

# Antidepressant Drug Therapy and Suicide in Severely Depressed Children and Adults

## A Case-Control Study

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**Context:** The Food and Drug Administration has issued a boxed warning concerning increased suicidal ideation and behavior associated with antidepressant drug treatment in children and adolescents. It is unknown whether antidepressant agents increase the risk of suicide death in children or adults.

**Objective:** To estimate the relative risk of suicide attempt and suicide death in severely depressed children and adults treated with antidepressant drugs vs those not treated with antidepressant drugs.

**Design:** Matched case-control study.

**Setting:** Outpatient treatment settings in the United States.

**Participants:** Medicaid beneficiaries from all 50 states who received inpatient treatment for depression, excluding patients treated for pregnancy, bipolar disorder, schizophrenia or other psychoses, mental retardation, dementia, or delirium. Controls were matched to cases for age, sex, race or ethnicity, state of residence, substance use disorder, recent suicide attempt, number of days since hospital discharge, and recent treatment with antipsy-

chotic, anxiolytic/hypnotic, mood stabilizer, and stimulant medications.

**Main Outcome Measures:** Suicide attempts and suicide deaths.

**Results:** In adults (aged 19-64 years), antidepressant drug treatment was not significantly associated with suicide attempts (odds ratio [OR], 1.10; 95% confidence interval [CI], 0.86-1.39 [521 cases and 2394 controls]) or suicide deaths (OR, 0.90; 95% CI, 0.52-1.55 [86 cases and 396 controls]). However, in children and adolescents (aged 6-18 years), antidepressant drug treatment was significantly associated with suicide attempts (OR, 1.52; 95% CI, 1.12-2.07 [263 cases and 1241 controls]) and suicide deaths (OR, 15.62; 95% CI, 1.65-infinity [8 cases and 39 controls]).

**Conclusions:** In these high-risk patients, antidepressant drug treatment does not seem to be related to suicide attempts and death in adults but might be related in children and adolescents. These findings support careful clinical monitoring during antidepressant drug treatment of severely depressed young people.

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**W**IDESPREAD PUBLIC and professional debate has surrounded the decision by the Food and Drug Administration (FDA) to direct manufacturers to include a boxed warning of increased suicidal behavior in children and adolescents treated with antidepressant agents.<sup>1,2</sup> The FDA's decision followed a meta-analysis<sup>3</sup> of placebo-controlled trials that revealed a significant overall increase in suicidal behavior or ideation in children and adolescents treated with newer antidepressant agents. No suicide deaths were reported in any of these trials.

Uncertainty exists about whether the use of antidepressant medications also increases the risk of suicide attempts in vulnerable adults.<sup>4</sup> This issue has been examined in 2 recent meta-analyses<sup>3,6</sup> of trials designed to

assess the efficacy of antidepressant agents for the treatment of depression and other psychiatric disorders and is currently under investigation by the FDA.<sup>7</sup> In 1 meta-analysis,<sup>5</sup> which relied on adverse events reported in published articles, treatment with selective serotonin reuptake inhibitors (SSRIs) was associated with a significantly greater risk of nonfatal suicide attempts than treatment with placebo (odds ratio [OR], 2.28; 95% confidence interval [CI], 1.14-4.55). There was no significant difference in the rate of suicide attempts between adults treated with SSRIs vs tricyclic antidepressant drugs (OR, 0.85; 95% CI, 0.51-1.43). The second review,<sup>6</sup> which included published and unpublished industry trials, found that SSRIs had a non-significant protective effect for suicidal thoughts (OR, 0.77; 95% CI, 0.37-1.55) but also posed a nearly significant risk of self-harm (OR, 1.57; 95% CI, 0.99-2.55).

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## STUDY COHORT

In the ongoing controversy surrounding antidepressant drug therapy and suicidality, suicide attempts have commonly served as a proxy for suicide deaths. Compared with attempted suicide, suicide death is far less common<sup>8</sup> and therefore far more difficult to study. At present, it is not known whether antidepressant drug treatment affects the risk of completed suicide in adults or children. Meta-analyses<sup>5,6,9</sup> of adult randomized controlled trials that included few suicides suggest similar suicide completion rates for patients treated with SSRIs, tricyclic antidepressant drugs, other antidepressant agents, or placebo. No large-scale experimental or observational studies, to our knowledge, have compared the suicide death rates of untreated vs treated adults or children.

