A Case-Control Study of Antidepressants and Attempted Suicide During Early Phase Treatment of Major Depressive Episodes

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Objective: To estimate the relative risk of suicide attempts in child and adult outpatients initiating antidepressants for major depressive episodes compared to those not treated with antidepressants.

Method: A nested matched case-control study was performed with Medicaid administrative data (January 1, 1999–December 31, 2000) of outpatients treated for a major depressive episode. Beneficiaries initiating treatment for a major depressive episode were selected, excluding those who had recently received inpatient psychiatric treatment or outpatient treatment of pregnancy, major depressive episodes, bipolar disorder, schizophrenia or other psychoses, mental retardation, dementia, or delirium or recent treatment with a mood stabilizer, antidepressant, or antipsychotic. The outcome was treatment for a suicide attempt during the first 120 days after starting treatment for a major depressive episode. Controls were matched to cases on age, sex, race/ethnicity, recent treatment of substance use disorder, severity and type of major depressive episode, and other factors. Separate analyses were performed for adults (aged 19 to 64 years) and children (aged 6 to 18 years).

Results: Among children, antidepressant treatment was associated with a significant increase in suicide attempts (odds ratio [OR] = 2.08, 95% confidence interval [CI] = 1.06 to 4.10; cases, N = 51; controls, N = 239; p = .03). Among adults, antidepressant treatment was not significantly related to risk of suicide attempts (OR = 0.85, 95% CI = 0.57 to 1.28; cases, N = 185; controls, N = 893; p = .44), although among adult males, antidepressants were associated with a significant protective effect (OR = 0.32, 95% CI = 0.12 to 0.83; cases, N = 57; controls, N = 268; p = .01).

Conclusions: In these outpatients initiating treatment for a major depressive episode, antidepressant treatment appears to be associated with an increased risk of treated suicide attempts in children and a decreased risk in adult males.

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Major depression is prevalent in adults and youth.[1,2] During the course of 1 year, approximately 16.2% of adults,[1] 8.3% of adolescents,[2] and 2.5% of children[2] meet criteria for major depression. Depressed adults[3,4] and young people[5,6] are at substantially increased risk of attempting suicide, which in turn is a strong risk factor for suicide completion in both age groups.[7,8]

Concern has arisen that antidepressants, a mainstay treatment for depression, may paradoxically increase the risk of suicidal behavior in some cases. This possibility has been examined by combining results from randomized controlled clinical trials.[9–12] A pooled analysis of pediatric major depression trials revealed a significant association (risk ratio = 1.66, 95% CI = 1.02 to 2.68) between selective serotonin reuptake inhibitor (SSRI) treatment and development of suicidal ideation or attempts.[9] A meta-analysis that combined child and adult antidepressant randomized controlled trials reported that SSRI treatment compared with placebo significantly increased the risk of attempted suicide (OR = 2.70, 95% CI = 1.22 to 5.97).[10] In one meta-analysis of adult antidepressant trials, SSRIs posed a nonsignificantly increased risk of self-harm (OR = 1.25, 95% CI = 0.88 to 1.80).[11] Before entering these efficacy studies, study subjects are carefully screened for the presence and absence of several clinical characteristics selected to increase the likelihood that they will respond favorably to antidepressant medications.[13,14] In one study, only 14% of depressed outpatients attending a university psychiatric practice met common eligibility

TAKE-HOME POINTS

- For depressed male adults, antidepressant therapy is associated with a lower risk of suicide attempts during the early phase of treatment compared with no treatment.
- For depressed children and adolescents, antidepressant therapy is associated with a higher risk of suicide attempts during the early phase of treatment compared with no treatment.
- Close monitoring for warning signs of self-harm may be especially important for depressed young people starting antidepressant medications.

criteria for pharmacotherapy clinical trials.[13] Because antidepressant effects may be sensitive to sample composition,[15] concern has been expressed that results of such efficacy trials may not necessarily generalize to routine practice.[16]

