Risk of Suicidal Behavior With Antidepressants in Bipolar and Unipolar Disorders

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ABSTRACT

Objective: To examine the risk of suicidal behavior (suicide attempts and deaths) associated with antidepressants in participants with bipolar I, bipolar II, and unipolar major depressive disorders.

Design: A 27-year longitudinal (1981–2008) observational study of mood disorders (Research Diagnostic Criteria diagnoses based on Schedule for Affective Disorders and Schizophrenia and review of medical records) was used to evaluate antidepressants and risk for suicidal behavior. Mixed-effects logistic regression models examined propensity for antidepressant exposure. Mixed-effects survival models that were matched on the propensity score examined exposure status as a risk factor for time until suicidal behavior.

Setting: Five US academic medical centers.

Results: Analyses of 206 participants with bipolar I disorder revealed 2,010 exposure intervals (980 exposed to antidepressants; 1,030 unexposed); 139 participants with bipolar II disorder had 1,407 exposure intervals (694 exposed; 713 unexposed); and 361 participants with unipolar depressive disorder had 2,745 exposure intervals (1,328 exposed; 1,417 unexposed). Propensity score analyses confirmed that more severely ill participants were more likely to initiate antidepressant treatment. In mixed-effects survival analyses, those with bipolar I disorder had a significant reduction in risk of suicidal behavior by 54% (HR = 0.46; 95% CI, 0.31–0.69; $t = -3.74$; $P < .001$) during periods of antidepressant exposure compared to propensity-matched unexposed intervals. Similarly, the risk was reduced by 35% (HR = 0.65; 95% CI, 0.43–0.99; $t = -2.01$; $P = .045$) in bipolar II disorder. By contrast, there was no evidence of an increased or decreased risk with antidepressant exposure in unipolar disorder.

Conclusions: Based on observational data adjusted for propensity to receive antidepressants, antidepressants may protect patients with bipolar disorders but not unipolar depressive disorder from suicidal behavior.

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Meta-analyses of randomized controlled trials (RCTs) of antidepressants conducted by the United States Food and Drug Administration (FDA) have shown a significantly elevated risk of suicidal ideation or suicide attempts in adolescents, a protective effect in the elderly, and no significant effects in intermediate age groups.[1] These results led the FDA to issue a boxed warning on antidepressant labeling that reads in part, "Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior."[2]

Antidepressants are often used to treat depressive syndromes, which frequently include suicidal thoughts. However, it is not clear from RCT data if these drugs impact suicidal behavior. Antidepressants were found to protect against suicidal behavior (attempts and deaths) in participants with mood disorders in the National Institute of Mental Health Collaborative Depression Study (CDS).[3] A letter to the editor, however, inquired whether the benefit seen in that study was comparable for unipolar and bipolar patients and speculated that the benefit was quite likely limited to unipolar major depression.[4,5] The present study thus sought to examine the impact of antidepressants on suicidal behavior separately in patients with unipolar major depressive disorder, bipolar I disorder, and bipolar II disorder. We hypothesized that there would be a reduced risk of suicidal behavior in unipolar disorder and an elevated risk in bipolar disorder. Prior analyses showed the prospective risk of suicidal behavior for these diagnoses to be similar, regardless of attempt severity.[6]

METHOD

Participants

From 1978 through 1981, the CDS recruited patients who were treated for mood disorders at 1 of 5 academic medical centers in the United States (Boston, Chicago, Iowa City, New York, and St Louis). At intake, participants were at least 17 years of age, white (genetic hypotheses were tested), and English speaking and provided written informed consent in each site's Institutional Review Board–approved protocol. Analyses included 206 participants with bipolar I disorder, 139 with bipolar II disorder, and 361 with unipolar disorder. To utilize the most accurate diagnosis, participants were assigned according to their prospectively determined diagnosis rather than diagnosis at study intake.[6–11]

Assessments

The Schedule for Affective Disorders and Schizophrenia (SADS)[12] and medical records were used to make diagnoses based on Research Diagnostic Criteria (RDC).[13] The Longitudinal Interval Follow-up Evaluation (LIFE),[14] a semistructured instrument, assessed level of psychopathology, duration and dose of somatic treatments, and functional impairment. It was administered semiannually for the first 5 years of follow-up and annually thereafter. The interrater reliability

