SAFE USE OF SSRIS IN YOUNG ADULTS
Mr. B, age 20, has taken a semester leave from college because of gradually worsening depressed mood. Over the past 2 months he has lost interest in jogging and playing piano—which he usually enjoys. He reports reduced libido, middle insomnia, loss of appetite, feeling as if his head is "full of cotton," trouble concentrating, and waking in the morning with a sense of dread. His anxiety dissipates during the day, but he continues to feel sad and sometimes weepy, which is unusual for him.

Mr. B reports feeling hopeless at times and has had vague thoughts about life being "not worth it if I continue to feel like this" but denies specific suicide plans. Your initial impression is that Mr. B is in the midst of a major depressive episode and that a selective serotonin reuptake inhibitor (SSRI) is indicated. As you finish taking his history, you run through your mind the pros and cons of the recommendation you will make to him.

Do SSRIs raise or lower the risk for suicidal behavior in young adults such as Mr. B? The answer is complicated and goes beyond an “either/or” question, as the FDA acknowledged in May 2007 when it:

• extended the black-box warning of increased suicidality risk with antidepressants to cover adults age 18 to 24 as well as children and adolescents
• included language in the warning about the benefits of treating depression and the suicide risk associated with

Pediatric suicide rates increased in 2003-04 after the black-box warning, which has now been extended to patients age 18 to 24.

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How strong is evidence for new suicide warning?
FDA’s pediatric suicidality analysis: What the data showed

The FDA meta-analysis designed to investigate a reported association between antidepressants and suicidality in children and adolescents found contradictory results:

- Pooled adverse event data from 24 pediatric antidepressant trials totaling >4,400 patients showed a higher risk of suicidal ideation or behavior (no suicides occurred) with antidepressants (4%) vs placebo (2%).
- Systematically collected suicide-related item scores from 17 of the trials showed no evidence that antidepressants worsen suicidality or cause it to emerge.

One interpretation of these findings is that antidepressants’ effect on suicidality is small and therefore subject to measurement error.

Another is ascertainment bias; any side effect associated with active medication encourages discussion with the clinician and may distort the frequency of reported adverse events.

The FDA meta-analysis also found:

- Relative risk for suicidality ranged 10-fold among agents, from 0.9 with fluoxetine to 8.8 with venlafaxine.
- Most suicide-related events occurred in subjects having the highest baseline levels of suicidality.
- Hostility and agitation emerged with SSRI use, particularly during the first month of treatment.
- Patient age, sex, or history of suicide attempt/ideation did not affect the results.

Source: Reference 7

untreated depression, given concerns about declining antidepressant prescriptions and rising suicides among youth.1

To help you make informed decisions when treating depression in adults, this article reviews the studies leading up to and following the FDA’s meta-analysis of antidepressant trial data in patients age 18 and older. Our goal is to provide a framework for clinical treatment of adults age 18 to 24 and those age ≥25.

First hints of suicidality

SSRIs revolutionized depression treatment. From 1985 to 1999, annual U.S. antidepressant prescriptions quadrupled, with SSRIs accounting for 70% of the increase (see “Antidepressants and suicide risk, 1985 to 2007,” pages 36-37). At the same time, the age-adjusted suicide rate:

- dropped 22.5% for women (who account for twice as many antidepressant prescriptions as men)
- dropped 12.8% for men (without change in the rank order of suicide methods).2

For many patients, increased antidepressant use improved treatment of major depressive and other antidepressant-responsive disorders. In 1990, however, case reports suggested SSRIs might cause suicidal thoughts or behavior.3 Hypothesized mechanisms included increased aggression4 and akathisia.5 An FDA review found no proof, and a meta-analysis of data from 17 double-blind, randomized, controlled trials found no association between fluoxetine and suicidal thoughts or behavior.6

The debate rekindled in June 2003 when the British Committee on Safety of Medicines warned against using paroxetine or venlafaxine in children. After conducting its own meta-analysis, the FDA in 2004 ordered a black-box warning about suicidality and the use of antidepressants in children and adolescents (Box).7

After the pediatric ‘black box.’ Antidepressant prescriptions for children and adolescents declined in the years 2003 to 2004, as did diagnosis of pediatric depression.8-10 Antidepressant prescribing also showed signs of shifting from general practitioners to psychiatrists.11 At the same time, the suicide rate among youth age <17 rose 11% from 1.26/100,000 to 1.4/100,000—after 3 consecutive years of decline—according to new data from the Centers for Disease Control and Prevention.12 In patients age >60, SSRI prescriptions continued to rise and suicide rates fell,13 a pattern of change consistent with antidepressants protecting against suicide.

continued on page 35
An independent meta-analysis by Bridge et al.12 examined the pediatric trial data used in the FDA meta-analysis plus 7 additional studies. Its findings differ in 2 important ways from those of the FDA review:

- Antidepressants—including others besides fluoxetine—showed efficacy in treating anxiety disorders and depression in children and adolescents.
- The frequency of suicide-related adverse events (no trial patients committed suicide) was approximately 3% on active medication—25% lower than the FDA estimated rate—and 2% on placebo, similar to the FDA estimate.