Given the statistical limitations imposed by the low incidence of suicide deaths, ecologic studies have sought to examine associations between rates of antidepressant drug prescription and suicide. Several such studies suggest that increasing rates of antidepressant drug prescriptions to adults<sup>10-12</sup> and youths<sup>13,14</sup> have coincided with declining rates of adult and youth suicide, respectively. The results of these ecologic studies are consistent with those of epidemiologic studies that have established depression as an important risk factor for adult<sup>15,16</sup> and youth<sup>17,18</sup> suicide and clinical research that has demonstrated the efficacy of antidepressant medications in the treatment of adult<sup>19</sup> and adolescent<sup>20</sup> depression.

It is important to move beyond ecologic studies to examine longitudinal population-based data that include temporal relationships between antidepressant drug use and suicide attempts and death for individual patients. Post-mortem studies of serum antidepressant metabolites provide such an opportunity. These studies reveal that few suicide victims are receiving antidepressant agents,<sup>21,22</sup> especially SSRIs,<sup>23</sup> at the time of their death. Case-control studies might also offer insights into temporal associations between antidepressant drug treatment and risk of suicide. However, thus far, such studies have compared only the relative risk of suicide-related behaviors in patients treated with various antidepressant agents<sup>24-26</sup> rather than in patients who did or did not receive antidepressant treatment. To make informative comparisons between treated and untreated patients, it is necessary to assess cases and matched controls from a population that is relatively homogeneous with respect to clinical severity.

With this goal in mind, we designed a case-control study to compare the risk of suicide attempts and deaths after inpatient treatment for depression in children and adults who were treated with a range of antidepressant medications vs no antidepressant drug treatment. By limiting the analysis to patients after inpatient treatment of depression, we sought to ensure that cases (suicide attempt and suicide death) and controls (no suicide attempt and no suicide death) who did or did not receive antidepressant treatment had a high and comparable level of illness severity. Using administrative data drawn from the 50-state national Medicaid claims file, we assessed whether, compared with matched controls, suicide attempts and deaths were associated with treatment with various antidepressant medications or no antidepressant drug use.

Data were examined from the January 1, 1999, through December 31, 2000, national Medicaid Analytic Extract Files provided by the Center for Medicare and Medicaid Services. These files include detailed information on service claims, medications, demographic characteristics, and program eligibility for Medicaid beneficiaries in all 50 states. We first limited the sample to patients aged 6 to 64 years who had 1 or more hospitalizations for the treatment of a depressive disorder (*ICD-9* codes 296.2, 296.3, 300.4, and 311) during the study period. The study cohort was further limited by excluding patients who had at least 1 inpatient or 2 outpatient claims<sup>27</sup> for pregnancy (*ICD-9* codes 650-676), bipolar disorder (*ICD-9* codes 296.0, 296.1, and 296.4-296.8), schizophrenia (*ICD-9* code 295), other psychoses (*ICD-9* codes 297-299, excluding 298.0), mental retardation (*ICD-9* codes 317-319), or dementia/delirium (*ICD-9* codes 290-294). These patient groups were excluded, respectively, for the following reasons: antidepressant drug prescribing practices may be affected by clinical concerns about the safety of antidepressant drug use during pregnancy and breastfeeding,<sup>28,29</sup> antidepressant agents may induce mania and other high-risk-activated states in bipolar disorder,<sup>30</sup> uncertainty surrounds the efficacy of antidepressant medications in patients with schizophrenia and related disorders,<sup>31</sup> and concern exists about the accuracy of assessing depression in patients with pervasive cognitive deficits.<sup>32,33</sup> Because not all Medicaid beneficiaries are enrolled in plans that report outpatient prescription claims, we further limited the study cohort to beneficiaries who filled at least 1 prescription for any psychotropic or non-psychotropic medication during the entire 2-year study.

All the study procedures were approved by the institutional review boards of the New York State Psychiatric Institute and the Center for Medicare and Medicaid Services. Working files were stripped of personal identifiers. Passwords were used to protect data access.

## SELECTION OF SUICIDE ATTEMPT CASES AND CONTROLS

Cases were selected on the basis of a diagnostic claim for a suicide attempt (*ICD-9* codes E950-E959) that was preceded by psychiatric hospitalization for the treatment of depression. For each case, the date of this suicide attempt after the psychiatric hospitalization was defined as the event date. To reduce uncertainty introduced by the absence of inpatient prescription claims in Medicaid administrative data, cases were excluded if the patients had received inpatient treatment for 15 or more days during the 60 days preceding their event date. Twelve suicide deaths (8.6%) and 107 suicide attempts (10.5%) were excluded by this eligibility criterion. Cases and controls were also excluded if patients were ineligible for Medicaid benefits at any point during these 60 days.

