Antidepressants and Suicide Risk: Considerations in Treating Patients with Major Depression

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For nearly 2 decades, there has been concern regarding the relationship between antidepressants and risk for suicide. This concern ultimately led the US Food and Drug Administration (FDA) to issue a public health advisory in 2004 warning of a possible increased risk of suicide in children and adolescents treated with certain antidepressant drugs.[1] In October 2004, the FDA instructed manufacturers of antidepressants to add a black box warning to packaging about the increased risk of suicide associated with the use of antidepressants in pediatric patients. This warning was expanded in 2007 to include warnings of increased suicidal thinking and behavior in adults aged 18 to 24 years during the first 2 months of treatment.[1]

Following the initial advisory in 2004, some primary care physicians stopped treating their patients for depression and instead referred them to psychiatrists for treatment.[2,3] Due to the lack of psychiatrists in underserved areas, patients with depression were at risk for receiving substandard care. Recent studies have shown that the suicide rate in adolescents has increased since 2004, a trend that some have attributed to decreased utilization of selective serotonin reuptake inhibitors (SSRIs) by the general medical community.[3–6] Questions regarding the relationship between antidepressant use and suicidality remain, despite subsequent observational studies and analyses of available trial data that have sought to clarify this issue. As a result, physicians may be uncertain about how to manage patients who present with depression. This article reviews evidence concerning antidepressants and suicidality, discusses the FDA's warnings and their impact on patient care, and makes recommendations for managing patients with depression in light of the warnings.

TAKE HOME POINTS

- A black box warning for antidepressant agents states that antidepressants have been shown to increase the risk of suicidal thinking and behavior in pediatric patients (< 18 yr) and in adults aged 18 to 24 years. This warning shoud not deter physicians from prescribing antidepressants to patients who would benefit from them, but close communication and follow-up care after initiating antidepressant therapy are essential.
- Physicians should review the increased risk with patients younger than 24 years before prescribing antidepressants, explain that some people have increased suicidal symptoms during the first months of treatment, and provide close patient monitoring in the first weeks of treatment.
- Adults should be started at the lowest recommended dose, and even lower doses should be considered in patients aged 24 years and younger.
- A follow-up appointment should be arranged, and patients should be encouraged to contact the physician if their symptoms worsen or if they develop intolerable side effects, especially agitation, anxiety, or suicidality.

EVIDENCE UNDERLYING FDA ADVISORY ACTIONS

Questions regarding a link between antidepressants and suicidality emerged in 1990, when Teicher and colleagues[7] reported on 6 adult patients with depression who were free of recent serious suicidal ideation and developed intense suicidal thoughts after taking the SSRI fluoxetine for a mean duration of 26 days. Their suicidal thoughts persisted and did not fully abate until the medication was discontinued, with the thoughts

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persisting for a mean duration of 90 days. The authors noted that other factors may have contributed to the suicidality, including the disease process itself. In 1991, the FDA held public meetings to discuss fluoxetine's potential role in suicidality following complaints to the FDA by patients and families.[8] Attendees reported how they perceived that the medication had caused or worsened suicidal behavior in their friends or loved ones. In response to the public concern, the manufacturer of the Prozac brand of fluoxetine (Eli Lilly & Company) conducted a meta-analysis of clinical trial data from 17 double-blinded studies involving adults with major depressive disorder to assess a possible association between fluoxetine and suicidality.[9] They found no increased risk of suicidal acts due to fluoxetine.

Children and Adolescents

In early 2003, the United Kingdom Committee on Safety of Medicines issued an advisory that the SSRI paroxetine should not be used to treat children or teenagers under age 18 years for depression.[10] This advisory was based on reports from unpublished trial data indicating increased self-harm and suicidality in pediatric patients taking paroxetine. In late 2003, the Committee expanded the advisory to state that SSRI antidepressants have an unfavorable risk–benefit ratio in the treatment of major depression in those younger than age 18 years.[11] Fluoxetine was excluded from this advisory because it showed a favorable risk–benefit ratio in clinical trials.