The number needed to treat (NNT)—number of patients who must be treated to get a therapeutic response that would not have happened with placebo—ranged from 3 to 10. The number needed to harm (NNH)—number of patients who must be treated for 1 suicidal ideation/nonfatal attempt to occur that would not have happened with placebo—ranged from 112 to 200. The authors interpreted this as “indicating a favorable overall risk-to-benefit profile for antidepressants in the treatment of pediatric [major depressive disorder], [obsessive-compulsive disorder] (OCD), and non-OCD anxiety disorders.”12 These findings appear to support the efficacy of antidepressants in pediatric patients and a favorable risk-benefit ratio.

What about adults? Overall effect. A subsequent FDA meta-analysis of antidepressant clinical trial data in adults13 found 8 suicides in 372 trials totaling nearly 100,000 persons. All occurred in the 295 trials with psychiatric indications. Among these psychiatric trials, 59% had a suicidal behavior/ideation event in either the test-drug or placebo arm, and 41% had none. Eleven antidepressants were included in the meta-analysis:

- 6 SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline)
- 2 SNRIs (duloxetine and venlafaxine)

FDA meta-analysis: Suicide rates by age in antidepressant trials

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>Suicide rate (%) (test drug / placebo)</th>
<th>Suicide attempt rate (%) (test drug / placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 to 24</td>
<td>0.03 / 0.00</td>
<td>0.55 / 0.27</td>
</tr>
<tr>
<td>25 to 30</td>
<td>0.00 / 0.03</td>
<td>0.23 / 0.11</td>
</tr>
<tr>
<td>31 to 64</td>
<td>0.01 / 0.00</td>
<td>0.13 / 0.15</td>
</tr>
<tr>
<td>≥65</td>
<td>0.00 / 0.04</td>
<td>0.03 / 0.25</td>
</tr>
</tbody>
</table>

Source: Reference 13

FDA meta-analysis: Risk of suicidality in adults taking antidepressants

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Protective benefit appeared greater for adults age ≥25 than for those age 18 to 24</td>
<td></td>
</tr>
<tr>
<td>Elevated risk appeared to apply to adults age &lt;25 with any psychiatric disorder, not just depression</td>
<td></td>
</tr>
<tr>
<td>A “slight suggestion” of increased risk was seen with SNRIs vs other classes, but no significant differences among drugs or drug classes</td>
<td></td>
</tr>
<tr>
<td>Risk was increased in adults who did not respond to active drug treatment</td>
<td></td>
</tr>
<tr>
<td>Risk was not affected by patient sex, race, geographic location, inpatient vs outpatient care, or treatment with SSRIs vs non-SSRIs</td>
<td></td>
</tr>
<tr>
<td>Risk may be lower with sertraline than with other antidepressants, although this trend could be a false-positive result related to multiple tests</td>
<td></td>
</tr>
<tr>
<td>A “sensitivity analysis” using alternate statistical methods to test the robustness of the findings yielded similar results</td>
<td></td>
</tr>
</tbody>
</table>

SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors

Source: Reference 13
Clinical Point

Antidepressants’ antisuicidality benefit appears greater for patients age ≥25 than for those age 18 to 24

Table 3A

4 studies found no relationship between SSRI use and suicide in adults

<table>
<thead>
<tr>
<th>Study design</th>
<th>Main results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis of FDA data by Khan et al;16 &gt;48,000 patients in trials that included fluoxetine, sertraline, paroxetine, citalopram</td>
<td>No difference in suicide rates among SSRIs, other antidepressants, or placebo</td>
<td>Patients not representative of general clinical population; Trials mostly short-term; tended to exclude suicidal patients</td>
</tr>
<tr>
<td>Case-control study in UK primary care practice by Jick et al;17 antidepressant users, 555 with suicidal behavior vs 2,062 without</td>
<td>Risk of suicidal ideation or behavior did not differ between SSRIs vs non-SSRIs</td>
<td>Observational study Confounding by indication*</td>
</tr>
<tr>
<td>Case-control study in UK primary care practice by Martinez et al;19 ≥146,000 persons, first antidepressant prescription for depression</td>
<td>No evidence that risk of suicide or nonfatal self-harm was greater with SSRIs than with tricyclics</td>
<td>Observational study Confounding by indication*</td>
</tr>
<tr>
<td>Meta-analysis in UK by Gunnell et al;21 477 clinical trials (N=40,000) of SSRIs vs placebo in depression</td>
<td>No evidence that SSRIs increased suicide risk</td>
<td>Lack of individual or trial-level data Evidence suggests nonfatal suicidal ideation/self-harm events are underreported</td>
</tr>
</tbody>
</table>

SSRI: selective serotonin reuptake inhibitor; UK: United Kingdom
*Confounding by indication: Clinicians may preferentially prescribe SSRIs to patients thought to be at risk for suicide because of these drugs’ relative safety in overdose.