A recent pooled analysis conducted by the U.S. Food and Drug Administration (FDA) of randomized controlled trials provides evidence that among youth and young adults, but not older adults, antidepressant treatment is associated with a significant increased risk of treatment-emergent suicidality.[12] In these analyses, antidepressant treatment was associated with an elevated risk of suicidal ideation or more serious suicidal behavior for patients under age 25 years with major depression (OR = 1.88, 95% CI = 1.25 to 2.84) and with a nonsignificantly decreased risk for adults with major depression (OR = 0.85, 95% CI = 0.67 to 1.07).[12] These results contributed to the recent decision by the FDA that all antidepressant medications carry an expanded black-box warning incorporating information regarding an increased risk of suicidal symptoms in young adults 18 to 24 years of age.[17]

The association between antidepressant treatment and attempted suicide has also been studied through observational designs.[18–22] Overall, this research suggests that antidepressants may slightly increase the risk of attempted suicide among depressed youth, but not depressed adults. A case-control study of severely depressed outpatients following inpatient treatment of depression reported that antidepressants were associated with an increased risk of suicide attempts for youth, though not adults.[20] In a cohort study of outpatient depressed adolescents, treatment with SSRIs was associated with a nonsignificant increase in the risk of medically injurious suicide attempts.[19] In a long-term cohort study, fluoxetine was related to a nonsignificant reduction in risk of suicide attempts among adults with major depressive disorder, schizoaffective disorder, mania, or hypomania.[18] Case-control studies comparing risk of suicide attempts among different antidepressants in primary care patients have found little evidence of differential effects in adults[21,22] and weak evidence that SSRIs as compared with tricyclics are associated with greater risk of suicide attempts in youth.[21] However, none of the previous observational studies have examined whether antidepressant treatment increases or decreases the risk of suicide attempts among youth and adults who are initiating treatment for depression.

We present a case-control study using data from all 50 states that compares the risk of medically injurious suicide attempts separately in children and adults during the first 4 months following initiation of outpatient community treatment for a major depressive episode with or without antidepressants. We sought to assess whether the risk of suicide attempts associated with initiation of antidepressant use differs between adults and children. To help insure that cases (suicide attempt) and controls (no suicide attempt) treated with or without antidepressants had a comparable level of pretreatment risk of attempting suicide, we matched controls to cases on major depressive episode type and severity and several other relevant characteristics. An analysis is also presented concerning associations between psychotherapy and attempted suicide.

METHOD

Study Cohort

Data were examined from the January 1, 1999 through December 31, 2000 national Medicaid Analytic eXtract Files (MAX) provided by the Centers for Medicare and Medicaid Services, Baltimore, Md. The data include detailed information concerning service claims, procedures, medications, demographic characteristics, and program eligibility for Medicaid beneficiaries in all 50 states. All study procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute and the Centers for Medicare and Medicaid Services.

We first limited the cohort to patients aged 6 to 64 years who had a first outpatient treatment claim for a major depressive episode (first listed ICD-9-CM: 296.2, 296.3, or 296.5) during the study period and were continuously eligible for Medicaid services for at least 90 days before and 120 days after this index claim. In order to focus the analysis on new treatment episodes of known depression severity, patients were excluded if the fifth digit of the index major depressive episode claim indicated partial (5) or full (6) remission, unspecified illness severity (0), or was absent. To further focus the analysis

on new treatment episodes, patients were also excluded if they had received electroconvulsive therapy (Current Procedural Terminology [CPT] code: 90870 or 90871); filled a prescription for an antidepressant medication, an antipsychotic medication, or a mood stabilizer; received any inpatient treatment for a mental disorder (first listed ICD-9-CM: 290–319); or received treatment for a suicide attempt (ICD-9-CM: E950–E959) during the 90-day period prior to the index diagnosis date.