Clinical Points

- Meta-analyses by the US Food and Drug Administration of clinical trial data showed antidepressants increase "suicidality" in children and adolescents although no suicide deaths were observed. A similar relationship was suggested in young adults, although in older adults antidepressants were protective.
- Our observational data shows a protective effect in adults, although this finding appears confined to bipolar disorder, wherein the potential benefit on clinical symptoms is controversial and not established.

for the LIFE was recovery from mood episodes (intraclass correlation coefficients [ICC] = 0.95), changes in symptoms (ICC = 0.92), and reappearance of symptoms (ICC = 0.88).[14]

Symptom severity was quantified using the Psychiatric Status Ratings (PSRs), which range from 1 (not present) to 6 (definite criteria, severe symptoms) for major depression and mania and from 1 (no symptoms) to 3 (definite criteria) for minor depression and hypomania. Raters assigned PSRs for each week since the prior interview by identifying salient time points (eg, birthdays and holidays) to facilitate participant recall of the timing of significant clinical deterioration or improvement.

Classification of Antidepressant Exposure

Participants were classified as either *exposed* to antidepressant medication or *unexposed* for each week of follow-up. Antidepressants that were examined included amitriptyline, amoxapine, bupropion, citalopram, clomipramine, selegiline, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine. Consistent with the FDA boxed warning, neither dose nor concomitant use of medications had bearing on classification of weekly exposure. The unit of analysis in this study was *antidepressant exposure interval*, defined as a period of consecutive weeks during which antidepressant exposure status classification remained constant. A change among antidepressants extended the duration of the existing interval. Antidepressant exposure intervals terminated in 1 of 3 ways: (1) suicide attempt or completed suicide, (2) change in antidepressant exposure status (from antidepressant present to absent or vice-versa), or (3) end of follow-up. The week following each suicide attempt was the start of a subsequent exposure interval. Many participants had numerous periods of antidepressant exposure and other unexposed periods during this 27-year follow-up study. The exposure intervals, which varied widely in duration, were examined in survival analyses of "time until suicidal behavior."

Classification of Outcome

Suicidal behavior was defined as a suicide attempt or death. The former was systematically screened as part of the LIFE using the SADS.[12] Participants were asked if they had "tried to kill yourself" or "done anything that could have killed you?" For this analysis, responses were classified as a suicide attempt regardless of the degree of suicidal intent or lethality. Participant reports were corroborated with available clinical records, and date, method, and medical severity of suicide attempts and deaths were recorded.

Data Analytic Procedures

Analyses were conducted separately for participants with bipolar I, bipolar II, and unipolar disorders. The primary objective was to compare the rate of suicidal behavior during antidepressant exposure intervals with rates during intervals that were not exposed to antidepressants. Two sets of longitudinal analyses were conducted: (1) a model of propensity for antidepressant exposure and (2) a treatment safety model for suicidal behavior. The antidepressant exposure interval (treated or untreated) was the unit of analysis in each stage. The longitudinal analyses accounted for within-participant variation in exposure status and propensity scores, multiple correlated exposure intervals within-participant, and the varying duration of exposure intervals.[15,16]

Preliminary Analyses: Propensity for Antidepressant Exposure

Randomized treatment assignment was not used in the CDS, which was an observational study. Self-selection and clinician decision determined treatment. Information regarding treatment was obtained from participants, their therapists, and medical records when available. Thus, exposure to antidepressants could be related to a variety of factors, such as severity of illness, which in turn influenced suicidal behavior. The course of illness in mood disorders varies considerably. Using treatment intervals as the unit of analysis, one can assess variables that determine the likelihood of treatment at that point in time. Thus, propensity score–based matching was implemented as an adjustment for comparisons of exposed and unexposed intervals.[17]

