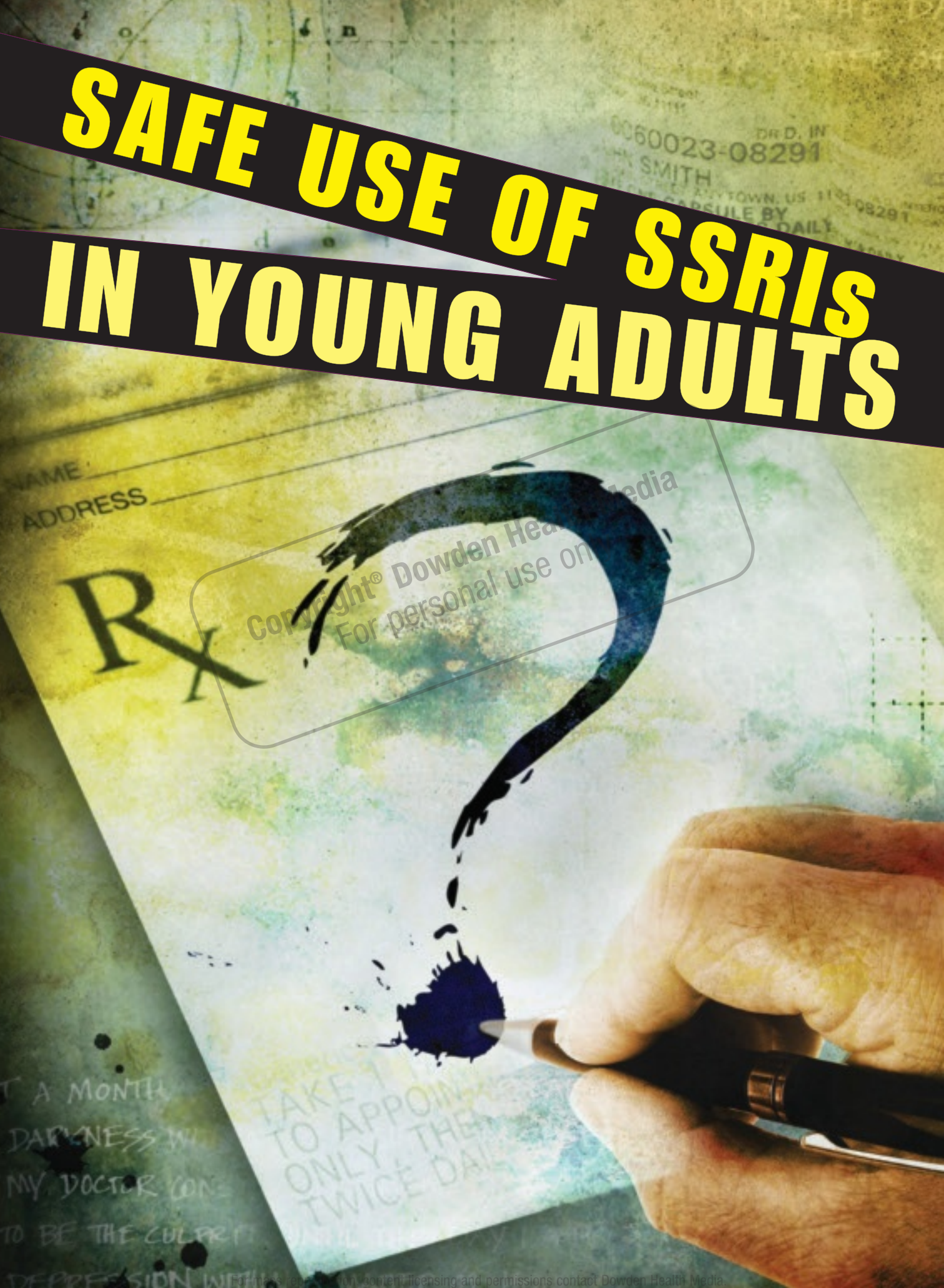
SAFE USE OF SSRIs IN YOUNG ADULTS



Current PSYCHIATRY

How strong is evidence for new suicide warning?

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

Michael F. Grunebaum, MD
Assistant professor of clinical psychiatry

J. John Mann, MD
The Paul Janssen Professor of Translational Neuroscience
Vice chair and director of research

. . . .