We also excluded from the cohort patients who had at least 1 claim for pregnancy (ICD-9-CM: 650–676), schizophrenia (ICD-9-CM: 295) or other psychoses (ICD-9-CM: 297–299, excluding 298.0), mental retardation (ICD-9-CM: 317–319), or dementia/delirium (ICD-9-CM: 290–294) during the 90 days prior to index diagnosis date. These patient groups were excluded, respectively, because antidepressant prescribing practices may be affected by clinical concerns over the safety of antidepressants during pregnancy and breastfeeding[23,24]; uncertainty surrounds the efficacy of antidepressant medications in patients with schizophrenia and related disorders[25]; and concern exists over the accuracy of assessing depression in patients with pervasive cognitive deficits.[26,27] Because we sought to focus the analysis on *new* episodes of treatment for major depressive episodes occurring in the context of major depression, single episodes (ICD-9-CM 296.2); major depression, recurrent episodes (296.3); and bipolar disorder, currently depressed (296.5), we excluded from the cohort patients who had any claim for these conditions or any other mention of bipolar disorder (ICD-9-CM 296.0, 296.1, 296.4, 296.6–296.8) or depression (ICD-9-CM 298.0, 300.4, 309.1, 311) during the 90 days prior to the index diagnosis.

Selection of Suicide Attempt Cases and Controls

Among the study cohort, cases were selected on the basis of a diagnostic claim for a suicide attempt that occurred within the first 120 days following the index diagnosis claim. For each case, the date of this suicide attempt following the major depressive episode claim was defined as the event date.

For each patient defined as a case, up to 5 controls were selected matched by age (± 3 years), sex, and race/ethnicity (white, nonwhite). Classification of race/ethnicity, which is related to risk of suicide attempt,[28] was based on Medicaid designations. Controls were also matched to cases by the presence or absence of a claim for a substance use disorder (ICD-9-CM: 291, 292, 303–305), other depression-related disorders (ICD-9-CM: 298.0, 300.4, 309.1, 311), psychotherapy (CPT/Healthcare Common Procedure Coding System: 9804–90829, 90841–90847, 90849, 90853, 90855, 90857, 90875, 90876, G0071–G0094, H0510, H5020, H5025, H5030, X9500, X9502, X9504, X9506, X9508, X9510, X9512, Z0300), and major depressive episode type (major depression, single episode; major depression, recurrent; bipolar disorder, depressed) and severity as measured by the fifth ICD-9-CM/DSM-IV digit as mild (1), moderate (2), severe without psychotic features (3), and severe with psychotic features (4). Controls were individually matched to cases based on these criteria during the 90 days prior to the index diagnosis date and were assigned an event date that was the same number of days following their index diagnosis date as the event date of the case to which they were matched.

A total of 236 cases with suicide attempts were matched to 1132 controls.

Suicide Attempts

A medical claim with a first listed diagnosis of ICD-9-CM 950–959 defined a suicide attempt. These codes include all types of intentional self-injury.[28–30] For descriptive purposes, such suicide attempts were classified by major self-injury category into drug ingestion (E950), cutting (E956), and a residual group of all other types of intentional self-injury (other E950–E959).

Antidepressant Therapy and Psychotherapy

Antidepressant 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 antidepressant* or *any antidepressant*. The any antidepressant group was then subclassified as having received any SSRI including fluoxetine, paroxetine, sertraline, citalopram, escitalopram, or fluvoxamine or any other antidepressant. Equivalent dosing of antidepressant use was quantified with the Antidepressant Treatment History Form.[31] This scale rates the adequacy of antidepressant medication regimens on a 4-point scale from low (1) to high (4). Antidepressant treatment duration was dichotomously coded as < 30 days or ≥ 30 days of use during the 35 days prior to the event date.

Psychotherapy was defined as utilization of 1 or more psychotherapy visits during the 14 days up to and including the event date. Because we matched on psychotherapy during the period before the index diagnosis date, it would be inappropriate to compare cases and controls with respect to any psychotherapy use that occurred during this period. For example, a patient who attempted suicide 5 days after their index diagnosis date would be assessed for psychotherapy during a 14-day period that included 9 days of the matching period. For this reason, cases with suicide attempts within 14 days of the index diagnosis date were excluded from the psychotherapy analysis.[32] Several common mental health–related procedure codes, such as 90801 (psychiatric diagnostic interview examination) and 90862 (pharmacologic management with no more than minimal psychotherapy), were not included in the definition of psychotherapy.

Analysis

The selected adult and child suicide attempt cases were characterized with respect to matched variables including age, gender, race/ethnicity, and treatment of substance use disorder or depression-related disorder in the 90 days preceding the index diagnosis date as well as major depressive episode subtype and severity.