The propensity score was calculated using parameter estimates from a mixed-effects logistic regression analysis that examined the association of clinical and demographic characteristics with exposure to an antidepressant (the binary dependent variable). Each of the predictors was assessed prior to the exposure interval. Predictors of exposure were chosen based on earlier research[3,18] and availability of assessments at the beginning of the treatment interval. Predictors included gender, marital status, education level, socioeconomic status (SES), major depressive symptoms at intake (for the bipolar subjects only), age at start of the exposure interval, level of psychopathology (mean PSRs across the 8 weeks prior to the interval), trajectory of psychopathology during those 8 weeks (ie, whether the affective syndrome was worsening, stable, or improving based on PSRs), number of affective episodes prior to the exposure interval (1, 2, 3, 4, and 5 or more), use of lithium immediately before exposure interval, use of a second-generation antipsychotic immediately before

exposure interval, history of suicide attempt from study intake to the start of the interval, and study site. Anticonvulsant drugs were not considered because prior analyses of these data found no relationship between anticonvulsant usage and suicidal behavior.[18]

The propensity score represents the conditional probability of exposure to antidepressants, given the predictors of antidepressant treatment, ranging from 0 to 1. A score close to 0 denotes an exposure interval with demographic and clinical characteristics not associated with exposure, whereas a propensity score close to 1 represents an interval with features associated with exposure. To address correlated treatment intervals for the same individual, the model included a participant-specific intercept as a random effect. Each participant's propensity scores could vary during the course of follow-up because the algorithm included several time-varying variables. Propensity models were analyzed with the SuperMix software.[19] The propensity score included 2 predictors that characterized psychopathology in the 8 weeks prior to the exposure interval. All analyses excluded exposure intervals that were initiated during the first 8 weeks after study intake. Anxiety and psychosis were not assessed for each week of follow-up for all participants and were not included for determination of the propensity score. Analyses included all other exposure intervals during the 27 years of follow-up.

Propensity Score Matching

The propensity adjustment was implemented with matching. Full matching was used in that each matched set included at least 1 unexposed and 1 exposed interval, but the number of intervals classified as exposed and unexposed was not necessarily equal. An *optimal* matching procedure was used that minimized the sum of propensity score differences within matched sets.[20–22] The OptMatch package (Version 0.7–1)[23,24] for R (Version 2.12.2) implemented the matching. Our matching criterion required that propensity scores within a matched set differ by no more than a caliper of 0.40 propensity score standard deviation units. Sensitivity analyses compared safety results with a caliper of 0.10.

Primary Analyses: Safety Models

A mixed-effects grouped-time survival model with a complementary log-log function examined the number of weeks from the start of an antidepressant exposure interval until suicidal behavior.[25] Time-zero for treated periods represented the first week of any period of consecutive weeks receiving any antidepressant as previously defined and for untreated periods represented the first week of any period of consecutive weeks not receiving an antidepressant. Survival intervals that did not terminate with suicidal behavior ended either with a change in antidepressant exposure status or with the end of follow-up (and were classified as censored). Censoring was assumed to be unrelated to suicidal behavior. In the grouped-time models, time is categorized in ordinal groupings. The application of the propensity adjustment with repeated within-subject survival intervals, as we have here, has been shown to reduce bias with observational data.[15,16] Safety analyses included 2 crossed random effects (participant-specific intercept and matched-set intercept), exposure status as a binary fixed effect, and covariates, as described below. A 2-tailed α level of.05 was used for each statistical test described in this report.

RESULTS

Demographic and clinical characteristics of the participants are shown separately for those with bipolar I (N = 206), bipolar II (N = 139), and unipolar disorders (N = 361; Table 1). The study sample included primarily inpatients at study intake (bipolar I: 88.8%; bipolar II: 71.9%; unipolar: 76.7%), and a majority of each diagnostic group were women (bipolar I: 59.2%; bipolar II: 66.2%; unipolar: 62.6%). Although those with bipolar disorder tended to be somewhat younger at study intake (bipolar I: mean = 36.8 years, SD = 12.8; bipolar II: mean = 36.3 years, SD = 13.2; unipolar: mean = 40.2 years, SD = 15.0), a greater proportion of bipolar participants had already had at least 5 major depressive episodes (bipolar I: 32.5%; bipolar II: 28.1%; unipolar: 10.8%). The extracted Hamilton Depression Rating Scale scores[26] indicated severe depression at intake in all 3 diagnostic groups.