Department of psychiatry
Division of molecular imaging and neuropathology
College of Physicians and Surgeons
Columbia University/New York State Psychiatric Institute
New York

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

SSRIs and suicide

Clinical Point

In 2003 to 2004, after the 'black-box' warning, pediatric antidepressant prescriptions declined and suicide rates increased 11%

Box

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 aggression[4] 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.[8] 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.[11] In patients age >60, SSRI prescriptions continued to rise and suicide rates fell,[9] a pattern of change consistent with antidepressants protecting against suicide.

continued on page 35

continued from page 28

Table 1

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

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

Source: Reference 13

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 adults[13] 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)

Table 2

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

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

SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors
Source: Reference 13

Clinical Point

FDA's meta-analysis of suicide risk in adults found 8 suicides in 372 antidepressant trials totalling nearly 100,000 persons

continued

SSRIs and suicide

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

Study design	Main results	Limitations
Meta-analysis of FDA data by Khan et al;[16] >48,000 patients in trials that included fluoxetine, sertraline, paroxetine, citalopram	No difference in suicide rates among SSRIs, other antidepressants, or placebo	Patients not representative of general clinical population Trials mostly short-term; tended to exclude suicidal patients
Case-control study in UK primary care practice by Jick et al;[17] antidepressant users, 555 with suicidal behavior vs 2,062 without	Risk of suicidal ideation or behavior did not differ between SSRIs vs non-SSRIs	Observational study Confounding by indication*
Case-control study in UK primary care practice by Martinez et al;[18] >146,000 persons, first antidepressant prescription for depression	No evidence that risk of suicide or nonfatal self-harm was greater with SSRIs than with tricyclics	Observational study Confounding by indication*
Meta-analysis in UK by Gunnell et al;[19] 477 clinical trials (N>40,000) of SSRIs vs placebo in depression	No evidence that SSRIs increased suicide risk Weak evidence of increased self-harm risk	Lack of individual or trial-level data Evidence suggests nonfatal suicidal ideation/self-harm events are underreported

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***).[13]

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

Case reports suggest link between suicide and SSRI use

FDA analysis finds no association between SSRIs and increased suicide risk

1985 | 1990 | 1991 | 1999

Antidepressant prescriptions quadruple; age-adjusted suicide rate drops 22.5% for women and 12.8% for men

Table 3B

2 studies found SSRIs may increase suicide risk in adults

Study design	Main results	Limitations
Meta-analysis (1967 to 2003) by Fergusson et al;[20] 702 trials comparing SSRIs vs placebo or other drug for any condition (N>87,000)	Suicide attempts almost twice as likely with SSRIs vs placebo, but no difference in fatal attempts; no difference in risk between SSRIs and TCAs	Many methodologic limitations in clinical trials, such as underreporting of suicidal behavior Limited to public data
Case-control study of geriatric population in Ontario by Juurlink et al;[21] 1,138 suicides vs 4,552 controls matched for demographic characteristics and antecedent illness patterns	SSRIs were associated with higher risk of suicide than other antidepressants during first month of therapy (adjusted OR: 4.8, 95% CI=1.9–12.2) Risk independent of recent diagnosis of depression or receipt of psychiatric care Violent suicides more common with SSRIs than other antidepressants No difference in suicide risk after first month Absolute risk of suicide with antidepressants was low	Confounding by indication* 14% of suicide sample excluded from analysis

CI: confidence interval; OR: odds ratio; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants; 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.

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 antiarrhythmic treatment of atrial fibrillation (AF),[15] 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 analysis[7] but not with the more recent findings of Bridge et al[12] 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

continued on page 40

Clinical Point

Suicide attempt rates decline steadily after antidepressant or psychotherapy begins in depressed adults (including those age <25)

2003: UK agency warns of suicide-related events in children treated with paroxetine and venlafaxine
2004: FDA conducts meta-analysis, requires black-box warnings of risk of suicidality in youth taking antidepressants
2006: FDA meta-analysis finds age-dependent effect of antidepressants on suicidality risk in adults
2007: FDA expands warning of increased suicidality risk with antidepressants to adults age <25

Pediatric depression diagnoses and antidepressant prescriptions decline; suicides increase 11%

Bridge et al meta-analysis finds 25% lower rate of suicide-related events in youth than the FDA found

continued from page 37

SSRIs and suicide

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

Table 3C

3 studies found SSRIs may lower suicide risk in adults

Study design	Main results	Limitations
Case-control forensic toxicology by Isacsson et al;[22] 14,857 suicides compared with 26,422 deaths by accident or natural causes in Sweden (1992 to 2000)	SSRIs less likely than other antidepressants to be detected in suicide victims	Naturalistic study Possible residual confounding
Observational study by Simon et al;[23] 82,285 antidepressant treatment episodes among 65,103 health plan outpatients (1992 to 2003)	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	Potential uncontrolled confounding Geographically limited sample Possible misclassification in computerized records Lack of data on medication adherence Death certificates may underestimate suicide rates
Observational study by Gibbons et al[24] of suicide attempts in veterans treated for depression; 226,866 patients treated with SSRI, other antidepressant, or no antidepressant (2003 to 2004)	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	Sample of veterans, 92% male Dataset did not include suicides, so results pertain only to suicide attempts

SSRIs: selective serotonin reuptake inhibitors

and suicidal behavior (deaths or attempts):

- 4 found no relationship (***Table 3A, page 36***)[16-19]
- 2 found SSRIs may increase risk (***Table 3B, page 37***)[20-21]
- 3 found SSRIs may reduce risk (***Table 3C***).[22-24]

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.[25]

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.[26]
- 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%.[27]

Similarly, in 1 suicide study, no antidepressants were detected postmortem in >50% of persons for whom they had been prescribed.[28] Systematic review finds substantial literature showing antidepressants' efficacy for major depressive disorder.[29]

Population studies in the United States[30] and many other[31,32]—but not all[33]—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[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[7,13]—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***).