A case-control analysis was first performed with suicide attempt cases and their matched controls. The dependent or outcome variable was presence or absence of a suicide attempt, and the independent or predictor variable of interest was patient prescription of antidepressant medication. In some analyses, psychotherapy was the independent variable. Cochran-Mantel-Haenszel χ^2 analyses were first used to compare the strength of associations between cases and controls with respect to their specific antidepressant treatment. The effect of antidepressant treatment (independent variable) on the odds of suicide attempt (dependent variable) was modeled using conditional logistic regressions. Separate analyses were performed for children and adolescents, 6 to 18 years of age, and for adults, 19 to 64 years of age, and within these age groups for males and females and for 3 major depressive episode subtypes and 4 categories of clinical severity. The lower bound of the age range was selected corresponding to the youngest patient age in the antidepressant controlled trials reviewed by the FDA,[10] and the upper bound of patient age was selected because Medicare eligibility at age 65 compromises the completeness of the claims record of older patients. Alpha was set at .05 (2-tailed) for all analyses.

RESULTS

Background Characteristics

Adult and child suicide attempt cases were predominantly of white non-Hispanic ancestry and were predominantly females (Table 1). At their index diagnosis date, a majority of the adult and child suicide attempt cases were diagnosed with single or recurrent episodes of major depression and with moderate or severe without psychosis symptom severity. Considerably fewer suicide attempt cases were diagnosed with bipolar depression or with either mild or severe with psychosis symptom severity (Table 1). Most of the adult and child suicide attempt cases had not received psychotherapy, treatment for a substance use disorder, or treatment of a depression-related disorder during the 90 days prior to their index diagnosis date (Table 1).

For adult (78.9%) and child (72.6%) suicide attempt cases, most of the intentional injuries were drug ingestions. A smaller proportion of the adult (9.2%) and child (15.7%) attempts were cutting or other types of intentional self-injuries (adults: 11.9%, children: 11.7%) (data not shown). For adult and child cases, the most common setting in which the suicide attempts were treated was outpatient (adults: 52.4%, children: 47.1%), followed by inpatient (adults: 35.7%, children: 39.2%) and the emergency department (adults: 11.9%; children 13.7%).

Table 1. Background Matched Characteristics of Depressed Children and Adults With Suicide Attempts[a]

Characteristic	Children (N = 51)	Adults (N = 185)
Age, mean (SD), y	15.1 (1.4)	31.6 (10.1)
Female, sex, %	80.4	68.3
White, non-Hispanic, %	76.5	78.9
Major depressive episode, subtype, %		
Major depression, single episode	51.0	31.4
Major depression, recurrent	43.1	63.2
Bipolar disorder, depressed	5.9	5.4
Depression severity, %[b]		
Mild	7.8	4.3
Moderate	35.3	30.3
Severe without psychosis	39.2	49.2
Severe with psychosis	17.7	16.2
Recent treatment of substance use disorder, %[c]	5.9	23.8
Recent treatment of depression-related disorder, %[c]	27.4	18.9
Recent psychotherapy, %[c]	21.6	14.6

[a]Children and adolescents are aged 6 to 18 years, and adults are aged 19 to 64 years. Because controls were matched to cases on all variables, the background characteristics of the controls are not presented.
[b]On the basis of the fifth ICD-9-CM/DSM-IV digit of the index major depressive episode claim: mild (1), moderate (2), severe without psychotic features (3), and severe with psychotic features (4).
[c]Based on treatment of substance use disorders, depression-related disorders, and psychotherapy during the 90 days preceding index diagnosis date.

Treatment and Risk of Suicide Attempt

Children and adolescents treated with an antidepressant medication were significantly more likely to attempt suicide than those who were not treated with an antidepressant (Table 2). The strength of this association among children and adolescents, though not significant in subanalyses stratified by broad antidepressant class, was roughly similar for youth treated with SSRIs and other antidepressants. By contrast, there was not a significant association between antidepressant treatment and risk of suicide attempts among adults (Table 2). In the adult and child samples, recent provision of psychotherapy was not associated with risk of suicide attempts (Table 2). Among cases and controls prescribed antidepressants, there was not a significant association in the adult or child analyses between antidepressant dose or duration and risk of suicide attempt.