An FDA advisory committee reviewed these premarketing clinical trial data in February 2004 and commissioned a reanalysis of all pediatric antidepressant trials.[12] In March 2004, the FDA issued a public health advisory asking manufacturers of primarily newer antidepressants (Prozac [fluoxetine], Zoloft [sertraline], Paxil [paroxetine], Luvox [fluvoxamine], Celexa [citalopram], Lexapro [escitalopram], Wellbutrin [bupropion], Effexor [venlafaxine], Serzone [nefazodone], and Remeron [mirtazapine]) to add a warning to product labeling recommending close observation of adult and pediatric patients treated with these medications for worsening depression and emergence of suicidality.[1] In October 2004, the FDA required antidepressant manufacturers to add a black box warning on all antidepressants alerting health care providers of an increased risk of suicidality in children and adolescents and recommending more intense monitoring of these patients.[13]

The addition of the black box warning was based on analysis of pooled data from 24 short-term placebo-controlled trials of 9 antidepressant drugs (including SSRIs) in over 4400 children and adolescents with major depressive disorder or other psychiatric disorders. These data showed an increased risk of suicidal behavior or thinking during the first few months of treatment in those receiving antidepressants. The average risk of suicidality associated with antidepressant use was 4%, which was twice the placebo risk of 2%. Of these pediatric trials, 3 showed that the use of SSRIs decreased the risk of suicidal ideation or behavior (relative risk [RR], < 1).[14] Four trials showed that SSRIs had no effect on suicidality, and 13 trials showed that SSRIs increased suicidal ideation or behavior in the pediatric population (RR, > 1). The overall RR for suicidality for all trials and indications was 1.95 (95% confidence interval [CI], 1.28–2.98). The overall RR for suicidality in trials of SSRIs for treating depression was 1.66 (95% CI, 1.02–2.68). There were no suicide deaths in any of the pediatric trials. Also, no increased risk of suicidal behavior was observed when the data were pooled across all age-groups.

Young Adults

The black box warning was expanded in May 2007 to state that there is an increased risk of suicidal symptoms in young adults aged 18 to 24 years.[5] The expanded warning was based on the results of meta-analyses of 372 randomized clinical trials involving adults from the past 2 decades. The trials were conducted by 8 pharmaceutical companies and included 99,839 participants.[15] However, the primary analyses were based on 295 trials involving patients with psychiatric disorders. In these trials, there were 8 suicide deaths: 5 in patients assigned to the investigational drug, 2 in patients assigned to placebo, and 1 in patients assigned to an active comparator.[16] A total of 501 patients experienced suicidal ideation or nonfatal suicide attempts: 243 who received an investigational drug, 194 who received placebo, and 64 who received an active comparator. In the age-stratified analysis for adults ages 18 to 24 years, the risk of suicidal ideation was slightly elevated (odds ratio, 1.55 [95% CI, 0.91–2.70]). In addition, the association between antidepressants and suicidality became stronger with decreasing age. For adults 31 years and older, it appeared that antidepressants provided a protective effect, especially for those 65 years and older. Thus, the new warning indicated that there is no evidence of an increased risk in adults older than age 24 years. The warning also indicated that "depression and other serious psychiatric disorders are themselves associated with increases in the risk of suicide." This marks the first time the FDA's black box warning cautioned the public on the risk of the disease itself and of not treating the disease.[16]

Limitations of the Analyses

As noted, 77 trials of treatment for nonpsychiatric and nonbehavioral indications (eg, obesity, smoking, diabetic neuropathy) were excluded from the primary analyses of the adult trial data.[16] In these trials, the suicide risk per person-year of treatment was significantly lower than in trials for depression and other psychiatric indications, suggesting that suicidal symptoms are related more to depression than to antidepressants themselves. Other limitations of the FDA's meta-analysis must be noted. First, the clinical trials included in the meta-analysis evaluated short-term efficacy and were not designed to gauge long-term safety. Second, suicidal symptoms were susceptible to measurement bias. Suicidal ideation was documented in adverse-event reports and were not measured systematically using depression rating scales, such as the Hamilton Rating Scale for Depression. Third, patients most at risk for suicide tend to be excluded from trials sponsored by pharmaceutical companies. Fourth, confounding by indication makes it difficult to ascertain whether suicidality is caused by the disease process itself (eg, depression) or the treatment. Such confounding is a limitation of studies in which patients with a worse disease process (or prognosis) are allocated to a particular treatment, in this case antidepressants. These patients are likely to differ from patients who are not treated or are treated with something other than antidepressants. Patients receiving antidepressants are likely to be more ill than those who do not receive antidepressants. If these patients develop suicidal symptoms, it may appear that the treatment is worsening the disease.