For each patient defined as a case, up to 5 controls were matched by age ( $\pm 3$  years), sex, race or ethnicity (white, black, Hispanic, or other), state providing Medicaid services, and date of hospital discharge ( $\pm 30$  days). Cases were individually matched to controls, and cases were not eligible to serve as controls. Classification of race or ethnicity, which is related to risk of suicide attempt and completion,<sup>8</sup> was based on Medicaid designations. Controls were assigned an event date that was the same number of days after hospital discharge for the treatment of depression as the case to which they were matched. Controls were also matched to cases by the presence or absence of a claim for a substance use disorder (*ICD-9* codes 291,

292, and 303-305), recent suicide attempt (ICD-9 codes E950-E959), and use of an antipsychotic, stimulant, anxiolytic, or mood-stabilizing medication during the 60 days preceding their event date. A total of 784 cases with suicide attempts were matched to 3635 controls.

## SELECTION OF COMPLETED SUICIDE CASES AND CONTROLS

The procedures used to select cases and controls for the suicide attempt analyses were followed for the selection of suicide cases and controls, except that cases were selected for completed suicide. Date and cause of death were determined by matching Social Security number, date of birth, and sex from the Medicaid eligibility files to comparable death certificate data from the National Center for Health Statistics National Death Index.<sup>34</sup> Suicide was defined using an ICD-10 code of X60 to X84 as the primary cause of death. A total of 94 cases with completed suicide were matched to 435 controls.

## ANTIDEPRESSANT DRUG THERAPY

Antidepressant drug therapy was defined to include a prescription for an antidepressant medication in which the days supplied included or exceeded the event date. Cases and controls were first classified as having received no or any antidepressant drug therapy. The any-antidepressant-drug group was then subclassified as having received (1) any SSRI, including fluoxetine hydrochloride, paroxetine hydrochloride, sertraline hydrochloride, citalopram hydrobromide, and fluvoxamine maleate or (2) other antidepressant agents, including venlafaxine hydrochloride, mirtazapine, bupropion hydrochloride, trazodone hydrochloride, nefazodone hydrochloride, and tricyclic antidepressant agents. Tricyclic antidepressant agents included secondary and tertiary tricyclic antidepressants and the tetracyclic antidepressants amoxapine and maprotiline hydrochloride. No cases or controls were treated with monoamine oxidase inhibitors during the reference period.

## ANALYSIS

A case-control analysis was first performed with suicide attempt cases and their matched controls. The dependent or outcome variables were suicide attempt/nonsuicide and suicide death/nonsuicide, and the independent or predictor variable of interest was patient prescription of antidepressant medication. Cochran-Mantel-Haenszel  $\chi^2$  analyses were used to compare the strength of associations among cases and controls with respect to their antidepressant drug treatment. In these analyses, patients in each treatment group were compared with all other patients. The effect of each antidepressant drug treatment on the odds of suicide attempt was modeled using 3 conditional logistic regressions, with no antidepressant drug treatment as the reference group. Conditional logistic regression was used to accommodate the violation of independence created by matching. In these regressions, antidepressant drug treatment was the independent variable, and suicide attempt or completion was the dependent variable. The first regression compared any antidepressant drug treatment with no antidepressant drug treatment; the second regression compared SSRIs, venlafaxine, mirtazapine, bupropion, trazodone, nefazodone, and tricyclic antidepressant drug treatment with no antidepressant drug treatment; and the third regression compared treatment with each SSRI with no antidepressant drug treatment. The second and third regressions controlled for the presence of all other classes of antidepressant medications. In all of these models, patients treated with each antidepressant agent were

compared with patients receiving no antidepressant agents. Separate analyses were performed for children and adolescents 6 to 18 years of age, for adults 19 to 64 years of age, and within these age groups for males and females and for white and minority patients. The lower boundary of the age range was selected to correspond to the youngest patient in the antidepressant drug-controlled trials reviewed by the FDA,<sup>3</sup> and the upper boundary was selected because Medicare eligibility at age 65 years compromises the completeness of the claims records of older patients. Because of the small sample size of child suicide deaths, exact conditional regression was used in these analyses.<sup>35</sup> Statistical significance was set at  $\alpha=.05$  (2-tailed) for all the analyses.