In analyses stratified by patient sex, male but not female adults who were treated with antidepressants were significantly less likely to attempt suicide than those who were not treated with antidepressants (Table 3). Among children, there was little evidence that the risk of suicide attempts associated with antidepressant treatment was related to patient gender.

The analyses stratified by major depressive episode subtype and severity revealed that antidepressant medica-

Table 2. Association of Suicide Attempts With Antidepressant Drug Treatment and Psychotherapy in Depressed Children and Adults by Antidepressant Drug[a]

Treatment Group	Cases (%)	Controls (%)	p Value[b]	OR (95% CI)
Adults (n_1 = 185, n_2 = 893)				
Psychotherapy or antidepressant	32.8	37.3	.32	0.81 (0.54 to 1.23)
Any antidepressant	21.1	23.6	.44	0.85 (0.57 to 1.28)
Any SSRI	12.4	15.4	.28	0.80 (0.47 to 1.38)
Other antidepressant	10.8	11.5	.81	1.00 (0.57 to 1.78)
Psychotherapy[c]	13.0	13.7	.82	0.94 (0.53 to 1.68)
Any antidepressant, dosage[d]			.42	
1	15.8	14.1		1.03 (0.14 to 7.78)
2	15.8	28.6		0.42 (0.09 to 2.04)
3	50.0	43.2		0.75 (0.19 to 2.94)
4	18.4	14.1		1.00 (Reference)
Antidepressant duration[d]				
≥ 30 d	60.0	48.7	.28	1.76 (0.62 to 4.96)
Children (n_1 = 51, n_2 = 239)				
Psychotherapy or antidepressant	48.6	36.8	.20	1.61 (0.77 to 3.34)
Any antidepressant	33.3	20.5	.03	2.08 (1.06 to 4.10)
Any SSRI	27.4	18.0	.10	1.91 (0.90 to 4.07)
Other antidepressant	9.8	5.0	.14	3.05 (0.74 to 12.54)
Psychotherapy[c]	25.7	22.1	.69	0.98 (0.40 to 2.41)
Any antidepressant, dosage[d]			.19	
1	6.3	6.3		0.79 (0.06 to 10.31)
2	6.3	25.0		0.78 (0.05 to 13.37)
3	81.1	52.0		10.67 (0.74 to 152.84)
4	6.3	16.7		1.00 (Reference)
Antidepressant duration[d]				
≥ 30 d	44.4	44.1	.52	0.71 (0.25 to 2.02)

[a]Controls matched to cases for age, sex, race/ethnicity, recent treatment of substance use disorder, recent treatment of depression-related disorder, major depressive episode subtype, symptom severity, and psychotherapy prior to index diagnosis date.
[b]Cochran-Mantel-Haenszel statistic.
[c]Any psychotherapy visit within 14 days of the event date. Sample sizes for psychotherapy analyses for adults (n_1 = 131, n_2 = 628) and children (n_1 = 35, n_2 = 163) are lower than for antidepressant analyses because cases and controls with event dates within 14 days of index diagnosis were removed for the analysis.
[d]Analysis limited to patients prescribed antidepressants; dosage ratings based on Antidepressant Treatment History Form[31] from low (1) to high (4); duration percentages represent proportion of patients receiving claims consistent with ≥ 30 days of antidepressant treatment during the 35 days immediately prior to event date.

Table 3. Association of Suicide Attempts With Antidepressant Drug Treatment in Depressed Children and Adults Stratified by Sex[a]

Treatment Group	Cases (%)	Controls (%)	p Value[b]	OR (95% CI)
Adults				
Female (n_1 = 128, n_2 = 625) any antidepressant	26.6	24.2	.48	1.18 (0.74 to 1.88)
Male (n_1 = 57, n_2 = 268) any antidepressant	8.8	22.4	.01	0.32 (0.12 to 0.83)
Children				
Female (n_1 = 41, n_2 = 194) any antidepressant	31.7	21.6	.13	1.81 (0.83 to 3.96)
Male (n_1 = 10, n_2 = 45) any antidepressant	40.0	15.6	.08	3.17 (0.83 to 12.05)

[a]Controls matched to cases for age, sex, race/ethnicity, recent treatment of substance use disorder, recent treatment of depression-related disorder, and major depressive episode subtype and symptom severity, and psychotherapy prior to index diagnosis date.
[b]Cochran-Mantel-Haenszel statistic.

tion treatment was significantly associated with suicide attempts among children with bipolar disorder, depressed subtype and with major depressive episodes of mild severity. However, these associations were based on small samples and therefore are considered unreliable (Table 4).

