Antidepressants and Suicide in Adolescents and Adults
A Public Health Experiment with Unintended Consequences?
Jack Alan McCain

INTRODUCTION
In 2004, the FDA required a boxed (“black box”) warning to be added to package inserts for antidepressants in order to call attention to an increased risk of suicidal thoughts and behavior (suicidality) in children and adolescents taking these drugs. In 2007, the FDA extended the age range covered by the warning to include young adults up to 24 years of age. However, these well-meaning actions may have precipitated unintended consequences—a decline in the prescribing of antidepressants for pediatric patients,1 a decline in the diagnosis of depression in adults,2,3 and possibly even an end to decreasing rates of youth suicide4—the consequences of an experiment gone awry.4,5

Before 1990, youth suicide rates in the U.S. had increased over the course of several decades. The rates were said to have tripled between 1953 and 1957 and between 1983 and 1987, rising from 2.46 to 9.64 per 100,000 persons 15 to 24 years of age; however, the increase might not have been as great as was initially believed, owing to a possible undercounting of youth suicides.7 Starting in 1990, however, the suicide rate in the U.S. among youths and young adults between 10 and 24 years of age began declining steadily, falling from 9.48 to 6.78 per 100,000 persons between 1990 and 2003.3 Yet between 2003 and 2004, the suicide rate increased by 8%, to 7.32 per 100,000—the largest single-year increase since 1990.

From 2003 to 2004, the increase in the rate of suicide was 18% in the 10- to 19-year-old age group.4 Between 2004 and 2005, the suicide rate in this age group decreased slightly but still was greater than expected on the basis of the established trend (Figure 1). Bridge and colleagues calculated 326 excess suicide deaths in 2004 and 292 excess suicides in 2005 in the 10- to 19-year-old group.4

It may be no coincidence that the long decline in youth suicide rates in the U.S. began soon after the start of the selective serotonin reuptake inhibitor (SSRI) era, which started in 1987 with the introduction of fluoxetine (Prozac, Lilly). In the years following, the class of SSRIs and the related serotonin–norepinephrine reuptake inhibitors (SNRIs) expanded rapidly, as did the indications for these drugs. Today the class of SSRIs and SNRIs includes about a dozen distinct molecular entities (Table 1). Some of these agents are available in different formulations, with numerous indications for mood and anxiety disorders such as major depressive disorder (MDD) and obsessive–compulsive disorder (OCD). Indications for these medications also extend to bulimia and fibromyalgia and to diverse off-label uses, such as chronic fatigue syndrome, attention-deficit/hyperactivity disorder (ADHD), autism, and premature ejaculation.

As new indications were won, drug companies mounted campaigns to alert the public to the existence of conditions such as generalized anxiety disorder (GAD) and social phobia, also known as social anxiety disorder (SAD), which some critics regarded as the medicalization of normal shyness.9–11 (The acronym SAD can also refer to seasonal affective disorder.) GAD and SAD were not listed in the first or second editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), published in 1952 and 1968. Rather, they made their appearance in DSM-III in 1980, when the single diagnosis of anxiety neurosis was divided into seven parts: agoraphobia, GAD, OCD, panic disorder, post-traumatic stress disorder (PTSD), and obsessive–compulsive disorder.

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Figure 1  Annual suicide rates for U.S. youths 10 to 17 and 18 to 19 years of age from 1996 to 2005. (From Bridge JA, Greenhouse JB, Weldon Ah, et al. JAMA 2008;300:1025–1026. Copyright © 2008, American Medical Association.)
(PTSD), simple phobia, and social phobia.

In large part, the popularity of the newer antidepressants for a wide range of indications, including most of these new disorders, was fueled by the perception that they were better tolerated and far safer than older agents. For instance, the tricyclic antidepressants (TCAs), notable older-generation agents, are lethal in overdose quantities. The presence of suicidal thoughts and feelings is one of the criteria pointing toward a diagnosis of depression. Such a diagnosis tends to be followed by a prescription for pharmacotherapy, sometimes in combination with psychotherapy but often only as monotherapy. Because untreated depression is a risk factor for suicide, prescribing an apparently safe drug would seem to be a logical strategy for reducing the number of depression-induced suicides. The perceived safety of the newer antidepressants made it easy for primary care physicians (PCPs) to prescribe them—and they did, in vast amounts.

In many countries, a correlation has been found between increases in prescriptions for newer antidepressants and decreased suicide rates. However, the experience has been the opposite in Iceland and Norway, where suicide rates have risen or have remained unchanged even as antidepressant prescribing increased substantially. None of these studies establish a causal relationship between antidepressant use and suicide rates, of course, and many other factors can affect suicide rates, such as patterns of alcohol and drug abuse, lack of access to overall health care and mental health care, prevalence of psychiatric disorders, unemployment, poverty, suicide-prevention programs, legal driving age, war, and the way in which medical examiners classify untimely deaths. But the preponderance of the ecological evidence points to a potential protective effect for antidepressants with respect to suicide.

Not long after SSRIs were introduced, however, an unsettling thought was raised: that instead of protecting patients, SSRIs might have resulted in a number of suicides. Fluoxetine and paroxetine (Paxil, GlaxoSmithKline) were of particular concern in the early years of the SSRI era. Early suspicion about fluoxetine was raised in an article describing six cases in which severely depressed patients experienced intense feelings of suicidality soon after beginning fluoxetine therapy. Later, SSRIs were said to be more strongly associated with suicide than TCAs. In 2003, the Committee on Safety of Medicines in the United Kingdom blamed suicides on paroxetine and concluded that this drug should be contraindicated in patients with MDD who were younger than 18 years of age. Other actions in 2003 by governmental agencies in the U.K. and the U.S. heightened concerns about the safety of antidepressants (Table 2).