Finally, it is important to recognize the challenges of designing a study to evaluate risk for suicide in patients treated with antidepressants. Because suicide is a rare event, as seen from the FDA's meta-analysis in which there were 36 suicide attempts and no completed suicides in trials involving roughly 4000 patients, a trial large enough to detect a doubling of suicide death would require hundreds of thousands of participants. Designing a study on this scale is not feasible, so researchers are left to draw conclusions using observational studies. These studies, while important and useful, carry their own limitations of bias or confounding. These studies are not the ideal method to prove causality, which is best left to the randomized, controlled trial.

OBSERVATIONAL STUDIES

In 2003, prior to the FDA's first warnings, Khan et al[17] conducted a meta-analysis of data from adult clinical trials of antidepressants, which included 26,109 patients on SSRI antidepressants, 17,273 on other antidepressants, and 4895 placebo patients. There were 77 completed suicides. The authors found no statistical difference in suicide rate between patients assigned to SSRIs, other antidepressants, or placebo. They acknowledged that their analysis could not assess whether SSRIs are associated with suicidal behavior since data on such behavior was incomplete. Subsequently, a number of studies have been conducted to assess the association between antidepressants and suicidality, thus attempting to evaluate the validity of the FDA's black box warning.

Jick and colleagues[18] conducted a matched case-control study using data from the UK General Practice Research Database on 159,810 patients treated for depression between 1993 and 1999.They found that nonfatal suicidal behavior (suicidal ideation, suicide attempt) was 4 times more likely to occur within 9 days or less after receiving a first prescription for an antidepressant and 3 times more likely to occur between days 10 and 29 after a first prescription. They offered 2 explanations for this association. First, antidepressant treatment may not be immediately effective and patients generally do not experience a benefit for up to several weeks. Thus, there is a greater risk of suicidal behavior in patients newly diagnosed and treated than in those who have been treated for a longer time. Second, at the time when patients initiate antidepressant therapy, their illness is often most severe. Indeed, this severity is what prompts the initiation of antidepressant therapy.

In a study of antidepressant use and rate of suicide in all US counties, Gibbons et al[19] analyzed the National Vital Statistics from the Centers for Disease Control and Prevention for all individuals who committed suicide between 1996 and 1998. They found that an increase in the prescription of SSRIs and newer generation non-SSRIs was associated with lower suicide rates, while a high prescription rate of tricyclic antidepressants was associated with a higher suicide rate. According to the authors, a high prescription rate of tricyclic antidepressants may be a marker for poor access to high-quality mental health care, poor detection of mental health disorders, and poorer treatment compliance. Also, tricyclic antidepressants are more toxic than SSRIs in overdose, which could also account for higher observed rates of death.[20]

Simon and colleagues[21] reviewed computerized health plan records for residents of Washington and Idaho to evaluate risk for suicide death and suicide attempt with initiation of antidepressant therapy. The records consisted of 65,103 patients with 82,285 episodes of antidepressant treatment between January 1992 and