DISCUSSION

The current analysis focuses on the risk of suicide attempts following treatment initiation for a major depressive episode in the community. Among children and adolescents, antidepressant treatment appeared to exacerbate the risk of suicide attempts. There was no significant overall effect for adults. The direction and magnitude of these findings resemble results from pooled analyses of randomized controlled trials conducted by the FDA.[9,12] These results reinforce the clinical importance of closely monitoring young people for signs related to suicidal behavior during the early phase of antidepressant therapy for major depressive episodes.

Table 4. Association of Suicide Attempts With Antidepressant Drug Treatment in Depressed Adults and Children Stratified by Depression Type and Severity[a]

Treatment Group	Cases (%)	Controls (%)	p Value[b]	OR (95% CI)
Adults				
Major depression, single episode (n_1 = 58, n_2 = 281)				
Any antidepressant	19.0	25.6	.28	0.66 (0.31 to 1.41)
Major depression, recurrent (n_1 = 117, n_2 = 570)				
Any antidepressant	23.1	23.7	.84	0.95 (0.58 to 1.55)
Bipolar disorder, depressed (n_1 = 10, n_2 = 42)				
Any antidepressant	10.0	9.5	.93	0.90 (0.10 to 8.26)
Severity				
Mild (n_1 = 9, n_2 = 39)	22.2	33.3	.39	0.46 (0.07 to 2.82)
Moderate (n_1 = 55, n_2 = 271)	30.9	29.5	.82	1.08 (0.57 to 2.04)
Severe without psychosis (n_1 = 91, n_2 = 444)	15.4	21.0	.22	0.67 (0.36 to 1.28)
Severe with psychosis (n_1 = 30, n_2 = 139)	20.0	18.0	.79	1.16 (0.39 to 3.41)
Children				
Major depression, single episode (n_1 = 26, n_2 = 125)				
Any antidepressant	30.8	24.0	.45	1.44 (0.55 to 3.76)
Major depression, recurrent (n_1 = 22, n_2 = 103)				
Any antidepressant	31.8	18.4	.13	2.17 (0.78 to 6.10)
Bipolar disorder, depressed (n_1 = 3, n_2 = 11)				
Any antidepressant	66.7	0	.002	Undefined
Severity				
Mild (n_1 = 4, n_2 = 20)	75.0	15.0	.005	Undefined
Moderate (n_1 = 18, n_2 = 88)	33.3	22.7	.33	1.74 (0.56 to 5.35)
Severe without psychosis (n_1 = 20, n_2 = 86)	30.0	19.8	.22	1.99 (0.65 to 6.10)
Severe with psychosis (n_1 = 9, n_2 = 45)	22.2	20.0	.88	1.13 (0.21 to 6.02)

[a]Controls matched to cases for age, sex, race/ethnicity, recent treatment of substance use disorder, recent treatment of depression-related disorder, and major depressive episode subtype and symptom severity, and psychotherapy prior to index diagnosis date.
[b]Cochran-Mantel-Haenszel statistic.

