Antidepressants, Teen Suicide and “Black Box Warnings”

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In order to diagnose depression, the Diagnostic and Statistical Manual Version IV with revisions (DSM-IV TR) is used. The diagnostic criteria are similar in children and adolescents to those utilized to diagnose depression in adults, with the exception that DSM notes that children and adolescents may exhibit an irritable mood rather than a depressed mood. In all age groups, suicidal thinking or behavior can be one of the diagnostic criteria, characterized in DSM as “abnormal morbid thoughts of death (not just fear of dying) or suicide.”

Clinical and epidemiological studies in children and adolescents have shown that a typical episode of a Major Depressive Disorder (MDD) lasts two to nine months; with a probability of major depression recurring at 40% within two years and 70% by five years; similar to the rates of recurrence that have been reported for adults (Birmaher et al., 1996). Children and adolescents who suffer from MDD may experience a drop in school performance, an increase in family tension/problems, and conflicts with peers.

It is not uncommon to see coexisting psychiatric disorders in depressed youth (40% to 90% of the time). The most frequent coexisting disorders are dysthyemic

In children and adolescents, the most frequently diagnosed mood disorders are major depressive disorder, dysthyemic disorder, and bipolar disorder. The annual prevalence rate of depression is estimated to be 2–3% in children aged 8–12 years, and slightly higher (4–8%) in youth aged 11½ to 18 years (American Academy of Child and Adolescent Psychiatry [AACP], 1998) as compared with rates of 6.6% in adults aged 18 and older (Kessler, 2003).
disorder (these youths display a chronically depressed mood or irritability lasting at least one year, but do not meet criterion for major depression), anxiety disorders (both at 30% to 80%), disruptive behavior disorders (10% to 80%), and abuse of alcohol or illicit substances (20% to 30%) (AACAP, 1998).

MDD in the pediatric population is associated with significant risk of suicidal thinking, attempts and even completed suicide. Approximately half of teenagers with MDD attempt suicide at some time during their lives and among children with MDD, there is a four-to-five-fold higher lifetime risk of suicide attempts, compared with healthy children without depression (Kovacs, Goldston, & Gatsonis, 1993; Rao et al., 1993). Kovacs et al. noted similar results in a study of outpatient youths with MDD. They noted that, at study entry, 66% of subjects acknowledged a history of suicidal ideation, and 9% had already made at least one suicide attempt. The rate of suicide attempts in this study reached 24% by age seventeen.

Because mood disorders substantially increase the risk of suicide, suicidal behavior is a matter of serious concern for clinicians who deal with the mental health problems of children and adolescents. The incidence of suicide attempts reaches a peak during the mid-adolescent years, and mortality from suicide increases steadily throughout the teen years (Centers for Disease Control [CDC], 1999; Hoyert, Kochanek, & Murphy, 1999). The incidence of suicide among adolescents nearly tripled from 1952 to 1995. Although the suicide rate among youth significantly decreased in the mid-1990s, suicide deaths remain high in 15- to 24-year-olds, making it the third leading cause of death for this age group in the United States (CDC, 2004).

Patients who were younger than 18 years were approximately 6.1 times more likely to be prescribed an antidepressant in 1993–94 than in 1985. The Substance Abuse and Mental Health Services Administration (SAMHSA) in 2002 reported data from the National Household Survey on Drug Abuse indicating that about three million youths between the ages of 12 to 17 seriously thought about suicide and over one-third (37%) actually attempted suicide. Females (16%) were more likely than males (8%) to report contemplating suicide during the past year. The risk was higher among youths between the ages of 14 to 17 than among those 12 to 13. The general likelihood of suicide risk was similar among white, black, Hispanic and Asian youth. The risk of
suicide among youth was similar no matter if they lived in urban, suburban, or non-metropolitan locations.

The change in suicide rates during the 1990s coincides with an increase in the use of antidepressants and mood stabilizers in children and adolescents. Olsson et al. (1998) found that between 1985 and 1993–94, the estimated number of psychiatric visits including an antidepressant prescription more than doubled from 4.2 million to 11 million. The increase in antidepressant prescriptions was particularly pronounced among visits by younger patients. Patients who were younger than 18 years were approximately 6.1 times more likely to be prescribed an antidepressant in 1993–94 than in 1985.

**Do Antidepressants Increase the Risk of Suicide in Children and Adolescents?**

The question, while counter-intuitive, has created both controversy and debate. In 2003, in the United Kingdom, their counterpart to the U.S. Food and Drug Administration (FDA) issued a warning to physicians about a possible increased risk of suicidal ideation and/or suicides in children and adolescents taking serotonin reuptake inhibitors (SSRI). In response to the U.K.’s warning, the U.S. FDA issued a warning and held hearings about SSRIs.

In June 2003, the FDA's Talk Paper for Paxil advises that caretakers of pediatric patients receiving treatment with Paxil, or with any of the antidepressants, talk to their doctor regarding the use of the drug. Patients should not discontinue use of any of these drugs without first consulting with their physicians, and it is important that the medication not be abruptly discontinued (with reference made to labeling for individual drugs). See Box 1.