Propensity for Antidepressant Exposure

Analyses of the propensity for antidepressant exposure and the safety models involved 2,010 exposure intervals (980 exposed to antidepressants; 1,030 unexposed) from 206 participants with bipolar I disorder; 1,407 exposure intervals (694 exposed; 713 unexposed) from 139 participants with bipolar II disorder; and 2,745 intervals (1,328 exposed to antidepressants; 1,417 unexposed) from 361 participants with unipolar disorder. Among the findings in the diagnosis-specific propensity models (Table 2), the more severely symptomatic were significantly more likely to initiate exposure to an antidepressant. The between exposure group balance on the variables in the respective propensity models was examined after matching on propensity for exposure. Due to residual imbalance, the diagnosis-specific propensity score matched safety analyses included covariates: bipolar I (lithium and symptom severity); bipolar II (symptom severity); unipolar (lithium and trajectory of symptom severity).

Primary Safety Analyses

Bipolar I disorder. The unadjusted rate of suicidal behavior when bipolar I participants were exposed to antidepressants was about half that of when they were unexposed (6.8% vs 12.3%; Table 3). In unadjusted mixed-effects survival analysis, antidepressant exposure was associated with a 43% reduction in risk of suicidal behavior in those with bipolar I disorder (hazard ratio [HR] = 0.57; 95% CI, 0.41–0.78; $t = -3.47$; $P = .001$). In propensity score adjusted models, mixed-effects survival analyses indicated that for those with bipolar I disorder, the risk of suicidal behavior was reduced by 54% during periods of antidepressant exposure compared

Table 1. Demographic and Clinical Characteristics of Study Participants

	Bipolar I (N = 206)		Bipolar II (N = 139)		Unipolar (N = 361)	
Characteristic	N	%	N	%	N	%
Gender						
Women	122	59.2	92	66.2	226	62.6
Men	84	40.8	47	33.8	135	37.4
Marital status						
Never married	81	39.3	48	34.5	98	27.1
Married	77	37.4	58	41.7	187	51.8
Divorced/separated/widowed	48	23.3	33	23.7	76	21.1
Hollingshead SES[a]						
I	8	3.9	6	4.3	18	5.0
II	27	13.1	29	20.9	61	16.9
III	68	33.0	50	36.0	91	25.2
IV	55	26.7	36	25.9	116	32.1
V	48	23.3	18	12.9	75	20.8
Intake site						
New York	31	15.0	27	19.4	41	11.4
St Louis	43	20.9	28	20.1	117	32.4
Boston	31	15.0	26	18.7	55	15.2
Iowa City	52	25.2	27	19.4	90	24.9
Chicago	49	23.8	31	22.3	58	16.1
Intake status						
Inpatient	183	88.8	100	71.9	277	76.7
Outpatient	23	11.2	39	28.1	84	23.3
No. of major depressive episodes prior to intake						
0	36	17.5	30	21.6	129	35.7
1	35	17.0	28	20.1	93	25.8
2	34	16.5	17	12.2	51	14.1
3	17	8.3	15	10.8	31	8.6
4	17	8.3	10	7.2	18	5.0
5 or more	67	32.5	39	28.1	39	10.8
No. of manic episodes prior to intake[b]						
0	36	17.5	79	56.8	361	100.0
1	35	17.0	17	12.2		
2	34	16.5	11	7.9		
3 or more	101	49.0	32	23.1		

	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
Global Assessment Scale	31.9	31	11.3	36.4	35	8.9	38.2	39	10.5
Hamilton Depression Rating Scale-17-item (extracted)[c]	25.8	26	8.0	27.5	28	6.9	26.4	26	6.8
Age, y	36.8	35	12.8	36.3	33	13.2	40.2	37	15.0
Follow-up duration, y	19.0	22	9.6	17.3	20	8.2	15.5	18	8.8

[a]Socioeconomic status (SES) ranges from I (higher SES) to V (lower SES).
[b]Reflects the number of hypomanic episodes prior to intake for bipolar II patients.
[c]See Endicott et al.[26]

with unexposed intervals, controlling for the variables in the propensity model (HR = 0.46; 95% CI, 0.31–0.69; $t = -3.74$; $P < .001$). The sensitivity of these results to the matching caliper (ie, the maximum distance between exposure intervals within a matched set) was examined by altering the matching caliper from 0.40 to 0.10. Interpretation of results does not change (HR = 0.45; 95% CI, 0.30–0.66; $t = -3.98$; $P < .001$).

