicide rate in high-risk populations, older adolescents and males, and underserved populations, minorities and low income youth (Olfson et al.).

However, a more recent study comparing the use of CBT, sertraline (an SSRI), CBT plus sertraline, and a placebo in the treatment of youth with anxiety disorders found that, when compared to the placebo, sertraline was not associated with increased suicidality (Walkup et al., 2008). There were no suicide attempts and there were no significant differences in the rate of suicidal ideation between any of the groups (Walkup et al.). This study, however, focused on anxious, rather than depressed youth. Thus, the study does not directly assist in understanding the risk associated with employing SSRIs in treating depressed youth.

Limitations of the Research on Suicidality and Antidepressants

When making decisions about the risks associated with antidepressants, particularly SSRIs, it is important to understand the limits of the research. Suicidality can be very difficult to measure. This is because the statistical method used to evaluate the risk associated with treating children and adolescents with antidepressants can only be used in studies where a minimum of one adverse event took place (AACAP, 2007). Conversely, a study which fails to detect a significant increase in suicidal risk associated with antidepressant medication does not necessarily indicate that there is not a risk (Walkup et al., 2008).

Hammad et al. (2006) outlined some of the major limitations of the meta-analysis of suicidality in the antidepressant treatment trials. These studies' limitations are:

1. subsequent analysis using the same data increases the uncertainty of the results;
2. analysis is based on short term (4-16 weeks) outcomes, making any conclusions about the long-term consequences of antidepressants in youth impossible; and
3. measuring suicidal ideation and behavior is inherently difficult due to the distressing nature of the topic.

It is difficult to know whether the increase in suicidal ideation and behavior represents a true increase or simply a change in the rate of report (Hammad). Additionally, all of the trials used by the FDA in making the decision about the black-box warning excluded youth with severe suicidality (Guirgus-Blake, Wright & Rich, 2008). This makes conclusions about the effects of antidepressants on suicidality difficult to formulate. Knowing the effects of antidepressants on youth with severe suicidality is critical, but also currently beyond the present state of the research.

Conclusion

In summary, the accumulated evidence suggests that antidepressants are associated with a real increase in suicidality among youth and young adults. There is, however, evidence to suggest that the benefits associated with treating moderately to severely depressed youth with antidepressants outweighs the risks (Hammad et al., 2006; AACAP, 2007). According to the AACAP, when comparing youth treated for depression with SSRIs compared to placebo, 11 times more remission of depression than those who reported experiencing an adverse event, onset or increase of reported suicidal ideation or suicidal behavior.

The results of research conducted by Olfson et al. (2003) suggest that the use of antidepressants has significantly decreased the rate of suicides, while numerous drug treatment trials indicate that antidepressant use increases the rate of suicidal ideation and behavior among adolescents (Hammad, et al., 2006; TADS, 2004). There is also evidence that SSRIs are more effective than placebo medication in treating adolescents with depressive disorders and that the risks associated with SSRIs can be reduced when youth are concurrently receiving CBT (Sharp & Hellings, 2006; TADS). This is a significant finding in the discussion of the effects of antidepressants on suicide since depressive disorders are a significant predictor of suicidal ideation, suicide attempts and completed suicide (Gould et al., 2003). Another significant finding is that the period of greatest risk for increased suicidality appears to be in the early stages of SSRI treatment (Lock et al., 2005).

In a position paper of the Society for Adolescent Medicine, Lock et al. (2005) concluded that, after balancing the increased risk of suicidality among adolescents treated with SSRIs with their benefits, the evidence supports the use of SSRIs for adolescents with MDD. The American Medical Association (AMA) has asserted that its review of various studies supports the view that antidepressants reduce suicidal behavior and completed suicide attempts overall (2005). The organization does acknowledge, however, that the risk of such behavior appears to be highest during the initial course of drug therapy. The AMA's position is that antidepressants should continue to be available, with their use guided by sensible clinical judgment (AMA). The AACAP concluded that, with close supervision, the risk-to-benefit ratio supports using SSRIs in

the treatment of child and adolescent depression (2007). The Society for Adolescent Medicine, AMA, AACAP and American Psychological Association (APA) support the use of fluoxetine, the only medication approved by the FDA for the treatment of youth with depression, but recommend close monitoring by both parents and clinicians (FDA, 2004; Lock et al., 2005; AMA, 2005; AACAP, 2007; APA, 2006).

Sources

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Additional Resources

Cuffe, S. (2004). *Do Antidepressants Increase the Risk of Suicide in Children and Adolescents?* American Academy of Child & Adolescent Psychiatry (AACAP) DevelopMentor. [Online]. Available: http://www.aacap.org/cs/root/developmentor/do_antidepressants_increase_the_risk_of_suicide_in_children_and_adolescents

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American Academy of Child & Adolescent Psychiatry (AACAP)

Psychiatric Medication

http://www.aacap.org/cs/new_psychiatric_medications/psychiatric_medications

American Psychiatric Association (APA)

The Use of Medication in Treating Childhood and Adolescent Depression: Information for Patients and Families

<http://www.psych.org/Share/Parents-Med-Guide/HTML-Depression.aspx>

MayoClinic.com

Antidepressants and Children: Explore the Pros and Cons

<http://www.mayoclinic.com/invoke.cfm?id=MH00059>

National Institute of Mental Health (NIMH)

Antidepressant Medications for Children and Adolescents: Information for Parents and Caregivers

<http://www.nimh.nih.gov/about/updates/2005/antidepressant-medications-for-children-and-adolescents-information-for-parents-and-caregivers.shtml>

New York University Child Study Center

Guide to Psychiatric Medications for Children and Adolescents

http://www.aboutourkids.org/articles/guide_psychiatric_medications_children_adolescents

Organizations

American Academy of Child & Adolescent Psychiatry (AACAP)

3615 Wisconsin Avenue, N.W. — Washington, DC 20016-3007

<http://www.aacap.org>

American Academy of Pediatrics (AAP)

141 Northwest Point Blvd. — Elk Grove Village, IL 60007-1098

<http://www.aap.org>

American Psychological Association (APA)

750 First Street, N.E. — Washington, DC 20002-4242

<http://www.apa.org>

Center for Healthier Children, Families, and Communities

1100 Glendon Avenue, Suite 850 — Los Angeles, CA 90024

<http://healthychild.ucla.edu>

National Institute of Mental Health (NIMH)

Treatment of Children with Mental Disorders

6001 Executive Blvd., Room 8184, MSC 9663 — Bethesda, MD 20892-9663

<http://www.nimh.nih.gov>