On March 22, 2004, the FDA issued a public health advisory on “Worsening Depression and Suicidality in Patients Being Treated with Antidepressant Medications.” The advisory asked manufacturers to include a warning statement that recommends close observation of adult and child patients.

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**BOX 1**

**SUICIDALITY IN CHILDREN AND ADOLESCENTS**

**FDA LABELING CHANGE REQUEST LETTER FOR ANTIDEPRESSANT MEDICATIONS**

*UPDATED, OCTOBER 28, 2004*

Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of (Drug Name) or any other antidepressant in a child or adolescent must balance this risk 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 of the need for close observation and communication with the prescriber. (Drug Name) is not approved for use in pediatric patients except for patients with (Any approved pediatric claims here). (See Warnings and Precautions: Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

The FDA asked pharmaceutical companies to include a stronger label warning recommending close observation of adult and pediatric patients for the following medications used to treat depression and suicidal ideation. The drugs that are the focus of this new labeling language are all drugs included in the general class of antidepressants:

- Anafranil (clomipramine HCl)
- Aventyl (nortriptyline HCl)
- Celexa (citalopram HBr)
- Cymbalta (duloxetine HCl)
- Desyrel (trazodone HCl)
- Effexor (venlafaxine HCl)
- Elavil (amitriptyline HCl)
- Lexapro (escitalopram oxalate)
- Limbitrol (chlor Diazepoxide/ amitriptyline)
- Ludomil (Maprotiline HCl)
- Luvox (fluvoxamine maleate)
- Marplan (isocarboxazid)
- Nardil (phenelzine sulfate)
- Norpramin (desipramine HCl)
- Pameler (nortriptyline HCl)
- Parnate (tranylcypromine sulfate)
- Paxil (paroxetine HCl)
- Pexeva (paroxetine mesylate)
- Prozac (fluoxetine HCl)
- Remeron (mirtazapine)
- Sarafem (fluoxetine HCl)
- Serzone (nefazodone HCl)
- Sinequan (doxepin HCl)
- Surmontil (trimipramine)
- Symbyax (olanzapine/fluoxetine)
- Tofranil (imipramine HCl)
- Tofranil-PM (imipramine pamoate)
- Triavil (Perphenaine/Amitriptyline)
- Vivactil (protriptyline HCl)
- Wellbutrin (bupropion HCl)
- Zoloft (sertraline HCl)
- Zyban (bupropion HCl)

**SOURCE:** FDA PUBLIC HEALTH ADVISORY OCTOBER 15, 2004

The risk of suicidality for these drugs was identified in a combined analysis of short-term (up to four months) placebo-controlled trials of nine antidepressant drugs, including the selective serotonin reuptake inhibitors (SSRIs) and others, in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders.

As part of a joint meeting in September 2004, the FDA's Psychopharmacologic Drug and Pediatric Advisory Committees reviewed information from nine antidepressant drug development programs. Additionally, the group reviewed data from two other studies involving antidepressant medications. Overall, the committee reviewed data from 24 studies for 9 antidepressant medications involving more than 4,400 pediatric subjects.
Based on these data, the FDA determined that the following points are appropriate for inclusion in the boxed warning:

- 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).

Antidepressants, Teen Suicide and Black Box Warnings

MedGuides focus solely on serious side effects associated with certain medications or classes of medications and do not provide comprehensive drug information. A final ruling in 1998 provided the FDA with the authority to require MedGuides for five to 10 drug products per year for those with serious or significant side effects as determined by the FDA. MedGuides will be required if the FDA determines that one or more of the following circumstances exist:

- Patient labeling could help prevent serious adverse effects
- The drug product has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients’ decision to use, or to continue to use, the product
- The drug product is important to health and patient adherence to directions for use is crucial to the drug’s effectiveness

In March 2005, the FDA began requiring community pharmacies to supply a MedGuide with every antidepressant prescription dispensed. Besides MedGuides, the FDA gave manufacturers of antidepressants, such as Prozac (Eli Lilly), Effexor (Wyeth), Zoloft (Pfizer), Celexa (Forest), and Paxil (GlaxoSmithKline), a second label edict: Add “black box” warnings on the package inserts that are read by healthcare providers.

In the U.S., a black box warning appears on prescription medications that may cause serious adverse effects. It is so named for the black boarder that usually surrounds the text of the warning. Generally, the black box warning means that medical studies indicate the drug carries a significant risk of serious or even life-threatening adverse effects. The FDA can require a pharmaceutical company to place the black box warning on the labeling of prescription drugs or in the literature describing it. This is the strongest warning the FDA can require.