- 3 others (bupropion, mirtazapine, and nefazodone).

Overall, antidepressants showed a protective (antisuicidal) effect in adults as compared with placebo (odds ratio 0.85 [95% CI: 0.71 to 1.02, P=0.08]), with no difference in effect between SSRIs and non-SSRIs.

Age-specific findings. When the FDA analysis was stratified by age, however, antidepressants’ benefit appeared greater for patients age ≥25 than for those age 18 to 24. The data suggested:

- elevated suicidality risk among adults age <25
- neutral or possibly protective effect for adults age 25 to 64
- protective effect in adults age ≥65 (Table 1, page 35).

For 18- to 24-year-olds, the suicide rate was 0.03% (~1/4,000) in these mostly 8- to 12-week trials, and the suicide attempt rate was 0.55% (~1/200). For comparison, the lifetime prevalence of suicide was 2.2% to 8.6%—depending partly on illness severity—in a meta-analysis of patients with mood disorders.14

The odds ratio for suicidal behavior (preparatory acts, attempt, or suicide) for subjects age 18 to 24 on test drug vs placebo was

Antidepressants and suicide risk, 1985 to 2007

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Case reports suggest link between suicide and SSRI use</td>
<td>FDA analysis finds no association between SSRIs and increased suicide risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Antidepressant prescriptions quadruple; age-adjusted suicide rate drops 22.5% for women and 12.8% for men
2.31 (95% CI: 1.02, 5.64) [event rate/sample: 23/3810 vs 8/2604]. NNH was 333, which means 333 adults in this age group would need to be treated with an antidepressant for 1 to experience a suicidal behavior event that would not have happened with placebo.

Compare an NNH of 333 with the much lower NNH values associated with anti-arrhythmic treatment of atrial fibrillation (AF),19 an important cardiovascular cause of morbidity and mortality. A meta-analysis of 44 AF trials totalling 11,322 subjects found that—although “moderately effective” for maintaining sinus rhythm—all but 2 of the 10 drugs were pro-arrhythmic. Their NNH values of 17 to 119 are, at best, approximately one-third the NNH for antidepressants for suicidality in young adults based on adverse event reports. With NNH, higher is safer.

The age-related pattern the FDA found in its adult meta-analysis (Table 2, page 35)13 is consistent with its earlier pediatric analysis7 but not with the more recent findings of Bridge et al12 that included a larger data set.

**Mixed evidence**

Aside from the FDA meta-analysis,13 what is the evidence that antidepressants—or specifically SSRIs—may cause suicidality in adults? Among 9 major published studies in adults of the relationship between SSRIs...
Clinical Point
If you decide to prescribe an SSRI for a depressed young adult, start with a low dose (such as fluoxetine, 10 mg/d) for several days.

SSRIs and suicide

3 studies found SSRIs may lower suicide risk in adults

<table>
<thead>
<tr>
<th>Study design</th>
<th>Main results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control forensic toxicology by Isacsson et al.</td>
<td>SSRIs less likely than other antidepressants to be detected in suicide victims</td>
<td>Naturalistic study Possible residual confounding</td>
</tr>
<tr>
<td>Observational study by Simon et al.</td>
<td>Suicide risk in acute-phase treatment ~1/3,000; risk of suicide attempt leading to hospitalization ~1/1,000 No increased risk of suicide or serious attempt suggested during first month of treatment No greater risk seen with newer drugs (mostly SSRIs) General decline in risk of suicide attempts after starting antidepressant treatment</td>
<td>Potential uncontrolled confounding Geographically limited sample Possible misclassification in computerized records Lack of data on medication adherence Death certificates may underestimate suicide rates</td>
</tr>
<tr>
<td>Observational study by Gibbons et al.</td>
<td>SSRI treatment associated with ~1/3 lower risk of suicide attempts compared with no antidepressant treatment Finding consistent in veterans age 18 to 25 and in older veterans</td>
<td>Sample of veterans, 92% male Dataset did not include suicides, so results pertain only to suicide attempts</td>
</tr>
</tbody>
</table>

SSRIs: selective serotonin reuptake inhibitors

Evidence of protection

Epidemiologic studies. Suicide attempt rates in depressed youth and adults—including those age <25—are highest in the month preceding treatment and decline steadily after antidepressant treatment or psychotherapy begins, according to depression studies in a large group health plan. The pattern was the same whether a primary care physician or psychiatrist prescribed the antidepressant.