Table 4

SSRIs and suicidality: Limitations of the FDA's meta-analyses of pooled data

The pooled clinical trials were not designed to measure suicidality, so relevant data were not collected systematically
Suicidal patients who are most at risk tend to be excluded from industry-sponsored trials
Post hoc analyses of safety and effects on suicidality are subject to limitations of multiple testing and possible false-positives
The FDA "suicidality" outcome variable, which combined suicidal ideation and behavior, is subject to measurement bias. It was constructed after the trials were completed and relied on spontaneously reported adverse events (not systematic assessment). If subjects on active drug had more physical side effects, they might have had greater contact with their physicians and more opportunities to report suicidal ideation or behavior
The pooled trials were conducted over many years and study samples may have changed over time, with later studies enrolling more treatment-resistant subjects

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 breakup, 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***[34] for other prescribing recommendations.

continued

Clinical Point

Make weekly contact with the patient by phone or in person for the first few weeks after starting SSRI treatment

SSRIs and suicide

Clinical Point

When prescribing SSRIs, assess the patient regularly for suicidal thoughts, hopelessness, substance abuse, and impulsivity

Table 5

Clinical recommendations when starting young adults on antidepressant therapy

Start with a low dose (such as fluoxetine, 10 mg/d; sertraline, 25 mg/d; paroxetine, 5 mg/d; citalopram, 10 mg/d; or escitalopram, 5 mg/d) for several days
Schedule a follow-up appointment at the end of the initial consultation
Make weekly contact in person or by phone for the first weeks after starting an antidepressant
Don't prescribe large quantities of medication that could provide means for an overdose, but not so little that the patient is likely to run out
Don't provide refills early in treatment to encourage follow-up
Assess regularly for suicidal thoughts and common comorbidities such as hopelessness, substance abuse, and history of impulsive aggression
Document contacts with patient, risk/benefit discussions, information provided, and rationale for your assessment and plan
Consider augmenting pharmacotherapy with psychotherapy; evidence indicates combination treatment may be safer and more effective than either therapy alone[34]

Suicide is the third leading cause of death in persons age 18 to 24[11] 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 disorders[12] and reduce the risk of suicide attempts.[25]

When deciding whether to prescribe an SSRI to an adult, weigh the small possible elevated 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

1. Kuehn BM. FDA panel seeks to balance risks in warnings for antidepressants. *J Am Med Assoc* 2007;297:573-4.
2. Grunebaum MF, Ellis SP, Li S, et al. Antidepressants and suicide risk in the United States, 1985-1999. *J Clin Psychiatry* 2004;65(11):1456-62.
3. Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry* 1990;147:207-10.
4. King RA, Riddle MA, Chappell PB, et al. Emergence of self-destructive phenomena in children and adolescents during fluoxetine treatment. *J Am Acad Child Adolesc Psychiatry* 1991; 30(2):179-86.
5. Rothschild AJ, Locke CA. Reexposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. *J Clin Psychiatry* 1991;52:491-3.
6. Beasley CM, Dornseif BE, Bosomworth JC, et al. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *BMJ* 1991;303:685-92.
7. Hammad TA. Review and evaluation of clinical data. Food and Drug Administration. August 16, 2004. Available at: http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf. Accessed September 19, 2007.
8. Nemeroff CB, Kalali A, Keller MB, et al. Impact of publicity concerning pediatric suicidality data on physician practice patterns in the United States. *Arch Gen Psychiatry* 2007; 64(4):466-72.
9. Gibbons RD, Brown CH, Hur K, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry* 2007;164:1356-63.
10. Libby AM, Brent DA, Morrato EH, et al. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. *Am J Psychiatry* 2007;164(6):884-91.
11. U.S.Department of Health and Human Services. Centers for Disease Control and Prevention. Fatal injury reports. *Web-based injury statistics query and reporting system*. Available at: http://www.cdc.gov/NCIPC/wisqars. Accessed July 16, 2007.
12. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA* 2007;297:1683-96.
13. Levenson M, Holland C. Statistical evaluation of suicidality in adults treated with antidepressants. In: Laughren TP. Memorandum: overview for December 13 meeting of Psychopharmacologic Drugs Advisory Committee (PDAC). *Center for Drug Evaluation and Research, US Food and Drug Administration*. November 16, 2006. Available at: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-FDA.pdf. Accessed October 11, 2007.
14. Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. *Am J Psychiatry* 2000;157(12):1925-32.
15. Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, et al. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: a systematic review of randomized controlled trials. *Arch Intern Med* 2006; 166(7):719-28.
16. Khan A, Khan S, Kolts R, Brown WA. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. *Am J Psychiatry* 2003;160:790-2.
17. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *J Am Med Assoc* 2004;292(3):338-43.
18. Martinez C, Rietbrock S, Wise L, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. *BMJ* 2005;330(7488):389.

19. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. *BMJ* 2005;330(7488):385-9.
20. Fergusson D, Doucette S, Glass KC, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005; 330(7488):396.
21. Juurlink DN, Mamdani MM, Kopp A, Redelmeier DA. The risk of suicide with selective serotonin reuptake inhibitors in the elderly. *Am J Psychiatry* 2006;163(5):813-21.
22. Isacsson G, Holmgren P, Ahlner J. Selective serotonin reuptake inhibitor antidepressants and the risk of suicide: a controlled forensic database study of 14,857 suicides. *Acta Psychiatr Scand* 2005;111(4):286-90.
23. Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. *Am J Psychiatry* 2006; 163(1):41-7.
24. Gibbons RD, Brown CH, Hur K, et al. Relationship between antidepressants and suicide attempts: an analysis of the Veterans Health Administration data sets. *Am J Psychiatry* 2007;164(7):1044-9.
25. Simon GE, Savarino J. Suicide attempts among patients starting depression treatment with medications or psychotherapy. *Am J Psychiatry* 2007;164(7):1029-34.
26. Mann JJ, Apter A, Bertolote J, et al. Suicide prevention strategies: a systematic review. *JAMA* 2005;294(16):2064-74.
27. Rich CL, Isacsson G. Suicide and antidepressants in South Alabama: evidence for improved treatment of depression. *J Affect Disord* 1997;45:135-42.
28. Isacsson G, Bergman U, Rich CL. Antidepressants, depression and suicide: an analysis of the San Diego study. *J Affect Disord* 1994;32:277-86.
29. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet* 2003;361(9358):653-61.
30. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant medication use and rate of suicide. *Arch Gen Psychiatry* 2005;62(2):165-72.
31. Hall WD, Mant A, Mitchell PB, et al. Association between antidepressant prescribing and suicide in Australia, 1991-2000: trend analysis. *BMJ* 2003;326(7397):1008-11.

Related Resources

- Medicines and Health Care Products Regulatory Agency (UK). Committee on Safety of Medicines. Expert Working Group on Selective Serotonin Reuptake Inhibitors. Interim report, 2003. www.mhra.gov.uk.
- Mann JJ. A current perspective of suicide and attempted suicide. *Ann Intern Med* 2002;136(4):302-11.
- Paroxetine versus bupropion for treating people with high-risk major depressive disorder. Principal investigator: Michael F. Grunebaum, MD. National Institutes of Health. http://clinicaltrials.gov/show/NCT00429169.

Drug Brand Names

Bupropion • Wellbutrin
Citalopram • Celexa
Duloxetine • Cymbalta
Escitalopram • Lexapro
Fluoxetine • Prozac
Fluvoxamine • Luvox
Mirtazapine • Remeron
Nefazodone • Serzone
Paroxetine • Paxil
Sertraline • Zoloft
Venlafaxine • Effexor

Disclosures

Dr. Grunebaum reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Dr. Mann receives research support from GlaxoSmithKline and Novartis.

Acknowledgement

Dr. Grunebaum's research is supported by NARSAD (a not-for-profit mental health research association) and NIMH K23 MH076049; GlaxoSmithKline donated medication for his NIMH-funded clinical trial.

32. Nakagawa A, Grunebaum MF, Ellis SP, et al. Association of suicide and antidepressant prescription rates in Japan, 1999-2003. *J Clin Psychiatry* 2007;68(6):908-16.
33. Helgason T, Tomasson H, Zoega T. Antidepressants and public health in Iceland. Time series analysis of national data. *Br J Psychiatry* 2004;184:157-62.
34. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *JAMA* 2004; 292(7):807-20.

Clinical Point

To encourage patients to keep follow-up appointments, don't prescribe refills early in antidepressant treatment

Bottom Line

Suicide is mainly associated with depression. Monitor depressed patients when starting antidepressants, such as via weekly clinic or phone check-ins. Patients age 18 to 24 might be more at risk for behavioral adverse reactions to antidepressants than older adults. Further studies are needed, but these low risks appear to be far outweighed by the risk of untreated or undertreated depression.