

A NTIDEPRESSANTS AND THE RISK OF SUICIDAL BEHAVIOR

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Introduction

Research indicates that as many as 11 percent of adolescents will experience depression (National Institute of Mental Health (NIMH), n.d.a). Furthermore, according to NIMH, the leading causes of disability in persons aged 15 to 44 years old are depressive disorders. Because depressive disorders (i.e. depression) substantially increase the risk of suicide, much focus 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 in adolescents, it is imperative that the most effective treatment be made available while minimizing any associated risks (Lock, Walker, Rickert & Katzman, 2005).

Different treatments have been shown to be effective for children and adolescents diagnosed with depression. Certain antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs), have been shown to be effective in as many as 7.5 percent of American children who are taking antidepressants and other behavior-modifying medications (NIMH, n.d.b; Heasley, 2014). However, research has also revealed a possible relationship between suicidal thoughts or actions 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 “Depressive Disorders” section of the *Collection*.

Food and Drug Administration Advisory Statement

The first accounts of the use of SSRIs in youth with depression were 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) who were being treated with paroxetine (a type of SSRI) experienced an 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 in youth (23 of which were conducted by antidepressant drug manufacturers), specifically looking for the medication’s effects on suicide-related adverse events. This 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; and
- One to three percent 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 (2006).

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' joint 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 to describe the increased risk of suicidal thoughts and behavior in children and adolescents. The most recent update to the FDA's (2007) warning is outlined in Figure 1.

Figure 1
Key Points of FDA Black-Box Warning Label For Suicidality and Anti-Depressant Drugs

- 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.
- Taper dosage to prevent risks of discontinuation syndrome if stopping SSRI treatment.
- Patients who are started on antidepressant therapy should be observed closely for agitation, irritability, 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), should be present.

Sources: FDA, 2007; Wolf, 2005.

The FDA also recommends that clinicians should screen for bipolar disorder, because symptoms of depression may be part of a bipolar episode and antidepressants used alone may trigger a mixed/manic episode in these at-risk patients (FDA, 2007). The FDA warning instructs clinicians prescribing antidepressants to children to inform parents and custodial adults of the black-box warning. Although an advisory statement was issued, the Advisory Committees did have a split decision (15 yes; 8 no) regarding recommendations for a black-box warning for the increased risk of suicidality (Wolf, 2005). In response to the black-box warning, practitioners such as pediatricians and family 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). One study including 1.1 million adolescents and 1.4 million young adults using automated health care claims data between 2000 and 2010 found a reduction in antidepressant use of 31 percent for adolescents and over 24 percent for young adults (Lu et al., 2014).

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 to counteract suicidal behavior and the risk for suicide in untreated depression. 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 in spring 2000 through spring 2003 in 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), SSRI therapy (fluoxetine), combined CBT and SSRI therapy, and a placebo (TADS, 2004). TADS's data indicated that there was an increase in harm-related events among 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 just CBT.

The study team also concluded that, 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 percent of the youth treated with fluoxetine experienced a reduction in their depressive symptoms, compared to 35 percent for the placebo (Lock, Walker, Rickert & Katzman, 2005).

The primary conclusion of TADS was that fluoxetine treatment for depression in youth is effective, but accompanied 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 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 limited effectiveness, poor study design, too-low doses, and insufficient duration of treatment (AACAP).

A recent study conducted a meta-analysis of available data and concluded that out of 14 available antidepressants, the only effective antidepressant for children and adolescents with major depression is fluoxetine (Cipriani et al., 2016). This study found that fluoxetine was the only medication that had reliable research to back its effectiveness when compared with a placebo. However, it is important to note that children and adolescents taking antidepressant drugs should be closely monitored regardless of the treatment chosen, particularly at the beginning of treatment.

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 compared 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 an overall decrease in suicide rates (Olfson et al.). Furthermore, 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.).

Another 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 address the risk associated with employing SSRIs in treating depressed youth.

A recent study led by Harvard Medical School (Lu et al., 2014) investigated whether the FDA black-box warnings were linked to changes in antidepressant use, suicide attempts, and completed suicides among young people. The study found that FDA warnings and associated media coverage were associated with decreases in antidepressant use and small increases in suicide attempts. Health care organizations that provided care to 10 million people in 12 states participated in the study. The study noted that, after the FDA's warnings, use of commonly prescribed antidepressants fell by 30 percent in adolescents and 25 percent in young adults. The researcher also found that suicide attempts rose in adolescents and young adults. However, no changes were detected in completed suicides. The researchers cautioned that the study did have limitations because it only measured suicide attempts that received medical attention. Data sources also lacked information on patient outcomes and were limited to the insured population. The researchers concluded that reductions in antidepressant use, generated by concern over suicidal thoughts, might have left a portion of depressed young people without appropriate treatment, which may have caused a small increase in suicide attempts.

A comprehensive analysis of health care data of U.S. residents with depression who initiated antidepressant therapy with SSRIs found a connection between dosage and age. The study found that younger patients who began treatment with higher-than-recommended doses of antidepressants were more than twice as likely to try to harm themselves as those who were initially treated with the same drugs at lower, recommended doses (Miller, Swanson, Azrael, Pate, & Stürmer, 2014). The risk of suicide attempts seemed to be highest in the first 90 days on the medications (Miller et al.). This analysis did not detect an increase in suicide risk in youth and adolescents treated with recommended drug dosages.

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 limitations of the research. Suicidality can be very difficult to measure as these events are rare, and 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 has taken place (AACAP, 2007). Conversely, a study that 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, Laughren and Racoosin outlined some of the major limitations of the meta-analysis of suicidality in the antidepressant treatment trials (2006). These limitations are:

- Subsequent analysis using the same data increases the uncertainty of the results.
- Analysis is based on short term (4 to 16 weeks) outcomes, making any conclusions about the long-term consequences of antidepressants in youth impossible, although SSRI-related suicidality would be expected to occur within this time frame.
- Measuring suicidal ideation and behavior is inherently difficult due to the distressing nature of the topic.

A separate study noted other potential research limitations, such as the inability to adjust for the severity of the disorder or for antidepressant adherence (Miller et al., 2014). Moreover, 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, Laughren & Racoosin). 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). However, the inverse relationship between use of SSRIs and the rate of suicidal behavior is also compelling. Thus, categorical conclusions about the effects of antidepressants on suicidality are

difficult to formulate. Knowing the effects of antidepressants on youth with severe suicidality is critical, but more research is required for clearer direction.

Conclusion

In summary, the evidence suggests that antidepressants are associated with an increase in suicidal behavior 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, Laughren & Racoosin, 2006; AACAP, 2007).

The results of research conducted by Olfson et al. (2003) suggest that the use of antidepressants has significantly decreased the rate of suicides, yet 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, Shaffer & Greenberg, 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).

A position paper of the Society for Adolescent Medicine concluded that, after balancing the increased risk of suicidality among adolescents treated with SSRIs with their benefits, the evidence supported the use of SSRIs for adolescents with MDD (Lock et al., 2005). 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 suicidal 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).

Resources and Organizations

American Academy of Child, & Adolescent Psychiatry (AACAP)

<http://www.aacap.org/>

American Academy of Pediatrics (AAP)

<https://www.aap.org>

American Psychological Association (APA)

<http://www.apa.org/>

National Institute of Mental Health (NIMH)

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

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