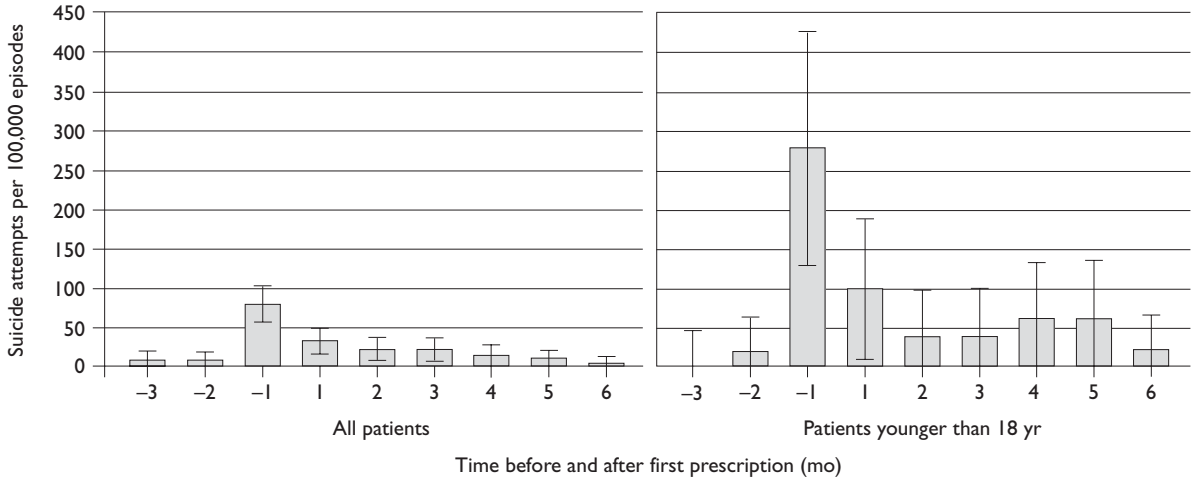

Figure. Rates of suicide attempt during 3 months before and 6 months after initial antidepressant prescription. (Adapted with permission from Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. Am J Psychiatry 2006;163:44. Copyright 2006 American Psychiatric Association.)

end of June 2003. They calculated that the risk of suicide death during acute-phase antidepressant treatment was 40 deaths per 100,000 treatment episodes, and the risk of suicide attempt was 93 attempts per 100,000 treatment episodes. By comparison, the risk of suicide in the US general population is 11 deaths per 100,000 persons per year.[22] The risk of suicide attempt was higher in the month after initiation of an antidepressant than in the subsequent 5 months. However, they noted that the greatest risk in both adults and adolescents was seen in the month prior to initiation of medication (**Figure**). Once treatment was begun, there was a sharp decline in risk and then a gradual reduction in risk over the next 6 months. Risk typically fell by more than one half in the month after starting treatment. The authors wrote that these data support the conclusion that treatment with antidepressants ultimately led to a decline in suicide risk rather than a medication-induced increase in risk.

In previous randomized, controlled trials, there has been a higher frequency of suicide attempts reported in children and adolescents taking antidepressants compared with patients taking placebo.[23,24] Gibbons et al[25] evaluated the relationship between antidepressant use and suicide risk in adolescents using the national county-level suicide rate. Focusing on SSRIs, their study used data from 3 sequential years and found that a higher rate of SSRI prescriptions was associated with a lower rate of suicide in children and adolescents. Olfson and colleagues[26] evaluated the relationship between regional changes in antidepressant medication treatment and suicide in adolescents from 1990 to 2000. They noted a positive association between regional antidepressant prescriptions and suicide rates in adolescents, indicating that regions with high rates of antidepressant treatment also had high rates of suicide. However, Olfson et al[26] also found that an increased rate of prescriptions for antidepressants (excluding tricyclic antidepressants) was associated with decreased rates of suicide per region. All classes of antidepressants were combined in the study. Both studies concluded that an increase in antidepressant medication, specifically SSRIs, was inversely related to the rate of suicide.

EFFECTS OF THE BLACK BOX WARNINGS

Despite the findings from these studies that affirm the benefits of antidepressant therapy under the careful observation of a physician, there have been declines in the prescription of antidepressants for those under age 18 years.[2] The number of antidepressant prescriptions dispensed to patients aged 18 years and younger dropped nearly 20% after the FDA issued its initial warning in March 2004.[2] In the month following the FDA warning, rates of prescriptions filled for adults also dropped significantly. In the case of adults, however, the rate of prescriptions has gradually increased over time and held steadily. Possible reasons for the decline in prescription rate include physicians' lack of experience with prescribing antidepressants, fear of malpractice litigation should their patients worsen with the medications, and reluctance by patients to take the medications.