In the U.S., concerns about antidepressants led the FDA in 2004 to require the addition of a boxed warning to the labeling of these medications. This warning mentioned an increased risk of suicidal thoughts and behaviors in association with the use of antidepressants in pediatric patients. More recently, the boxed warning was revised to include young adults up to 24 years of age.

Both versions of the warning discuss the need to carefully monitor patients who begin treatment with antidepressants;

### TABLE 1 Indications for Selective Serotonin Reuptake Inhibitors and Serotonin–Norepinephrine Reuptake Inhibitors

<table>
<thead>
<tr>
<th>Generic Name (Trade Name)</th>
<th>MDD</th>
<th>GAD</th>
<th>OCD</th>
<th>Panic Disorder</th>
<th>PTSD</th>
<th>PMDD</th>
<th>SAD</th>
<th>Bulimia nervosa</th>
<th>DPN</th>
<th>Fibromyalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram (Celexa)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desvenlafaxine (Pristiq)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fluoxetine (Prozac)</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Sarafem)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Fluvoxamine (Luvox)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine extended release (Luvox CR)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine controlled release (Paxil CR)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Venlafaxine (Effexor)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine extended release (Effexor XR)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

DPN = pain of diabetic peripheral neuropathy; GAD = generalized anxiety disorder; MDD = major depressive disorder; OCD = obsessive–compulsive disorder; PMDD = premenstrual dysphoric disorder; PTSD = post-traumatic stress disorder; SAD = social anxiety disorder (social phobia).
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### TABLE 2 Chronology of FDA-Approved Selective Serotonin Reuptake Inhibitors (SSRIs) for Depression

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>Fluoxetine (Prozac) becomes the first SSRI to be introduced in the U.S.</td>
</tr>
<tr>
<td>1990</td>
<td>A published series describes six adults considering suicide following treatment with fluoxetine (Teicher).</td>
</tr>
<tr>
<td>1991</td>
<td>After a contentious public meeting, the FDA's Psychopharmacologic Drugs Advisory Committee (PDAC) concludes that there is no clear evidence of an increased risk of suicidality in adults taking fluoxetine; no change to its label is recommended.</td>
</tr>
<tr>
<td>1999</td>
<td>A study suggests that in the month after an antidepressant is prescribed, suicide is more likely to occur if the drug is an SSRI instead of a tricyclic antidepressant (TCA) (Donovan).</td>
</tr>
<tr>
<td>2000</td>
<td>Using adult data from FDA reviews, Khan et al. find a similar risk of suicide or attempted suicide regardless of assignment to investigational drug, active comparator, or placebo (Khan).</td>
</tr>
<tr>
<td>2003</td>
<td>(Jan. 3): Fluoxetine becomes the first SSRI to gain FDA approval for treating children and adolescents with major depressive disorder (MDD).</td>
</tr>
<tr>
<td>2003</td>
<td>(June): The U.K.'s Medicines and Healthcare Products Regulatory Agency (MHRA) warns of the possibility of increased risk of suicidal ideas or suicide in pediatric patients taking paroxetine (Paxil).</td>
</tr>
<tr>
<td>2003</td>
<td>(June 19): The FDA announces it is reviewing reports of increased risk of suicidal thinking and suicide attempts related to the use of paroxetine in children and adolescents with MDD; it recommends that paroxetine not be used to treat pediatric MDD.</td>
</tr>
<tr>
<td>2003</td>
<td>(Sept.): The U.K. Committee on Safety of Medicines issues a report concluding that paroxetine is contraindicated in MDD patients younger than 18 years of age.</td>
</tr>
<tr>
<td>2003</td>
<td>(Oct. 27): The FDA issues a public health advisory about the uncertainty of a link between antidepressants and suicidal behavior in young people and reminds clinicians of the existing statement in antidepressant labeling about the inherent risk of suicide attempts in MDD and the need to supervise high-risk patients when drug therapy is initiated.</td>
</tr>
<tr>
<td>2003</td>
<td>(Dec.): In the U.K., the MHRA states that except for fluoxetine, SSRIs have not proved effective for pediatric patients with depression and may increase their risk of suicidal thinking or attempted suicide.</td>
</tr>
<tr>
<td>2004</td>
<td>(Feb. 2): The PDAC and Pediatric Subcommittee of the Anti-infective Drugs Advisory Committee meet to discuss reports of suicidality (suicidal ideation and attempts) in clinical trials for antidepressants in pediatric patients with MDD. The committees also discuss how data from these trials might be best analyzed as well as further research to be conducted.</td>
</tr>
<tr>
<td>2004</td>
<td>(March 22): The FDA issues a public health advisory asking drug manufacturers to include a warning recommending the close observation of adult and pediatric patients taking antidepressants for worsening depression or emergence of suicidality.</td>
</tr>
<tr>
<td>2004</td>
<td>(Sept. 14): The joint advisory committee votes 15–8 to recommend adding a boxed warning to antidepressant labeling about an increased risk of suicidality associated with the short-term use of antidepressants in pediatric patients and to require that a medication guide be provided for caregivers with every prescription.</td>
</tr>
<tr>
<td>2004</td>
<td>(Oct. 15): In keeping with the PDAC's recommendations, the FDA issues a public health advisory requiring the labeling of antidepressants to contain a boxed warning stating that antidepressants are associated with an increased risk of suicidal thinking and behavior in children and adolescents. A medication guide about this risk is to be added. The boxed warning states:</td>
</tr>
</tbody>
</table>

#### Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of [insert established 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. [Insert established name] is not approved for use in pediatric patients. Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of [nine] antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (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 in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials. |
| 2006 | (Dec. 13): The PDAC votes 6–2 to expand the boxed warning to include adults 18 to 24 years of age. |
| 2006 | (Dec. 15): The Academy of Child and Adolescent Psychiatry expresses concern that extending language of the boxed warning will create additional barriers to the treatment of depression. |
| 2007 | (May 2): Following the PDAC's recommendation, the FDA requires prescribing information of all antidepressants to contain a boxed warning about the risk of suicidality in patients up to 24 years of age who are taking antidepressants. The warning is stated as follows: |

#### Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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. |
| 2008 | (Dec. 16): The FDA requires 23 antiepileptic drugs to carry a warning (but not a boxed warning) about the increased risk of suicidal thoughts and behaviors. |
| 2009 | (March 20): Escitalopram (Lexapro) is approved for MDD in adolescents 12 to 17 years of age. |
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incidentally, such advice had been given to clinicians long before the advent of SSRIs. The current version also mentions that depression and other psychiatric disorders are themselves associated with an increased risk of suicide. Recently, however, concern has grown that instead of promoting the monitoring of patients who initiate antidepressants, these well-intentioned actions have had unintended consequences: underdiagnosis and undertreatment of depression in patients of all ages and increased suicide rates in young people, following years of steady decline in the suicide rate.