## RESULTS

### BACKGROUND CHARACTERISTICS

Adult and child suicide cases were predominantly white, non-Hispanic males, and suicide attempt cases were predominantly white, non-Hispanic females. None of the suicide cases and 13 of the suicide-attempt cases (1.7%) were 12 years or younger. Approximately one quarter of the adult suicide-attempt cases and one tenth of the child and adolescent suicide-attempt cases received treatment for a substance use disorder during the 60 days before their attempt. Approximately one third of the adult suicide-attempt cases (38.8%) and a smaller proportion of the child and adolescent suicide-attempt cases (7.2%) received treatment with an anxiolytic or hypnotic medication during that period (**Table 1**).

During the 60 days preceding death, a substantial proportion of the adult suicide cases were treated with anxiolytic or hypnotic medications (52.3%), antipsychotic medications (23.3%), or mood stabilizers (17.4%), with fewer adult suicide cases receiving stimulants (1.2%). None of the child and adolescent suicide cases were treated with any of these medications during the 60 days before their death (Table 1).

In nearly two thirds of the cases (63.5%), suicide attempts or suicide deaths occurred in the first 4 months (120 days) after hospital discharge, and in nearly three quarters of these patients (74.4%), these events occurred in the first 6 months (180 days). Among patients treated with antidepressant agents, similar proportions of cases and controls for the suicide death analyses (58.0% vs 55.9%;  $\chi^2=0.1$ ;  $P=.78$ ) and for the suicide-attempt analyses (58.8% vs 56.3%;  $\chi^2=0.7$ ;  $P=.39$ ) received an antidepressant drug trial of at least 6 weeks' duration.

### SUICIDE ATTEMPTS

Children and adolescents treated with an antidepressant medication were significantly more likely to attempt suicide than those who were not treated with an antidepressant drug (OR, 1.52; 95% CI, 1.12-2.07) (**Table 2**). Children and adolescents who were treated with sertraline, venlafaxine, or tricyclic antidepressant drugs were significantly more likely to attempt suicide than those who were not treated with an antidepressant medication. In contrast, adults who were treated with an antidepressant medication were not significantly more likely to attempt suicide than adults who were not treated

**Table 1. Background Characteristics of Suicide Attempts and Completed Suicide in Depressed Medicaid Patients Aged 6 to 64 Years\***

	Suicide Attempts		Completed Suicide	
	Children and Adolescents (n = 263)	Adults (n = 521)	Children and Adolescents (n = 8)	Adults (n = 86)
Age, mean (SD), y	15.4 (1.8)	36.5 (9.4)	16.1 (1.5)	41.9 (10.0)
Male sex, %	25.5	26.1	62.5	59.3
White, non-Hispanic, %	73.9	88.4	62.5	96.3
Substance abuse, %	10.3	24.8	25.0	25.6
Recent suicide attempts, %	2.7	2.3	12.5	1.2
Psychotropic medications, %				
Antipsychotics	13.7	18.6	0	23.3
Mood stabilizers	12.9	13.0	0	17.4
Anxiolytic/hypnotics	7.2	38.8	0	52.3
Stimulants	3.8	2.1	0	1.2

\*Children and adolescents were aged 6 to 18 years and adults were aged 19 to 64 years. Controls were matched to cases for all the variables; therefore, the background characteristics of the controls are not given. The race or ethnicity variable is missing for 6 children or adolescent suicide attempts, 20 adult suicide attempts, and 5 completed adult suicides.

**Table 2. Association of Suicide Attempts With Antidepressant Drug Treatment in Depressed Medicaid Child and Adolescent Patients Aged 6 to 18 Years**