Evidence from psychological autopsies—which attempt to reconstruct a decedent’s thoughts, feelings, and actions before death—indicates that:

- Approximately 60% of suicides occur in persons with a mood disorder.
- Since the advent of SSRIs, the rate of postmortem detection of antidepressants in suicides has increased from 8% to 15%, whereas the rate of suicide deaths caused by antidepressant overdose remains at approximately 5%.

Similarly, in 1 suicide study, no antidepressants were detected postmortem in >50% of persons for whom they had been prescribed. Systematic review finds substantial literature showing antidepressants’ efficacy for major depressive disorder.

Population studies in the United States and many other—but not all—countries report a correlation between increased antidepressant prescriptions and lower suicide rates. Because of their limitations, however, population studies cannot make a causal connection between antidepressant prescribing and suicide rates.
Randomized, controlled trials (RCTs) reduce sources of bias, but designing an RCT to test whether or not antidepressants prevent suicide is not feasible. Given suicide’s relative infrequency (~11 per 100,000 persons/year in the United States\textsuperscript{11}), an RCT would require a sample of many thousands.

Meta-analyses of data pooled from smaller trials—such as the FDA studies of antidepressants and suicidality\textsuperscript{2,13}—are done to gain statistical power from larger samples, but these also have methodologic limitations (Table 4). Proxy outcomes—such as suicide attempts and ideation in high-risk samples—also can be studied, as we are doing in our clinic (see Related Resources, page 43).

**CASE CONTINUED**

Hypomanic, or just in love?

Mr. B reports no medical problems and is taking no medications. He talked to a college counselor 3 times during his freshman year when he was upset after a romantic break-up, found it helpful, and says his feelings resolved. He reports trying marijuana and cocaine “a few times.” During his sophomore year he felt very happy and energized about a new relationship for approximately 1 week, but says he was sleeping normally and functioning well in school during that time.

He describes his father as very “serious” and sometimes pessimistic, but he does not know if his father ever had mental health treatment. On mental status exam, Mr. B is neat, cooperative, and looks worried. His speech is slightly labored and ruminative. His psychomotor state is normal. He has no psychotic symptoms, and his cognitive exam is normal. Because he is out of school, he has no health insurance.

**Clinical recommendations**

Case presentations such as Mr. B’s raise questions you must consider when prescribing SSRIs, particularly to young adults:

• Was his “energized” episode a mild hypomanic period or just normal feelings of “being in love”?  
• Is he minimizing substance use, which is a common comorbidity in depressed persons who die by suicide?  
• He has melancholic symptoms; does he have psychotic ruminations he is not sharing?  
• Without health insurance, how frequently will he be able to make follow-up appointments?

Prescribing any antidepressant for a specific patient is a complex, individualized decision based on weighing risks vs benefits. If you decide to prescribe an SSRI for Mr. B (who has never taken antidepressants), start with a low dose—such as fluoxetine, 10 mg/d, or sertraline, 25 mg/d—for several days. Because patients might not bring up suicidal thoughts or feelings, encourage openness and ask nonthreatening questions, such as, “Have you felt hopeless or had any thoughts that life isn’t worth it lately?” See Table 5, page 42\textsuperscript{14} for other prescribing recommendations.

continued
Suicide is the third leading cause of death in persons age 18 to 241 and a risk inherent in depression. Recent meta-analyses and large clinic population studies of adolescents and young adults suggest antidepressants—particularly SSRIs—show efficacy for depression and anxiety disorders12 and reduce the risk of suicide attempts.25

When deciding whether to prescribe an SSRI to an adult, weigh the small possible risk in patients age 18 to 24 against the risk of untreated depression. The increase in suicide rates in children and adolescents after antidepressant prescription rates dropped in 2004 is consistent with a net beneficial effect of antidepressants. As in all collaborative treatment discussions, provide patients with comprehensive information on depression treatment options so that they can make informed decisions.

References


Related Resources

Drug Brands Names
- Bupropion • Wellbutrin
- Citalopram • Celexa
- Duloxetine • Cymbalta
- Escitalopram • Lexapro
- Fluoxetine • Prozac
- Fluvoxamine • Luvox
- Mirtazapine • Remeron
- Neffazodone • Serzone
- Paroxetine • Paxil
- Sertraline • Zoloft
- Venlafaxine • Effexor

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