SUICIDE IN THE UNITED STATES

In the U.S., as of 2005, suicide accounted for 32,637 deaths (1.3% of the total of 2,448,017 deaths that year), ranking it as the 11th leading cause of death. Among people between the age of 10 and 54 years, however, suicide ranked no lower than fifth in any age group within that age span. In adolescents and young adults 10 to 34 years of age, suicide was the third leading cause of death (Figure 2), accounting for 12% of the 79,924 deaths in that age group. Reflecting the relative rarity of death from natural causes in young people, suicide accounted for 270 deaths (7%) in 10- to 14-year-olds; 4,212 deaths (12%) in the 14- to 24-year-olds; and 4,990 deaths (12%) in 25- to 34-year-olds. Among people 55 years of age and older, the 9,614 deaths by suicide reported in 2005 gave suicide a ranking of 18th among leading causes of death. Of these suicides, 77% (7,441) occurred in white men.

Overall, the age-adjusted suicide rate per 100,000 persons in the U.S. was 10.9 in 2005, but in patients with depression, the suicide rate has been estimated to range from 275 to 1,352 per 100,000 persons. By this measure, the rate of death by suicide among depressed patients exceeds the rates of death in the general population from the two leading causes—heart disease (211 per 100,000) and malignancies (184 per 100,000).

Concern over the ethics of assigning depressed patients to receive placebo in clinical trials led to a study of clinical trial data for all antidepressants approved by the FDA from 1987 through 1997. By filing a request under the Freedom of Information Act, the investigators obtained data for all published and unpublished trials. Their safety analysis included 19,639 subjects (4,491 patient-exposure years). For the five antidepressants for which data on suicide and attempted suicide were available, no statistically significant difference was found between the annual rate of suicide or attempted suicide in patients receiving placebo versus those receiving investigational drugs or active comparators (Table 3).

The authors pointed to several characteristics of the volunteers in trials that distinguish them from patients in general practice:

- The participants tend to have only moderate, not severe or mild, depression.
- They lack physical or psychiatric comorbidities.
- They are not actively suicidal; such patients would be intentionally excluded from trials.

### TABLE 3 Annual Rates of Suicide and Attempted Suicide Per Patient-Exposure Year (PEY)

<table>
<thead>
<tr>
<th></th>
<th>Investigational Drugs*</th>
<th>Active Comparators</th>
<th>Placebo</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>12,879</td>
<td>3,681</td>
<td>3,079</td>
<td>19,639</td>
</tr>
<tr>
<td>PEYs</td>
<td>3,206</td>
<td>729</td>
<td>556</td>
<td>4,491</td>
</tr>
<tr>
<td>Suicides, No.</td>
<td>27</td>
<td>5</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>Suicides per PEY</td>
<td>0.8%</td>
<td>0.7%</td>
<td>0.4%†</td>
<td>0.76%</td>
</tr>
<tr>
<td>Attempted suicides, No.</td>
<td>90</td>
<td>25</td>
<td>15</td>
<td>130</td>
</tr>
<tr>
<td>Attempted suicides per PEY</td>
<td>2.8%†</td>
<td>3.4%</td>
<td>2.7%†</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

* Sertraline, paroxetine, nefazodone, mirtazapine, and bupropion. Although fluoxetine and venlafaxine were approved during the period examined by Khan et al., they could not be included in the safety analysis because the FDA database did not include data for suicide or suicide attempt in fluoxetine studies; suicide and suicide attempts were combined in venlafaxine studies.
† Comparisons between placebo and investigational or active drugs are not statistically significant.


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Because these subjects are not severely ill, they tend to have a higher response rate to placebo.

Subjects receiving placebo are not untreated; they are recipients of the components of psychotherapy by virtue of their participation in the trial.

If this safety analysis shows that participants receiving placebo in clinical trials of antidepressants were not placed at increased risk of suicide or attempted suicide, the results suggest an important corollary: patients assigned to the study drug or to the active comparator were not placed at an increased risk of suicide or attempted suicide compared with placebo patients.

**BOXED WARNINGS**

The meta-analysis that led to the first boxed warning for antidepressants took a somewhat different approach; it involved data submitted to the FDA from all placebo-controlled, randomized controlled trials of antidepressants in pediatric patients.19 There were 23 such trials, to which was added the Treatment for Adolescents with Depression Study (TADS), sponsored by the National Institute of Mental Health.20,21 Sixteen of the 24 trials enrolled patients with MDD, and eight trials addressed other conditions. All were short-term studies, lasting from four to 16 weeks. Altogether these studies included 4,582 patients. In the trials of depression, efficacy was seen in only three of 15 manufacturer-sponsored trials plus TADS. There were no suicides in this population; the number of patients was not large enough to detect a small increase in the risk of suicide. However, the risk of suicidality was 4% in patients receiving antidepressants and 2% in patients receiving placebo.