Treatment	Participants, %*		P Value†	Odds Ratio (95% CI)
	Cases (n = 263)	Controls (n = 1241)		
No antidepressant drugs	54.4	63.9	.007	1.00
Any antidepressant drug	45.6	36.1	.007	1.52 (1.12-2.07)
Any SSRI	29.7	25.5	.21	1.24 (0.86-1.79)
Fluoxetine hydrochloride	4.9	6.9	.16	0.69 (0.35-1.37)
Paroxetine hydrochloride	9.9	7.4	.27	1.36 (0.80-2.30)
Sertraline hydrochloride	12.9	7.7	.003	1.88 (1.15-3.06)
Citalopram hydrobromide	2.3	3.8	.21	0.68 (0.28-1.67)
Fluvoxamine maleate	0.4	0.3	.92	0.91 (0.09-8.93)
Other antidepressant drugs				
Tricyclic agents	4.2	1.4	.002	3.09 (1.32-7.22)
Venlafaxine hydrochloride	7.2	3.4	.007	2.33 (1.25-4.33)
Mirtazapine	3.8	2.1	.13	1.64 (0.68-3.94)
Bupropion hydrochloride	4.9	4.6	.97	1.07 (0.53-2.19)
Trazodone hydrochloride	4.9	4.0	.59	0.86 (0.35-2.42)
Nefazodone hydrochloride	2.3	1.1	.27	1.62 (0.58-4.53)

Abbreviations: CI, confidence interval; SSRI, selective serotonin reuptake inhibitor.

\*Controls are matched to cases for age, sex, race or ethnicity, state, substance use disorder, recent suicide attempt, and treatment with antipsychotic, anxiolytic/hypnotic, stimulant, and mood-stabilizing drugs.

†By Cochran-Mantel-Haenszel  $\chi^2$  test.

with an antidepressant drug (OR, 1.10; 95% CI, 0.86-1.39) (**Table 3**).

In analyses stratified by patient sex, male ( $P = .04$ ) and female ( $P = .05$ ) children and adolescents, but not adults, who were treated with antidepressant agents were significantly or nearly significantly more likely to attempt suicide than those who were not treated with antidepressant agents (**Table 4**). Among white children and adolescents (OR, 1.68; 95% CI, 1.17-2.40;  $P = .004$ ) but not minority children and adolescents (OR, 1.08; 95% CI, 0.57-2.02;  $P = .82$ ), antidepressant drug treatment was significantly associated with attempted suicide. Among white adults (OR, 1.15; 95% CI, 0.88-1.49;  $P = .30$ ) and minority adults (OR, 0.85; 95% CI, 0.40-1.85;  $P = .69$ ), there

was no significant association between antidepressant drug treatment and attempted suicide.

#### COMPLETED SUICIDE

Adults who were treated with an antidepressant medication were no more likely to complete suicide than adults who were not treated with an antidepressant agent (OR, 0.90; 95% CI, 0.52-1.55) (**Table 5**). Although adult suicide cases were significantly less likely to be treated with sertraline than matched controls (1.2% vs 7.6%;  $P = .03$ ), adults treated with sertraline were not significantly less likely to complete suicide than adults who did not receive an antidepressant drug (OR, 0.15; 95% CI, 0.02-1.16) (Table 5).

**Table 3. Association of Suicide Attempts With Antidepressant Drug Treatment in Depressed Medicaid Adult Patients Aged 19 to 64 Years**

Treatment	Participants, %*		P Value†	Odds Ratio (95% CI)
	Cases (n = 521)	Controls (n = 2394)		
No antidepressant drugs	53.2	55.9	.46	1.00
Any antidepressant drug	46.8	44.1	.46	1.10 (0.86-1.39)
Any SSRI	26.1	25.0	.72	0.94 (0.72-1.30)
Fluoxetine hydrochloride	7.5	7.6	.85	0.90 (0.59-1.36)
Paroxetine hydrochloride	8.2	7.1	.50	1.07 (0.71-1.60)
Sertraline hydrochloride	3.1	4.7	.09	0.61 (0.34-1.09)
Citalopram hydrobromide	6.5	5.4	.31	1.07 (0.68-1.70)
Fluvoxamine maleate	1.7	0.8	.02	2.03 (0.86-4.75)
Other antidepressant drugs				
Tricyclic agents	8.2	5.8	.10	1.10 (0.69-1.75)
Venlafaxine hydrochloride	9.4	7.1	.08	1.21 (0.81-1.82)
Mirtazapine	6.5	4.6	.09	1.18 (0.73-1.93)
Bupropion hydrochloride	5.6	4.5	.37	1.04 (0.63-1.74)
Trazodone hydrochloride	10.6	10.9	.63	0.65 (0.40-1.06)
Nefazodone hydrochloride	3.3	3.9	.40	0.73 (0.40-1.32)

Abbreviations: CI, confidence interval; SSRI, selective serotonin reuptake inhibitor.