A decline in prescription rates of antidepressants among primary care physicians could have a broad impact on public health. A US study found that in 2001

nearly 64% of visits to a physician for treatment of depression were to primary care physicians and 29% were to a psychiatrist.[27] If primary care physicians become reluctant to prescribe antidepressants, more patients with depression may go untreated. In a survey designed to gauge the effect of the FDA warnings on antidepressant prescribing,[28] the Mayo Clinic surveyed 344 doctoral-level health care professionals at the Mayo Clinic in Rochester, MN (ie, 44 psychiatrists, 89 generalists, and 211 specialists). Of those surveyed, 76% indicated that they prescribed antidepressants, and 94% reported that they were familiar with the 2004 black box warning for antidepressants. Of those who were aware of the black box warning, 76% reported continuing to prescribe antidepressants at the same rate, while 24% decreased or stopped prescribing antidepressants as a result of the warning. Of generalists who cared for children and adolescents, 82% reported that they had decreased or stopped antidepressant prescribing. No physician group in the survey increased the prescription of antidepressants.

To assess the effect that the FDA warnings have had on the diagnosis and treatment of depression in children, Libby and colleagues[5] evaluated a pediatric cohort with newly diagnosed episodes of depression using a national integrated claims database of managed care plans for the period October 1998 to September 2005 (N = 65,349). They found that diagnosis of pediatric depression and prescriptions for SSRIs were both increasing prior to the FDA warning, while after the warning, both of these trends were reversed. Among patients with depression, those receiving no antidepressant agent increased to 3 times the rate predicted by the preadvisory trend, and the number of SSRIs prescriptions filled was 58% lower than predicted by the preadvisory trend. More patients were treated by psychiatrists following the FDA warnings, but this did not compensate for the decrease in treatment by primary care physicians and pediatricians. Also, there was no evidence of an increase in the use of treatment alternatives, such as psychotherapy or atypical antipsychotics.

Data suggest that suicide rates in pediatric patients increased following the 2004 FDA warnings. Gibbons and colleagues[3] found that prescriptions for SSRIs in the United States and the Netherlands decreased by approximately 22% following the 2003/2004 FDA and European regulatory warnings. The decrease in antidepressant prescribing was associated with an increase in suicide rates in children and adolescents. In the Netherlands, the youth suicide rate increased by 49% between 2003 and 2005, and in the United States, the youth suicide rate increased by 14% between 2003 and 2004. A report released in September 2007 by the Centers for Disease Control and Prevention revealed that from 2003 to 2004 the suicide rate for children and young adults ages 10 to 24 years increased by 8%, the largest single-year increase during the period 1990 to 2004.[4] For girls aged 10 to 14 years, the suicide rate increased 76%. Suicide rates among females aged 15 to 19 years increased by 32%, and rates for males in that same age-group increased by 9%.

MANAGEMENT RECOMMENDATIONS

In the United States, most patients seek initial treatment for depression by primary care physicians.[27] With the exception of tricyclic antidepressants, the evidence supports the use of antidepressants in the treatment of depression under the careful observation of a physician. While there may be a slightly increased risk of suicidal behavior in children and young adults who begin antidepressant therapy, the failure to treat depression presents a greater risk to the patient as most suicides and serious nonfatal suicide attempts are committed by those untreated for major depression.[29] Thus, primary care physicians should continue to prescribe antidepressants, despite the recent controversy. When prescribing antidepressants, physicians must review the risks and benefits inherent in the treatment with the patient and their family, and physicians should inform patients that antidepressants will not usually give them immediate relief. Clinicians should keep in mind that depression is often most severe immediately prior to the onset of therapy and remains so in the subsequent days and weeks; however, patients usually show continued improvement in the following months. During the period in which antidepressants have not achieved full efficacy, patients may indeed experience considerable symptomatology as a result of their depression, including suicidal thoughts.