The expanded boxed warning was based on two sets of analyses incorporating 372 randomized clinical trials of antidepressants in patients with MDD and other conditions. One analysis employed the “exact method” for a common odds ratio. This stratified method assumes a common odds ratio across trials, is valid with low event rates and small numbers of subjects per trial, and does not use trials with no events. The other analysis used conditional (fixed effects) logistic regression, which allowed active controls to be considered.

Of the 99,839 participants in these trials, 77,382 were enrolled in the 295 trials that studied psychiatric conditions (162 trials of MDD, 25 trials of other depressive disorders, and 108 trials of other psychiatric disorders). These patients were the primary focus of interest. In this group, there were eight suicides, with 501 patients exhibiting suicidal ideation, preparatory acts, and unsuccessful attempts at suicide (Table 4).

Results of the analyses were similar. By one method, which included investigational drugs and active controls, the estimated odds ratio for suicidal behavior or ideation, compared with placebo, was 0.85 (95% confidence interval [CI], 0.71–1.02; \(P = 0.08\)). By the other method, which excluded

### TABLE 4 Suicide and Suicidality in 295 Trials of Antidepressants For Psychiatric Disorders

<table>
<thead>
<tr>
<th>Age class</th>
<th>Placebo (n = 27,164)</th>
<th>Investigational Drug (n = 39,729)</th>
<th>Active Comparator (n = 10,489)</th>
<th>Total (n = 77,382)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicides</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Suicide attempts</td>
<td>44</td>
<td>71</td>
<td>18</td>
<td>133</td>
</tr>
<tr>
<td>Preparatory acts</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>147</td>
<td>169</td>
<td>42</td>
<td>358</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>196</strong></td>
<td><strong>248</strong></td>
<td><strong>65</strong></td>
<td><strong>509</strong></td>
</tr>
</tbody>
</table>

*From FDA, 2006.22,24*

#### Figure 3 Odds ratios (ORs) by age group for suicidality in patients receiving a test drug or placebo in psychiatric indications. Pediatric data are those used in the FDA’s 2004 analysis. (From FDA, 2006.22)
active controls, the odds ratio was 0.86 (95% CI, 0.71–1.04; \( P = 0.12 \)).22

No increased risk of suicidality was observed in the overall data for adults, but stratification by age group showed that the odds ratio for suicidality in patients receiving antidepressants decreased as age increased, compared with patients receiving placebo. This held true to the extent that antidepressants protected against suicidality in adults 65 years of age or older to a statistically significant degree but presented an increased risk of suicidality in young adults that fell just short of statistical significance (Figure 3). Members of the advisory committee found this age-related trend to be compelling, and they voted 6–2 to extend the boxed warning to young adults 19 to 24 years of age.

Although the FDA had assembled a massive amount of data for its 2006 deliberations, the data set has its shortcomings. In addition to the problems with inclusion and exclusion criteria used in randomized controlled trials of antidepressants, the FDA analysis was hampered by various methodological limitations (Table 5).

The exclusion from the primary analyses of the 77 trials in nonpsychiatric disorders (behavior disorders in 43 trials, other disorders in 34 trials) is of interest because the incidence rates for suicidality in patients with nonpsychiatric disorders are considerably lower than the rates in the psychiatric disorders (Table 6). The exclusion of nonsuicidality indications is tantamount to arguing that antidepressants act differently in people with a psychiatric disorder—whether they have MDD, OCD, or social anxiety disorder—than they do in people with nonpsychiatric disorders. The differences in event rates could suggest, however, that it is the disease, not the drug, that underlies the emergence of suicidal symptoms.23 During the same meeting, in words conveying anguish and anger, members of the public presented poignant vignettes of relatives who had begun taking an antidepressant shortly before committing suicide, including the following cases:24

- A 32-year-old single man with no history of depression or mental illness committed suicide nine days after he was prescribed an SSRI for fatigue associated with work-related anxiety.
- A 43-year-old married man hanged himself about three weeks after the dose of his SSRI was doubled; it had been prescribed in part because he was having difficulty coping with raising his triplets.
- A 40-year-old married man shot himself after taking the fourth tablet of an SSRI prescription.

This meeting of the advisory committee, like others in years past that had dealt with antidepressants and suicide, was by no means a sterile intellectual discussion of statistical matters. Members of the FDA’s Psychopharmacological Drugs Advisory Committee (PDAC) listened to dry scholarly presentations of data—but they also witnessed expressions of extreme passion as anecdotal evidence was presented.24

### WHAT AUTOPSY REPORTS REVEAL

The concept of suicidality represents a continuum that begins with vague feelings that life isn’t worthwhile and progresses to

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**TABLE 5 Limitations of FDA Analyses**

<table>
<thead>
<tr>
<th>Randomized Controlled Trials</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Patients with severe depression were excluded.</td>
<td>- No risk–benefit estimate was available.</td>
</tr>
<tr>
<td>- Patients with other psychiatric comorbidities were excluded.</td>
<td>- Suicidality was determined from a review of adverse event reports, with a possibility of ascertainment bias.</td>
</tr>
<tr>
<td>- Actively suicidal patients were excluded.</td>
<td>- Timing of events could not be determined.</td>
</tr>
<tr>
<td>- Trials were short in duration (range, 4–84 weeks; mean, 10.3 weeks; median, 8 weeks) and could not address long-term safety.</td>
<td>- Attrition rates (up to 30% in trials of major depression disorder) were not considered.</td>
</tr>
</tbody>
</table>

**TABLE 6 Suicidality Incidence Rates per 10,000 Patient-Years**

<table>
<thead>
<tr>
<th></th>
<th>Suicides</th>
<th>Attempted Suicides</th>
<th>Preparation</th>
<th>Ideation</th>
</tr>
</thead>
<tbody>
<tr>
<td>All disorders</td>
<td>5</td>
<td>86</td>
<td>6</td>
<td>244</td>
</tr>
<tr>
<td><strong>Psychiatric indications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>10</td>
<td>157</td>
<td>12</td>
<td>416</td>
</tr>
<tr>
<td>Other depressive disorders</td>
<td>0</td>
<td>81</td>
<td>12</td>
<td>163</td>
</tr>
<tr>
<td>Other psychiatric disorders</td>
<td>4</td>
<td>73</td>
<td>4</td>
<td>220</td>
</tr>
<tr>
<td><strong>Nonpsychiatric indications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral disorders</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>Other disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>60</td>
</tr>
</tbody>
</table>

- a. Examples: bipolar disorder, premenstrual dysphoric disorder, postnatal depression, seasonal affective disorder.
- c. Examples: alcoholism, insomnia, obesity, smoking addiction.