\*Controls were matched to cases for age, sex, race or ethnicity, state, substance use disorder, recent suicide attempt, and treatment with antipsychotic, anxiolytic/hypnotic, stimulant, and mood-stabilizing drugs.

†By Cochran-Mantel-Haenszel  $\chi^2$  test.

**Table 4. Association of Suicide Attempts With Antidepressant Drug Treatment in Depressed Medicaid Adult Patients and Child and Adolescent Patients Stratified by Sex**

Group	Participants, %*		P Value†	Odds Ratio (95% CI)
	Cases	Control		
Children, 6-18 y				
Females	(n = 196)	(n = 929)		
No antidepressant drugs	44.4	36.4		1.00
Any antidepressant drug	55.6	63.6	.05	1.42 (1.00-2.02)
Males	(n = 67)	(n = 312)		
No antidepressant drugs	49.3	35.3		1.00
Any antidepressant drug	50.7	64.7	.04	1.86 (1.02-3.37)
Adults, 19-64 y				
Females	(n = 385)	(n = 1792)		
No antidepressant drugs	50.4	48.0		1.00
Any antidepressant drug	49.6	52.0	.66	1.10 (0.86-1.39)
Males	(n = 136)	(n = 602)		
No antidepressant drugs	36.8	32.4		1.00
Any antidepressant drug	63.2	67.6	.45	1.21 (0.74-1.98)

Abbreviation: CI, confidence interval.

\*Controls were matched to cases for age, sex, race or ethnicity, state, substance use disorder, recent suicide attempt, and treatment with antipsychotic, anxiolytic/hypnotic, stimulant, and mood-stabilizing drugs.

†By Cochran-Mantel-Haenszel  $\chi^2$  test.

Children and adolescents who were treated with an antidepressant drug were significantly more likely to complete suicide than children who were not treated with an antidepressant drug (OR, 15.62; 95% CI, 1.65-infinity) (Table 6). In addition, children and adolescent suicide cases were significantly more likely than matched controls to be treated with an SSRI (37.5% vs 7.7%;  $P = .005$ ). Children and adolescents who were treated with SSRIs were also more likely, although not significantly more likely, to complete suicide than children and adolescents who were not treated with an antidepressant agent (OR, 11.26; 95% CI, 0.97-infinity) (Table 6).

#### COMMENT

In children and adolescents, the risk of suicide attempts was 1.52 times higher after antidepressant drug treatment compared with no antidepressant drug treatment. This is consistent with the FDA meta-analysis<sup>3</sup> of pediatric randomized controlled trials of the newer antidepressant medications. In the present study, the comparable risk of suicide attempts for adults (OR, 1.10) was not statistically significant.

In line with results of meta-analyses<sup>5,6,9</sup> of randomized controlled trials, antidepressant drug treatment of

**Table 5. Association of Completed Suicide With Antidepressant Drug Treatment in Depressed Medicaid Adult Patients Aged 19 to 64 Years**

Treatment	Participants, %*		P Value†	Odds Ratio (95% CI)
	Cases (n = 86)	Control (n = 396)		
No antidepressant drugs	46.5	45.2	.70	1.00
Any antidepressant drug	53.5	54.8	.70	0.90 (0.52-1.55)
Any SSRI	29.1	30.0	.83	0.87 (0.44-1.73)
Fluoxetine hydrochloride	8.1	5.0	.27	1.36 (0.74-3.92)
Paroxetine hydrochloride	10.5	10.0	.93	0.93 (0.37-2.32)
Sertraline hydrochloride	1.2	7.6	.03	0.15 (0.02-1.16)
Citalopram hydrobromide	9.3	6.3	.28	1.40 (0.52-3.79)
Fluvoxamine maleate	0	1.0	.22	NA
Other antidepressants				
Tricyclics	11.6	9.9	.69	1.04 (0.42-2.61)
Venlafaxine hydrochloride	10.5	10.6	.89	0.85 (0.34-2.10)
Mirtazapine	12.8	7.8	.19	1.53 (0.57-4.09)
Bupropion hydrochloride	2.3	4.8	.24	0.35 (0.07-1.88)
Trazodone hydrochloride	8.1	9.3	.78	0.81 (0.26-2.50)
Nefazodone hydrochloride	2.3	4.6	.39	0.51 (0.11-2.43)

Abbreviations: CI, confidence interval; NA, not available; SSRI, selective serotonin reuptake inhibitor.