Once treatment with antidepressants is initiated, it is important that physicians monitor their patients closely for worsening symptoms in the ensuing weeks. In the United States, follow-up care after initiating antidepressant therapy is often insufficient.[30] Indeed, close communication and availability to patients are hallmarks of the doctor-patient relationship. Adults should be started at the manufacturer's lowest recommended dose, and even lower doses should be considered in patients aged 24 years and younger (eg, 50 mg/day sertraline for an adult, 25 mg/day for a young adult or adolescent). It is best to not prescribe more than 1 months' worth of medication, as a larger quantity could be used for an overdose, and to not provide refills initially in order to

Table 1. Management of Patients with Suicidal Ideation

Inquire directly as to the frequency and content of suicidal thoughts
Explain to patients that some people who take antidepressants have an increase in suicidal symptoms, especially early in treatment
Have the patient call their physician, crisis hotline, or 911 if suicidal thoughts intensify
See patients weekly until suicidal thoughts abate
Do not write prescriptions for more than 1 wk of medication while suicidal thoughts are present
Discourage patients from using any illicit drugs or alcohol
Evaluate a patient's access to means of suicide

Table 2. Risk Factors for Suicide

Diagnosis of a mood disorder, especially major depressive disorder
Current suicidal thoughts
Family history of suicide attempt or completed suicide
Access to a firearm
Recent severe stressful life event, such as death of a spouse, loss of employment, or diagnosis with a terminal illness
Previous suicide attempt
Hopelessness
Substance use (especially alcohol)
Parental divorce*
Poor parental support*
Family violence*

*Denotes risk factors specific to children and adolescents.

encourage follow-up. Physicians should arrange a follow-up appointment and encourage patients to contact the physician's office if their symptoms worsen or if they develop intolerable side effects, especially agitation, anxiety, or suicidality. If patients do become suicidal, there are important points to remember when caring for them (**Table 1**).[31] Most important, the patient should be seen immediately, and if this cannot be done, then the patient should be referred for hospitalization or other emergency services. In the interview, it is important to question the patient in a direct, nonthreatening manner regarding the frequency and content of suicidal thoughts. Patients should be seen weekly until suicidal thoughts abate, and reassurance should be provided to patients at each visit. Prescriptions should be written for no more than 1 week's worth of medication while patients are suicidal. Use of illicit drugs or alcohol should be discouraged as this can increase impulsive behavior and increase the risk of suicide.

With these strategies in mind, primary care physicians are well-equipped to treat patients with depression. In certain circumstances, however, it is best to refer patients to a psychiatrist. Patients who should be referred include those with severe, recurrent depression, those with symptoms of bipolar disorder, and those with depression with psychotic features. Patients who do not respond to treatment should be referred as well.

Physicians should be aware of risk factors that place patients at greatest risk for suicide. A 20-year prospective study that evaluated risk factors for suicide in 6891 psychiatric outpatients found that current suicidal ideation, hopelessness, prior suicide attempts, a history of recurrent major depression, a history of bipolar disorder, and being unemployed were significant risk factors for completed suicide.[32] Additional studies have since identified other key risk factors for the adult and pediatric populations (**Table 2**).[33,34] These results emphasize the importance of obtaining a thorough psychiatric history in patients presenting with depression. In addition to these observable risk factors, there may also be a genetic marker indicating an increased risk of suicide in some patients. Recently identified polymorphisms near cyclic adenosine monophosphate response element-binding protein were found to be associated with treatment-emergent suicidality among men with depression.[35] This finding could lead to identification of a small subset of patients at risk for worsening depression during antidepressant treatment.

CONCLUSION

The FDA's warnings regarding antidepressants and increased suicidality in patients under age 24 years may have had the unintended consequence of decreasing use of antidepressants for treatment of depression. Physicians should be aware of the slightly increased risk for suicidality when prescribing antidepressants to younger patients. This warning, however, should not deter primary care physicians from prescribing antidepressants to patients who would benefit from them. This warning serves as a reminder to review the risks and benefits inherent in the treatment with any medication, and physicians should inform patients that antidepressants will not usually give them immediate relief. During the period in which antidepressants have not achieved full efficacy, patients may experience considerable symptomatology as a result of their depression, including suicidal thoughts. Above all, physicians must be available to their patients and respond immediately should their depression symptoms worsen. **HP**

Acknowledgment: The authors thank Gus W. Krucke, MD, for his assistance with this article.

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