The warning recommends that health care providers carefully monitor patients receiving antidepressants for worsening of depression or suicidality, particularly at the beginning of therapy or during dosage changes. However, the FDA specifies that while they have not concluded that symptoms including anxiety, panic attacks, hostility, and hypomania are a precursor to either worsening depression or the emergence of suicidal impulses, it is concerned that patients who experience one or more of these symptoms may be at increased risk for worsening depression or suicidality.

Accumulating Opinions

A Web-based report prepared by the American Psychiatric Association (APA) and American Academy of Child and Adolescent Psychiatry (AACAP) on
**WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ANTIDEPRESSANTS?**

Parents or guardians need to know about four important things to help them decide whether their child or teenager should take an antidepressant:

- The risks of self-injury or suicide
- How to try to prevent self-injury or suicide
- What to watch for in children or teens taking antidepressants
- The benefits and risks of antidepressants

**1. RISK OF INJURY TO SELF OR SUICIDE**

Children or teenagers with depression sometimes think about suicide. They may even try to kill themselves. Antidepressants may increase suicidal thoughts or actions in some children and teens. Thinking about killing yourself or trying to kill yourself is called suicidality or being suicidal.

A large study combined the results of 24 different smaller studies of children and teenagers who took either sugar pills or antidepressants for one to four months. Although no one committed suicide in these studies, some young patients became suicidal.

On sugar pills, 2 out of every 100 became suicidal.

On the antidepressants, 4 out of every 100 young patients became suicidal.

**2. HOW TO TRY TO PREVENT SELF-INJURY OR SUICIDE**

To try to prevent self-injury and suicide in children and teens using antidepressants, everyone (patients, parents, teachers, and other important people in the lives of young people) should pay close attention to sudden changes in their moods or behaviors. These are listed below under “What to Watch For.” Whenever an antidepressant is started or its dose is changed, close attention is needed.

In general, after starting an antidepressant, patients should see their doctor

- Once a week for four weeks
- Every 2 weeks for the next month
- At the end of their 12th week taking the drug
- More often if problems or questions arise

**3. WHAT TO WATCH OUT FOR IN CHILDREN OR TEENS TAKING ANTIDEPRESSANTS**

If any of the following behaviors appear for the first time, seem worse, or worry the child, parent, or guardian, a medical professional should be contacted right away.

- New or more thoughts of suicide
- Trying to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- Being extremely hyperactive in actions and talking (hypomania or mania)
- Other unusual changes in behavior

**4. THE BENEFITS AND RISKS OF ANTIDEPRESSANTS**

Antidepressants are used to treat people with depression. Depression can lead to suicide. In some people, treatment with an antidepressant causes suicidal thinking or actions or makes them worse. The doctor, the patient, and the patient’s parents or guardians should discuss all treatment choices, including the use of antidepressants.

For some young people, the risks of suicidal behaviors caused by antidepressants may be especially high. These include young people with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure the doctor knows about them before the doctor prescribes any antidepressant.

Discuss all treatment choices, including the use of antidepressants.
the topic of The Use of Medication in Treating Childhood and Adolescent Depression: Information for Physicians is important to consider the clinical trial data in context. The FDA combined the rates for suicidal thoughts and suicide attempts under the general term “suicidality.” By doing this, a public impression is fostered that: a) there is a high rate of suicide attempts or even completed suicides in children and adolescents; and b) that it can be attributed to taking antidepressant medication, versus suicidal thoughts and actions declining with medication and psychotherapy treatments. Additionally, it is pointed out that there were no completed suicides in the studies reviewed by FDA.

The report shows that generally there are two key risk factors for suicide: the presence of one or more diagnosable mental disorders—particularly a depressive disorder or an aggressive/disruptive disorder—occurring alone or comorbid with an alcohol or other drug use disorder, and second, a prior suicide attempt.

Globally, there may other general factors associated with suicide. For example, impulsivity; a family history of mental or substance abuse disorder; a family history of suicide; family violence, including physical or sexual abuse; the presence of a weapon in the home; being incarcerated; and exposure to the suicidal behavior of others, including family, peers, or in the news or fictional stories.

Based on the available studies generally cited on antidepressants and the risk of suicidal thoughts, none of the risk factors above are specifically linked to the use of antidepressant medications by children and adolescents.

Treatment Options
More research is needed to expand our current knowledge of all of the available treatment options for child and adolescent depression and related comorbidities. Generally, the literature supports the use of cognitive-behavioral therapy, as well as psychotherapy, in the form of individual, group, or family therapy. However, regularly scheduled sessions and availability of providers and treatment options can present a barrier for many patients. Antidepressants, though under scrutiny, have had an impact on the lives of many children and their families. From a clinical perspective, one needs to consider the potential benefits of treatment versus the risks of non-treatment on a case-by-case basis. For any prescribed medication, the patient should be followed with appropriate monitoring, especially when beginning a medication for the first time. See Box 3.

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PROFESSIONAL RESOURCES

REFERENCES

CENTERS FOR DISEASE CONTROL AND PREVENTION. (1999). Suicide deaths and rates per 100,000.