\*Controls were matched to cases for age, sex, race or ethnicity, state, substance use disorder, recent suicide attempt, and treatment with antipsychotic, anxiolytic/hypnotic, stimulant, and mood-stabilizing drugs.

†By Cochran-Mantel-Haenszel  $\chi^2$  test.

**Table 6. Summary of Associations of Suicide Attempts and Completion With Antidepressant Drug Treatment in Depressed Medicaid Patients**

Group	Participants, %*		P Value†	Odds Ratio (95% CI)
	Cases	Controls		
Adults, 19-64 y				
Suicide attempts	(n = 521)	(n = 2394)		
No antidepressant drugs	53.2	55.9		1.00
Any antidepressant drug	46.8	44.1	.46	1.10 (0.86-1.39)
SSRI	26.1	25.0	.72	0.97 (0.72-1.30)
Suicide completions	(n = 86)	(n = 396)		
No antidepressant drugs	46.5	45.2		1.00
Any antidepressant drug	53.5	54.8	.70	0.90 (0.52-1.55)
SSRI	29.1	30.0	.83	0.87 (0.44-1.73)
Children, 6-18 y				
Suicide attempts	(n = 263)	(n = 1241)		
No antidepressant drugs	54.4	63.9		1.00
Any antidepressant drug	45.6	36.1	.007	1.52 (1.12-2.07)
SSRI	29.7	25.5	.21	1.24 (0.86-1.79)
Suicide completions	(n = 8)	(n = 39)		
No antidepressant drugs	50.0	87.2		1.00
Any antidepressant drug	50.0	12.8	.002	15.62 ( $\geq 1.65$ )‡
SSRI	37.5	7.7	.005	11.26 ( $\geq 0.97$ )‡

Abbreviations: CI, confidence interval; SSRI, selective serotonin reuptake inhibitor.

\*Controls were matched to cases for age, sex, race or ethnicity, state, substance use disorder, recent suicide attempt, and treatment with antipsychotic, anxiolytic/hypnotic, stimulant, and mood-stabilizing drugs.

†By Cochran-Mantel-Haenszel  $\chi^2$  test.

‡Exact conditional logistic regression.

adults was not associated with suicide death. However, children and adolescents treated with antidepressant agents were significantly more likely to complete suicide. Because this finding is based on only 8 suicide deaths and we cannot exclude the possibility that more severely ill patients tended to be treated with antidepressant drugs, the association should be interpreted with cau-

tion. With these caveats in mind, the present findings are consistent with recommendations for careful clinical monitoring during the treatment of depressed children and adolescents with antidepressant medications. In practice, physicians face the difficult challenge of balancing safety concerns against evidence that depression is a key risk factor for adult<sup>15,16</sup> and adolescent<sup>17,18</sup> suicide and that

antidepressant agents are effective for adult<sup>19</sup> and adolescent<sup>20</sup> depression.

For depressed young people, the risk of suicide attempt varied across antidepressant medications. The serotonin/norepinephrine reuptake inhibitor venlafaxine, which had the highest risk of suicidality in the FDA analysis<sup>3</sup> of pediatric randomized controlled trials, was associated in the present study with 2.3 times the risk of suicide attempts compared with no antidepressant drug treatment. Tricyclic antidepressant drugs, but not SSRIs (other than sertraline), were also significantly associated with suicide attempts in young people. This finding contrasts with a recent British case-control study<sup>26</sup> of newly diagnosed depression. In that study,<sup>26</sup> self-harm among youths aged 10 to 18 years prescribed SSRIs was higher than among youths prescribed tricyclic antidepressants. The sources of this discrepancy are not clear but may include the presumably greater illness severity of patients in the present study. The basis of the variation between antidepressant drugs in suicide-attempt risk among young people is also unclear but might relate to antidepressant drug-specific differences in tolerability<sup>35</sup> or discontinuation syndromes.<sup>36</sup>

In adults, there was no significant association between antidepressant drug treatment overall and risk of suicide attempt and comparatively little variation in risk across different antidepressant agents. These findings agree with earlier case-control research<sup>24,26</sup> that revealed no significant difference in risks of self-harm among adults prescribed SSRIs compared with tricyclic antidepressant agents. Although there were fewer events, similar relationships were observed for suicide deaths in the present study.