Adapted from FDA, 2006,22,24
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Specific thoughts about how suicide might be accomplished. These thoughts are followed by suicidal behaviors, such as acquiring the intended tools or objects to cause death, putting one’s affairs in order, and attempting suicide. If antidepressants precipitate suicidal thoughts and behavior in young people and if such suicidality leads to actual suicide, it is reasonable to expect that antidepressants would be detected at autopsy. It also is reasonable to expect that by 1999, antidepressants would have been prescribed for a substantial number of young patients in New York City.

In the four-year period from 1999 through 2002, 41 persons younger than 18 years of age committed suicide in New York City.25 Toxicology analyses were available for 38 of these suicides. To take the elimination half-life of antidepressants into account, the authors limited their review of toxicology analyses to the 36 people who committed suicide within three days of self-inflicted injury; as it happened, all 36 died within 26 hours of their injury. In this group, bupropion (Wellbutrin, GlaxoSmithKline) and sertraline (Zoloft, Pfizer) were found in only one person, a 16-year-old homeless man who died after an intentional drug overdose.

Because some suicides might have been misclassified, the authors also reviewed the medical examiner’s records for the 269 New York City residents younger than 18 years of age whose deaths were ruled accidental between 1999 and 2002. Toxicology analyses were available for 241 decedents, of whom 213 died within three days of injury. An antidepressant, imipramine (Tofranil, Mallinckrodt), was found in only two children in this group.25

The Leon study sheds no light on whether antidepressant-induced suicidal ideation and behavior were present in the unknown number of New York City youths taking antidepressants between 1999 and 2002; however, if such suicidality was present, it clearly didn’t result in actual suicide.25 Neither can this study address the question of whether any of these suicides could have been prevented by the use of antidepressants.

Leon et al. conducted two similar studies in New York City, one looking at youth suicides from 1993 through 1998 in the other investigating adult suicides between 2001 and 2004.7 In the earlier study, which was spurred by the reports linking paroxetine with youth suicides, 54 of the 66 recorded suicides met the previously mentioned criteria for analysis.5 Paroxetine was not found in the blood of any victims, although imipramine was detected in two persons and fluoxetine in two others. Thus, most of these youths weren’t taking antidepressants of any kind at the time of their death, either. Combining these two studies of pediatric suicides in New York City, we see that over the course of a decade during the SSRI era, antidepressants were detected in 6% (5/90) of suicides. In the other 94% (85/90), antidepressants had not been used at the time of death.

Based on these statistics, not using antidepressants seems to pose the greater risk for children. In their study of adults, Leon and colleagues found antidepressants in the blood of 23% (287/1,158) of victims overall but in only 14% (24/173) of those between 18 and 24 years of age.9

Similar results were obtained in a Swedish study.27 Isacsson et al. compared the presence of antidepressants in persons committing suicide with controls who died accidentally or from natural causes from 1992 through 2000. As part of the investigation of any unnatural death, the Swedish procedure is to screen for all antidepressants among some 200 substances. During this nine-year period, 14,857 suicides were investigated. These included 4,301 cases in which it was unclear whether death from drug overdose was intentional or accidental. The control group included 26,422 cases. Overall, SSRIs as a class were 17% less likely to be associated with a suicide compared with other antidepressants (odds ratio, 0.83; 99% CI, 0.77–0.90). The only exception was fluvoxamine (Luvox, Solvay) (odds ratio, 3.04; 99% CI, 1.15–8.04). Fluvoxamine was the first SSRI to be introduced in Sweden and was rarely used after 1994. In the U.S., fluvoxamine is not indicated for treating depression, only OCD, and, in the case of the recently approved extended-release fluvoxamine, OCD and social anxiety disorder. For fluoxetine and paroxetine, the SSRIs first associated with an increased risk of suicide, the odds ratios were 0.91 (99% CI, 0.60–1.38) and 0.87 (99% CI, 0.78–1.28), respectively.

In the patients younger than 15 years of age, antidepressants were present in seven of the 52 cases of suicide (13%); none of these agents were SSRIs. In the group between 15 and 19 years of age, antidepressants were present in 13 of the 326 cases of suicide (4%); six of these agents were SSRIs. Compared with non-SSRIs, the relative risk of suicide was 0.14 (95% CI, 0.05–0.43). Like the New York City statistics, the Swedish statistics suggest that antidepressants were underutilized in these young patients.

Population-Based Studies

A British case-control study by Jick et al. provides further insights into whether the SSRIs fluoxetine and paroxetine present a risk for depressed patients, especially young patients.28 Drawing on the massive U.K. General Practice Research Database (GPRD), which contained computerized health care records provided to three million residents, the researchers examined the population comprising the 159,810 patients who had filled at least one prescription for one of the four antidepressants most commonly used in the U.K. between 1993 and 1999. These prescriptions included two older agents (the TCAs amitriptyline and dothiepin) and two newer drugs (the SSRIs fluoxetine and paroxetine). Patients were between 10 and 69 years of age, and their first expression of suicidal behavior or ideation occurred within 90 days after receiving at least one prescription for one of the four antidepressants. In this group, 17 suicides occurred within 90 days after the start of the prescription. None of the 10- to 19-year-olds committed suicide. In the remainder of the GPRD population, however, there were 15 suicides in this age group; no one in this group had received an antidepressant.