Bipolar II disorder. When bipolar II participants were exposed to antidepressants, the unadjusted rate of suicidal behavior was slightly lower than when unexposed (10.2% vs 10.9%; Table 3). In unadjusted mixed-effects survival analysis, antidepressant exposure was associated with a 28% reduction in risk of suicidal behavior in those with bipolar II disorder (HR = 0.72; 95% CI, 0.53–0.98; $t = -2.07$; $P = .04$). Propensity score matched mixed-effects survival analyses indicated that for those with bipolar II disorder, the risk of suicidal behavior was reduced by 35% during periods of antidepressant exposure relative to unexposed intervals (HR = 0.65; 95% CI, 0.43–0.99; $t = -2.01$; $P = .045$). Sensitivity of these results to the matching caliper was examined with a caliper of 0.10. Although the parameter estimate changes modestly, interpretation of results does change (HR = 0.72; 95% CI, 0.46–1.11; $t = -1.50$; $P = .133$).

Unipolar disorder. The unadjusted rate of suicidal behavior when unipolar depressive participants were exposed to antidepressants was slightly higher than when unexposed (11.4% vs 10.5%; Table 3), whereas the number of suicide deaths in the unexposed intervals was twice that of exposed (8 vs 4). Mixed-effects survival analyses indicate that for those with unipolar disorder, the risk of suicidal behavior was neither significantly elevated nor reduced during periods of antidepressant exposure (HR = 0.88; 95% CI, 0.64–1.22; $t = -0.76$; $P = .447$), controlling for variables in the propensity model. Sensitivity analyses show that the interpretation of results does not change by modifying the

Table 2. Diagnosis-Specific Propensity Model Results[a]