Sertraline displayed a particularly complex risk profile. Alone among the SSRIs, it was associated with a statistically significant increased risk of suicide attempts in children and adolescents. However, it also demonstrated a trend toward a protective effect for adult suicide attempts. Sertraline had a relatively benign risk profile in the FDA analysis<sup>3</sup> of pediatric controlled trials and in the British case-control study<sup>26</sup> of newly diagnosed depression. Fluoxetine, another widely prescribed SSRI and the only antidepressant drug approved by the FDA for the treatment of pediatric depression, was not associated with suicide attempts or deaths in any analyses in the present study. A recent large controlled trial<sup>37</sup> reported that the effect of treatment with fluoxetine on reduction of suicidal ideation in depressed adolescents was similar to that of placebo, although there was a nonsignificant trend toward increased suicide-related events among fluoxetine-treated adolescents.

Fluvoxamine, which is not approved for the treatment of major depressive disorder, was significantly more commonly prescribed to adult suicide attempt cases than matched controls. Among deaths in which antidepressant agents were detected, 1 postmortem study<sup>23</sup> also reported that fluvoxamine was proportionately more commonly detected in suicides than in deaths of natural cause.

The present findings contrast with those of several ecologic studies.<sup>10-14</sup> For example, our group<sup>13</sup> previously reported that the regions of the United States that experienced the greatest increase in antidepressant drug prescription to young people between 1990 and 2000 tended

to be the same regions that enjoyed the greatest declines in youth suicide. The sources of this apparent discrepancy remain unclear. However, it is possible that the association between antidepressant drug use and suicide in youths in the present analyses is confined to a relatively narrow band of high-risk or clinically unstable young people after hospitalization for depression<sup>38</sup> and that in the general youth population, antidepressant drugs have a net protective effect on risk of suicide. It is also possible that confounding factors in these 2 observational analyses account for their apparently discrepant findings. In the ecologic study, for example, nonpharmacologic mental health services with similar geographic and temporal distributions to antidepressant drug treatment might account for the observed findings. In the case-control study, as described later in this article, unmeasured risk and protective factors might confound observed associations.

Several important limitations are inherent in the present case-control study. First, it is possible that antidepressant drugs are selectively prescribed to more severely depressed children and adolescents and that these more severely depressed youths are also at increased risk for suicidal behavior. We sought to minimize this important potential source of bias by limiting the analysis to a high-risk posthospital sample. In this sample, we also excluded patients with treated comorbid conditions that are known to affect risk of suicidality, such as bipolar disorder<sup>39</sup> and schizophrenia,<sup>40</sup> and we matched controls to cases with respect to pharmacological drug treatments, such as mood stabilizers and antipsychotic medications; substance use disorders<sup>41</sup>; recent suicide attempts<sup>42</sup>; and number of days since hospital discharge.<sup>43</sup> However, despite these manipulations, the possibility of confounding illness severity by antidepressant drug treatment selection persists. Second, no matching was performed on several important but unavailable factors related to suicide risk, such as family history of suicide,<sup>33</sup> imitation and contagion,<sup>44</sup> stressful precipitating events,<sup>45</sup> and access to lethal methods.<sup>46</sup> Third, although pharmacy claims measure psychotropic medication use with reasonable accuracy,<sup>47,48</sup> pill counts or electronic monitoring might have yielded more accurate information, especially for the short periods measured in this study. Some patients may take medications without generating a claim (eg, free samples or out-of-plan purchases), whereas others may take less than prescribed. It is also possible that antidepressant drug discontinuation syndromes related to medication nonadherence may have contributed to the observed associations. Fourth, the accuracy of the death category "suicide" has been questioned.<sup>49,50</sup> However, concern tends to focus on underreporting due to religious beliefs, social stigma, and other sources rather than on overreporting, which would pose a greater threat to this case-control design. Fifth, the study is limited to depressed Medicaid beneficiaries who likely differ from depressed privately insured patients in their pharmacologic treatment.<sup>51</sup> Sixth, the study included no adults older than 64 years; therefore, the results cannot be safely generalized to older adults, who differ from middle-aged adults in psychiatric suicide risk factors.<sup>30</sup> Finally, even among nonelderly individuals, the cases are only a small and highly selected sample of total suicide attempts and deaths. It is not known whether similar findings would be observed in a larger and more representative sample of depressed patients.

The present findings suggest that there may be an association between antidepressant drug treatment and suicide attempts and completed suicide in severely depressed children and adolescents in the Medicaid program after hospital discharge. This association is consistent with recommendations for close monitoring during this high-risk period.

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