Adjusted odds ratios for nonfatal suicidal behaviors are shown in Table 7. As published, the study had used only dothiepin as the reference group; however, because dothiepin isn’t available in the U.S. or Italy, at the request of a reader of the journal article, the authors performed a post hoc analysis using amitriptyline as the reference group.29 In both analyses, all comparisons failed to reach statistical significance, although the paroxetine comparisons did approach it. In patients 10 to 19 years of age, none of the adjusted odds ratios, when compared with dothiepin, were statistically significant: amitriptyline, 0.9 (95% CI, 0.3–2.8);
that led directly to an increase in suicides in this age group. A 14% increase in the suicide rate between 2003 and 2004 for youths 5 to 19 years of age was the largest annual increase since 1979, when the Centers for Disease Control and Prevention (CDC) began collecting suicide data. The authors also pointed out that a 22% decline in SSRI prescriptions for pediatric patients receiving antidepressants before or after their first prescription for the TCA, whereas 28% of fluoxetine users and 34% of paroxetine users received at least one additional prescription at some point.

**DISCUSSION**

During the FDA’s PDAC meeting in December 2006, J. John Mann, MD, a professor of psychiatry at Columbia University and immediate past president of the American Foundation for Suicide Prevention, recommended that the PDAC reverse its previous recommendation for a boxed warning. Instead, he recommended that the PDAC provide doctors with a warning only in the package insert to remind them of the need to monitor patients receiving antidepressants. His reasoning was that introducing the pediatric boxed warning in early 2004 had caused a 22% decline in SSRI prescriptions for pediatric patients that led directly to an increase in suicides in this age group.

In a paper providing details about this phenomenon, Gibbons et al. observed that the 14% increase in the suicide rate between 2003 and 2004 for youths 5 to 19 years of age was the largest annual increase since 1979, when the Centers for Disease Control and Prevention (CDC) began collecting suicide data. The authors also pointed out that a 22% decline in SSRI prescriptions in the Netherlands was followed by a 49% rise in the rate of youth suicides between 2003 and 2005. If a causal connection between SSRI use and youth suicide truly existed, they said, the expected observation would have been a decrease in youth suicides during this period.

It might be useful to place the still-unfolding story of antidepressants and suicide within the context of how people perceive risk and make decisions based on those perceptions. In short, it is not a rational process. Studies by psychologists have shown that if people believe some technology or activity has high benefit, they tend to assign it low risk; if they believe it presents high risk, they assign it low benefit. Further, if people receive information that causes them to raise their estimate of the benefit, they then lower their estimate of the risk. Similarly, receiving information that causes them to increase their estimate of a technology’s risk results in a corresponding lowering of its estimated benefit. If the topic at hand is heavily laden with emotion (youth suicide would certainly meet this condition, as would cancer or nuclear energy), some people would worry about a risk even if its probability is extremely small. Even an exceedingly small risk of a catastrophic event can be too much for them to bear.

Daniel Gardner considers such people to be to be “probability blind.” He writes, “The irony is that probability blindness is itself dangerous. It can easily lead people to overreact to risks and do something stupid like abandoning air travel because terrorists hijacked four planes [on September 11, 2001].”

Alternatively, some might reject antidepressants because of fears of treatment-induced suicide; however, the American Academy of Child & Adolescent Psychiatry (AACAP) is not among those who would do so. Citing an 11:1 risk–benefit ratio for SSRIs, that is, the number of adolescents needed to harm (112) versus the number needed to treat (10), the AACAP, in its current practice parameter for children and adolescents with depressive disorders, states:

> [G]iven the greater number of patients who benefit from SSRIs than who experience these serious adverse effects [suicidality], the lack of any completed suicides, and the decline in overall suicidality on rating scales, the risk/benefit ratio for SSRI use in pediatric depression appears to be favorable with careful monitoring.

From what we know, it is possible that in a small subset of depressed patients, an antidepressant promotes the emergence of suicidal thoughts and behavior and it might be reasonable to try to identify the mechanisms underlying this phenomenon. It has been suggested that some patients, especially young adults and the elderly, are placed at an increased risk of suicidality because of antidepressant-induced akathisia. It is also possible that depression in some patients, particularly younger patients who experience increased suicidality and low efficacy with antidepressants, has been misdiagnosed as unipolar depression instead of as a bipolar spectrum disorder.

Berk and Dodd suggest several factors that might lead to this erroneous conclusion:

1. The age of onset for bipolar disorder is earlier than that for MDD.
2. The depressive symptoms of bipolar disorder are more prevalent than manic symptoms.
3. Even when mania is present, it is often unrecognized by patients and goes untreated.
4. The diagnosis is further complicated by the presence of psychiatric comorbidities or mixed episodes.

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**TABLE 7 Relationship between Antidepressants and Nonfatal Suicidal Behaviors**

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Cases (n = 555)</th>
<th>Controls (n = 2,062)</th>
<th>Odds Ratio (95% CI)*</th>
<th>Odds Ratio (99% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dothiepin</td>
<td>167 (30.1%)</td>
<td>707 (34.3%)</td>
<td>1.00 (reference)</td>
<td>1.21 (0.80–1.83)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>77 (13.9%)</td>
<td>367 (17.8%)</td>
<td>0.83 (0.61–1.13)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>176 (31.7%)</td>
<td>588 (28.5%)</td>
<td>1.16 (0.90–1.50)</td>
<td>1.40 (0.92–2.13)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>135 (24.3%)</td>
<td>400 (19.4%)</td>
<td>1.29 (0.97–1.70)</td>
<td>1.55 (0.99–2.43)</td>
</tr>
</tbody>
</table>

* Odds ratios and the confidence interval (CI) are estimated from a logistic regression model conditional on matching factors and adjusted for time since the initiation of the antidepressant.


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fluoxetine, 1.3 (0.6–3.0); paroxetine, 1.7 (0.7–4.1).