	Bipolar I Disorder (N = 206)				Bipolar II Disorder (N = 139)				Unipolar Disorder (N=361)			
	Odds Ratio	95% CI	*t*	*P*	Odds Ratio	95% CI	*t*	*P*	Odds Ratio	95% CI	*t*	*P*
Social class												
I	1.00				1.00				1.00			
II	0.74	0.36–1.52	−0.83	.41	0.82	0.51–1.33	−0.79	.430	1.10	0.62–1.94	0.32	.753
III	0.86	0.41–1.78	−0.41	.68	0.90	0.53–1.52	−0.39	.697	1.13	0.63–2.01	0.41	.682
IV	0.89	0.41–1.91	−0.31	.76	0.90	0.47–1.74	−0.31	.759	1.15	0.62–2.15	0.45	.654
V	0.82	0.39–1.73	−0.52	.61	1.24	0.64–2.38	0.64	.520	1.27	0.69–2.32	0.77	.439
Education												
< High school	1.00				1.00				1.00			
High school	0.98	0.72–1.33	−0.15	.88	1.18	0.71–1.95	0.63	.528	1.26	0.97–1.63	1.73	.084
Some college	0.91	0.65–1.25	−0.60	.55	1.08	0.67–1.76	0.32	.746	1.10	0.82–1.46	0.63	.528
College graduate	0.90	0.62–1.33	−0.52	.60	1.18	0.67–2.07	0.58	.560	1.09	0.79–1.50	0.51	.607
Marital status												
Married	1.00				1.00				1.00			
Never married	1.13	0.87–1.47	0.93	.35	0.94	0.69–1.27	−0.42	.673	1.11	0.91–1.37	1.03	.304
Divorced/widowed/separated	1.04	0.81–1.33	0.28	.78	0.97	0.69–1.36	−0.20	.844	0.94	0.76–1.18	−0.50	.618
Study site												
New York	1.00				1.00				1.00			
St. Louis	0.94	0.67–1.31	−0.39	.69	1.13	0.77–1.66	0.63	.53	0.94	0.71–1.25	−0.41	.680
Boston	0.88	0.60–1.29	−0.66	.51	1.22	0.84–1.78	1.04	.30	0.71	0.52–0.98	−2.05	.040
Iowa	1.01	0.72–1.42	0.07	.95	0.97	0.67–1.40	−0.16	.87	0.94	0.71–1.25	−0.42	.677
Chicago	0.99	0.72–1.36	−0.06	.95	1.01	0.70–1.44	0.03	.97	1.07	0.78–1.46	0.41	.683
Gender												
Female	1.00				1.00							
Male	0.91	0.73–1.13	−0.86	.39	1.07	0.82–1.41	0.49	. 62	0.93	0.77–1.11	−0.83	.406
No. of prior episodes of depression												
0	1.00				1.00				1.00			
1	1.03	0.48–2.23	0.07	.94	1.11	0.54–2.28	0.28	.78	1.18	0.80–1.74	0.81	.418
2	0.82	0.45–1.49	−0.65	.51	1.37	0.69–2.71	0.91	.36	1.19	0.79–1.78	0.83	.409
3	0.88	0.45–1.71	−0.38	.70	1.79	0.86–3.75	1.56	.12	1.15	0.76–1.74	0.68	.498
4	0.84	0.45–1.59	−0.52	.60	0.99	0.49–2.00	−0.02	.99	1.42	0.95–2.13	1.72	.086
5	0.92	0.54–1.57	−0.31	.76	1.47	0.82–2.64	1.29	.20	1.42	0.98–2.05	1.87	.062
Suicide attempt prior to interval	0.71	0.58–0.88	−3.21	.00	0.95	0.75–1.22	−0.38	.71	1.06	0.89–1.27	0.67	.502
Age at start of interval												
< 30	1.00				1.00				1.00			
30–39	1.19	0.85–1.67	1.02	.31	1.06	0.74–1.53	0.34	.73	1.21	0.92–1.58	1.38	.167
40–49	1.35	0.95–1.91	1.70	.09	1.07	0.73–1.56	0.33	.74	1.28	0.96–1.69	1.71	.087
50–59	1.35	0.92–1.99	1.51	.13	1.06	0.67–1.66	0.24	.81	1.42	1.02–1.99	2.07	.038
60+	1.29	0.83–1.99	1.14	.26	0.91	0.56–1.48	−0.38	.70	1.33	0.97–1.82	1.77	.076
Symptom trajectory												
Stable	1.00				1.00				1.00			
Worsening	4.26	2.35–7.72	4.78	.00	6.27	2.89–13.61	4.65	.00	9.99	5.36–18.63	7.24	.000
Improving	0.66	0.29–1.52	−0.97	.33	0.30	0.09–0.95	−2.05	.04	0.32	0.13–0.75	−2.62	.009
Symptom severity	1.19	1.10–1.30	4.25	.00	1.24	1.13–1.37	4.42	.00	1.24	1.16–1.32	6.63	.000
Lithium	0.75	0.61–0.91	−2.91	.00	0.82	0.61–1.12	−1.24	.21	0.57	0.39–0.82	−3.00	.003
Second-generation antipsychotic	2.01	1.06–3.81	2.13	.03	n/a							
Major depression at intake	0.97	0.79–1.19	−0.32	.75	n/a							
Trajectory by severity interaction												
Severity by improving	0.73	0.62–0.86	−3.77	.00	0.68	0.55–0.84	−3.55	.00	0.64	0.54–0.76	−5.23	.000
Severity by worsening	1.09	0.87–1.35	0.75	.45	1.25	0.92–1.69	1.44	.15	1.23	0.99–1.54	1.84	.065
Lithium by second-generation antipsychotic interation	0.46	0.17–1.25	−1.52	.13	n/a							

[a]Comparison group for single dichotomous variables represents intervals without that feature. As an example, for the variable "suicide attempt prior to interval," the comparison group is intervals with no prior suicide attempt.
Abbreviation: CI = confidence interval.

matching caliper to 0.10 (HR = 0.88; 95% CI, 0.64–1.21; $t = -0.78$; $P = .438$).

DISCUSSION

This study's objective was to determine if the benefit of antidepressants for prevention of suicidal behavior that was observed in the CDS would differentiate in separate analyses of those with unipolar and bipolar disorders. Contrary to our hypothesis, we found a significant protective antidepressant effect in bipolar I and II disorders, but no significant effect in unipolar depressive disorder. The results from this longitudinal observational study underscore the need to examine moderators of treatment benefits and risks to better understand what treatment is appropriate for whom.[27,28] In the absence of a better understanding of such moderators, it remains unclear whether and how to use antidepressants in bipolar disorder. This point is similarly underscored in the recent Consensus Statement from the International Society for Bipolar Disorder Task Force that concluded "the use of antidepressants to treat depressive phases or components of bipolar disorder can neither be condemned nor endorsed without carefully evaluating individual clinical cases and