A previous case-control study of severely depressed Medicaid patients discharged from the hospital[18] reported that antidepressant treatments exacerbated the risk of medically injurious suicide attempts among children and adolescents, but not adults. These results collectively support the hypothesis that antidepressants have age-dependent effects on the risk of suicidal behavior among depressed individuals. Psychopharmacologic mechanisms for this apparent age-related susceptibility to adverse and protective antidepressant effects remain unknown. One possibility is that there is an age-related risk of antidepressant activation of manic symptoms that in turn precipitates suicidal behavior in susceptible individuals. In one observational study of administrative claims, patient age modified the association between antidepressant treatment and manic conversion.[33] In that study, the adjusted rate of manic conversion was approximately twice as great for 10- to 14-year-old patients than for 15- to 29-year-old patients.[33]

In the current adult analyses, antidepressant treatment appeared to have a protective effect with respect to suicide attempts for males, but not females. In the FDA analysis, there was little difference between the risk of suicidal ideation or behavior among adult males (OR = 0.75, 95% CI = 0.53 to 1.04) and females (OR = 0.89, 95% CI = 0.70 to 1.13) in analyses that involved all psychiatric diagnoses.[12] The gender difference in antidepressant protective effects among depressed adults in the current analysis should be viewed with caution pending replication. The clinical basis for such a gender difference is unclear. Although there are gender differences in the activity of antidepressant-metabolizing enzymes, gender differences in clinical efficacy of antidepressants remain understudied.[34] In one general population survey, a history of major depression was more closely related to attempted suicide in men than women, suggesting that gender differences may exist in the determinants of suicide attempts.[3]

Suicidal behavior is common in bipolar disorder, especially during the depressed phase.[35,36] It has been hypothesized that patients with bipolar disorder are vulnerable to antidepressant-related suicidal behavior through antidepressant induction of rapid cycling, switching, or mania.[37] In the current analysis, we found no evidence to suggest that antidepressant treatment increased the risk of attempted suicide among adults with bipolar depression. In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, no association was reported between antidepressant exposure and new-onset suicidal ideation or behavior among adults with bipolar disorder.[38] In the current study, there was an insufficient number of bipolar depressed youth cases (N = 3) to draw meaningful inferences.

The current study provided little evidence that SSRIs and other antidepressants were differentially related to risk of attempted suicide. This observation is in line with

previous case-control research[21,39] and pooled analyses of clinical trial data.[9,12]

We found no significant association between a recent psychotherapy visit and risk of attempted suicide while controlling for the use of an antidepressant. However, the failure to find that psychotherapy visits as provided in community practice protect against suicide attempts should not be interpreted as diminishing the potential value of psychotherapy in the management of high-risk patients. In one controlled trial of adults with a recent suicide attempt, most of whom had major depression, a 10-session cognitive therapy intervention reduced the rate of repeat suicide attempts.[40]

The current study has several important limitations. First, antidepressants may be selectively prescribed and taken by more or less severely ill patients and such differences in illness severity may confound the observed associations. We sought to minimize this potential source of bias through rigorous selection of a diagnostically homogeneous cohort and careful matching of controls to cases. Previous research with administrative data suggests Medicaid patients who do and do not receive antidepressants for new episodes of major depression have comparable levels of psychosocial function.[32] Nevertheless, we cannot exclude the possibility that the pattern of results is attributable in part or in full to differential misclassification of the severity code by patient age and case/control status. Most Medicaid patients treated for major depressive episodes do not receive a fifth digit severity code rating, and the interrater reliability of these ratings in clinical practice remains unknown. Second, although pharmacy claims measure psychotropic medication utilization with reasonable accuracy,[41,42] inaccuracies may be present in the administrative database. Similarly, it was not possible to assess the adequacy of the psychotherapy treatment. Third, the accuracy of ICD-9-CM external-cause-of-injury codes (E-codes) used to determine treatment for a suicide attempt has been questioned.[43] However, because concern tends to focus on underreporting rather than overreporting of suicide attempts, such a bias would be minimized in a case-control design. Fourth, the study is limited to depressed Medicaid recipients 6 to 64 years of age who may differ from privately insured patients[44] and older adults[45] in several relevant respects. Fifth, because the study draws on claims data from 1999–2000, it does not include information on duloxetine. Finally, because of the power demands imposed by rigorous matching, our cases are a small and selected sample of total suicide attempts. It is not known whether similar findings would be observed in a more broadly representative sample.

Antidepressant treatment appears to increase the risk of medically injurious suicide attempts in children and adolescents, but not adults, during the first few months of treatment of new major depressive episodes. The results confirm and reinforce the importance of careful monitoring of these young people for warning signs of impending self-harm.

Drug names: citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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