The authors suggest that the odds ratios for paroxetine, which approach statistical significance, might reflect not a modest increase in risk for nonfatal suicidal behaviors but, rather, a tendency among clinicians to favor the newest antidepressant over an older drug for patients with severe depression. This interpretation is supported by the finding that about 20% of TCA users received one or more prescriptions for another antidepressant before or after their first prescription for the TCA, whereas 28% of fluoxetine users and 34% of paroxetine users received at least one additional prescription at some point.
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In a study of patients with bipolar disorder (with a mean age of 40 years and 42% with a history of suicide attempts), however, Bauer et al. noted that neither the initiation of antidepressant therapy nor a change in antidepressant therapy was associated with new-onset suicidality.36 About half of these patients were being treated with one or more mood stabilizers, but the authors could not assess any protective effects that might be ascribed to them. It has been argued that antidepressants should be used judiciously but not routinely for bipolar disorder because of the risk of antidepressant-induced mania and rapid cycling and the greater efficacy of lithium compared with antidepressants for preventing suicide in patients with bipolar depression.37

In one study of bipolar patients receiving a mood stabilizer, Sachs et al. found that the addition of an antidepressant (paroxetine or bupropion) was not associated with improved effectiveness, but neither was it associated with an increased risk of treatment-emergent mania or hypomania or an increased risk of suicidality.38 The authors noted that it may be desirable for clinicians and family members to closely monitor patients with bipolar disorder who have begun antidepressant therapy.

We cannot expect that antidepressants will always prevent suicides in depressed patients anymore than we can expect statins to eliminate heart attacks. Recent research suggests that in adolescent patients with moderate-to-severe MDD, it may be desirable to complement antidepressant therapy with cognitive behavioral therapy20,21 or even an antipsychotic agent such as aripiprazole (Abilify, Bristol-Myers Squibb/Otsuka), which is indicated for adjunctive treatment of MDD in adults; risperidone (Risperdal, Janssen);39 or quetiapine (Seroquel, AstraZeneca).40 On the other hand, the recent finding that atypical antipsychotic agents present the same risk of sudden cardiac death as older antipsychotic drugs41 might also make some clinicians reluctant to use them.

Andrew C. Leon, a biostatistician who was a voting member of the PDAC when it voted on both boxed warnings and who conducted the New York autopsy studies mentioned previously,25,26 states that the FDA intended the current version of the warning to advocate the close monitoring of patients who begin antidepressant therapy and to implicitly raise the issue of the risk of untreated depression.42 Friedman and Leon25 explain that the FDA could not explicitly state that untreated depression increases the risk of suicide because doing so would constitute a treatment recommendation.

If the message that the FDA intended to transmit with its various public health advisories and boxed warnings was “to monitor” patients, the clinicians apparently did not receive it. Using the PharMetrics claims database, which includes more than 85 million insured people nationwide, Morrato et al. retrospectively examined the frequency of provider visits in patients receiving antidepressants for new episodes of depression diagnosed between October 1998 and March 2005.32 They used two standards to judge such contact:

- The National Committee for Quality Assurance’s (NCQAs) HEDIS measure of care, which calls for three or more contacts with a primary care or mental health practitioner during the first 12 weeks of treatment
- the more stringent recommendations from the medication guide that the FDA said patients should receive.

The medication guide initially called for weekly visits during the first month, twice-weekly visits during the second month, and one visit at the end of the third month, for a total of seven visits over three months; the current version recommends monitoring patients and keeping follow-up appointments without quantifying visits.

The authors note that the high number of visits in the first version lacked an evidence base and was substantially greater than would be expected for most other medical visits. The study found that prior to the FDA’s October 2003 advisory, fewer than 5% of pediatric patients met the FDA recommendation of seven visits in three months. After the advisory was issued, there was no statistically significant change in these proportions.

Before the advisory was issued, about 60% of pediatric patients 5 to 18 years of age (n = 27,370) and 40% of adult patients older than 18 years of age (n = 193,151) in this study satisfied the less stringent HEDIS measure calling for three visits during the first 12 weeks of treatment. During the period of 1.5 years after issuance of the advisory, there was no statistically significant change in these percentages either. As used by NCQA, the HEDIS measure applies only to patients...
18 years of age or older; the 40% compliance rate achieved in this study was about twice as high as the nationwide results reported by NCQA between 2001 and 2007 (Figure 4).\textsuperscript{44,45} During this period, there was little or no improvement nationwide in the percentage of managed care patients receiving the recommended number of provider contacts.

But if the message to perform close monitoring wasn’t received or heeded, the message that some clinicians, patients, and family members might have received instead was “Danger! Stop!” Another analysis of PharMetrics claims data found an increase between 1999 and 2004 in the rate at which new episodes of pediatric MDD were diagnosed but a sharp decline in the rate in 2005 (Figure 5).\textsuperscript{46} In this study by Libby et al., an average of 59% of pediatric patients filled a prescription for an antidepressant within one month of a diagnosis of depression during the four years before the advisory, increasing at an annual rate of 1.94%. If the historical trend had continued, the prescription fill rate would have been 67% by September 2005 (Figure 6). In fact, the observed rate was 28%.

In contrast, before the advisory, there was no established trend for pediatric patients filling no prescription for an antidepressant after a diagnosis of depression, and the “no-fill” rate predicted for September 2005 was 19%. The observed rate was 64%; in other words, the rates essentially flip-flopped between the pre-advisory period and the post-advisory period.

Contrary to the FDA’s claim that pediatric prescriptions for antidepressants had risen by 7% between the first half of 2003 and the first half of 2004,\textsuperscript{46} Nemeroff et al.\textsuperscript{1} also found that antidepressant prescribing for pediatric patients declined (Figure 7) following the issuance of the October 2003 advisory and that it remained flat after the first (pediatric) boxed warning was recommended. Moreover, the Nemeroff study reported

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\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Percentage of cases with prescription fills for selective serotonin reuptake inhibitors (SSRIs) and cases with no antidepressant fills, within 30 days after diagnosis, in monthly pediatric cohorts with depression before and after the FDA’s Public Health Advisory on the use of antidepressants in pediatric patients. Based on the historical trend established during the period prior to the FDA’s advisory in October 2003, the predicted percentage of antidepressant prescription fills within 30 days after diagnosis in September 2005 was 67%, compared with an observed rate of 28%. The predicted “no-fill” rate was 19%, and the observed rate was 64%. (From Libby AM, Brent DA, Morrato EH, et al. \textit{Am J Psychiatry} 2007;164[6]:884–891.\textsuperscript{46})}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Annual rates of depression in the pediatric general medical and specialty managed care enrollee population, 1999–2005 by sex (65,349 patients). (From Libby AM, Brent DA, Morrato EH, et al. \textit{Am J Psychiatry} 2007;164[6]:884–891.\textsuperscript{46})}
\end{figure}
a substantial shift in the mix of specialists writing prescriptions for antidepressants for pediatric patients. From December 2003 through February 2004, pediatricians wrote 28% of such prescriptions; family practitioners, general practitioners, and doctors of osteopathy wrote 21%; and psychiatrists wrote 44%. During the corresponding quarter in 2004–2005, however, psychiatrists wrote 63%, whereas the share written by pediatricians and PCPs dropped to 21% and 9%, respectively.

An analysis of the Medco database found that the FDA’s warning about paroxetine, issued in June 2003, apparently ended a period of rapid increase in pediatric antidepressant use, which had increased at an annualized rate of 36% during the 12 months prior to the paroxetine warning. The use of antidepressants by adults 18 to 64 years of age and adults 65 years of age or older had increased at lower annualized rates (11% and 10%, respectively) in the period before the paroxetine warning, and subsequent declines among adults were less marked. It is interesting that Olfson and colleagues stated that the patterns they observed in the Medco population were: generally consistent with what would be expected if the FDA warnings achieved their intended effects of increasing perceptions of risk of antidepressant treatment [emphasis added], especially in young people.

This differs from the rationale cited earlier—to advocate close monitoring and implicitly raise the possibility of the risk of untreated depression.

In the PharMetrics database, changes in diagnostic and prescribing trends also were observed in an adult managed care population after the advisory was issued. Overall, the rate of diagnosed episodes of depression increased from six per 1,000 enrollees in 1999 to 11 per 1,000 in 2004. Among women and men, the predicted rates would have been 17.4 and 8.0 per 1,000, respectively, in 2005. Instead, the observed rates for women and men were 12.4 and 5.8 per 1,000, respectively. As a percentage of all depression diagnoses (N = 475,838) in this population, the percentage of recurrent episodes declined, whereas the percentage of new episodes increased during the post-advisory period. The authors suggest that this change reflected a reluctance among patients in the post-advisory period to disclose symptoms of depression or a reluctance among physicians to diagnosis depression, or both.

Most recently, a new analysis of the PharMetrics database shows that in the post-advisory period through June 2007, the percentage of new episodes of depression diagnosed by PCPs or pediatricians was 44% lower than pre-advisory trends would have predicted. Likewise, PCPs’ diagnoses of depression in young adults (19 to 24 years of age) and adults (25 to 89 years of age) during this period declined by 37% and 29%, respectively, compared with predicted rates. A decline in SSRI prescribing also was noted during the post-advisory period through June 2007 in all three cohorts. This decline occurred without any compensating increase in other forms of treatment.

It is interesting that when the FDA decided in December 2008 to require antiepilepsy drugs to carry warnings about an increased risk of suicidal thoughts and behaviors, it did not go so far as to require a boxed warning (see Table 2). Indeed, during the FDA’s meeting in July 2008 to discuss this topic, speakers representing the American Epilepsy Society and the Epilepsy Foundation raised the example of antidepressants when they pointed to the black box as an approach to be
avoided, for fear that it might dissuade patients from continuing or initiating antiepileptic therapy, with dire consequences.

**CONCLUSION**

Over the past 50 years, rates of suicide in young Americans have not been static. A long period of decline in the suicide rate that began in 1990 coincided with the widespread availability and acceptance of SSRIs and other new antidepressants. That decline appears to have ended recently, and its end seems to have coincided with a reduction in antidepressant prescribing that followed official pronouncements associating antidepressants with an increased risk of suicidal thoughts and behaviors—but not with an increased risk of actual suicide.

Evidence for and against antidepressants with respect to suicide is circumstantial, notably because suicidal patients and severely depressed patients were excluded from the randomized clinical trials used in the meta-analyses that led to the current boxed warning. Because of the rarity of suicide and the ethical problems associated with assigning suicidal or severely depressed patients to a placebo group, it is unlikely that a new randomized controlled trial would clarify whether antidepressants prevent or precipitate suicide. Further, no amount of new evidence is likely to make the relatives of patients who committed suicide soon after beginning an antidepressant prescription abandon their belief that the drug was responsible for the death. Likewise, clinicians who have become leery of antidepressants probably will remain so.

Antidepressants seem to have joined the ranks of dental amalgams, childhood immunizations, and electromagnetic fields—all topics that engender strong emotions on either side of the argument even if the data support only one side. Risk-averse people who demand proof that a technology prove to be absolutely safe before they feel comfortable using it can never find such proof—for antidepressants or anything else. Litigation-averse clinicians, understandably, will continue to be wary when they prescribe antidepressants.

Perhaps recent events will lead to some positive developments, such as increased study and use of nonpharmacological therapies for depression, greater access to and reimbursement for mental health services, and more attention (such as monitoring) to depressed patients. Even if they do not, the CDC will continue to compile suicide statistics, adding to the circumstantial evidence that will determine whether the ongoing public health experiment is a success or a failure.

**REFERENCES**

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