Table 3. Suicidal Behavior by Antidepressant Exposure Status

Antidepressant Exposure Status	Number of Antidepressant Exposure Intervals (%)	Suicidal Behavior, No. of Events	Unadjusted Rate/Interval	Propensity Score Adjusted Hazard Ratio[a]	95% CI	*t*	*P*
Bipolar I disorder							
Not exposed	1,030 (51.2%)	127[b]	12.3%	1.00			
Exposed	980 (48.8%)	67[c]	6.8%	0.46	0.31–0.69	−3.74	< .001
Bipolar II disorder							
Not exposed	713 (50.7%)	78[d]	10.9%	1.00			
Exposed	694 (49.3%)	71[e]	10.2%	0.65	0.43–0.99	−2.01	.045
Unipolar disorder							
Not exposed	1,417 (51.6%)	149[f]	10.5%	1.00			
Exposed	1,328 (48.4%)	152[g]	11.4%	0.88	0.64–1.22	−0.76	.447

[a]Adjusted results are matched on the propensity score.
[b]123 suicide attempts; 4 suicide deaths.
[c]63 suicide attempts; 4 suicide deaths.
[d]75 suicide attempts; 3 suicide deaths.
[e]70 suicide attempts; 1 suicide deaths.
[f]141 suicide attempts; 8 suicide deaths.
[g]148 suicide attempts; 4 suicide deaths.
Abbreviation: CI = confidence interval.

circumstances."[29(p1257)] While our study cannot weigh in on the effectiveness of antidepressants for bipolar depression, our findings should temper concerns related to risk of treatment-associated suicidal behavior.

Some clinicians and researchers maintain that antidepressant use for bipolar disorder can trigger a switch from depression to mania,[30,31] yet the results of research on this risk have been equivocal.[32–36] Here we did not see adverse effects of antidepressants on suicidal behavior in bipolar disorder. Most, if not all, of the short-term antidepressant trials that comprised the FDA meta-analyses related to suicidal behavior excluded bipolar disorder.[1] Unlike the FDA study, the analyses reported here were focused exclusively on suicidal behavior and did not include ideation. Strengths of our study include the ability to focus on suicidal behavior itself as an outcome, rather than suicidal ideation as a surrogate for risk of suicidal behavior, the frequency at which this outcome was observed, and the use of a clinically representative sample. The FDA meta-analysis included 8 suicides and 134 suicide attempts.[37] The analysis reported herein includes 20 suicides and 472 suicide attempts. The FDA meta-analysis also found a protective effect of antidepressants on suicide in older adults (age ≥ 65 years) and our analysis includes many treatment intervals involving middle and older adults. In summary, the apparent protective effect we observed could reflect the longer duration of follow-up relative to short-term clinical trials, the inclusion of an adult sample (recruited at a median age in the mid-30s and followed for up to over a quarter century), the focus upon suicidal behavior as an exclusive outcome, and the inclusion of persons with bipolar disorder, wherein the protective effect was observed.

Our failure to identify a protective effect of antidepressants on suicidal behavior in those with major depression is in contrast to several studies. As an example, one observational study found a protective effect of antidepressants against suicidality in a large cohort of depressed veterans,[38] as did meta-analyses of randomized controlled trials of fluoxetine and venlafaxine.[39] Similarly, the risk of suicide attempts was higher in the month before antidepressant medication initiation and declined after initiation among patients in a large health plan.[40,41] It is unclear if either study included bipolar depression. One relevant report did use a bipolar cohort and reached conclusions contrary to those described here.[42] A comparison between that analysis and the current study highlights a methodological point of particular importance to observational studies of treatment effects. Yerevanian et al[42] found that patients had higher rates of suicidal behavior when they were receiving antidepressants, but did not correct for the fact that individuals receive antidepressants when they are depressed, or more severely depressed. Our propensity analyses targeted such confounding.

Limitations of our study involve the observational nature of treatment assignment. Participants were not randomized to treatment; therefore, a propensity adjustment was used to account for imbalance between exposed and unexposed intervals. However, the propensity adjustment removes bias related only to variables included in the model and there may be residual confounding from variables related to clinical status or treatments not included, such as anticonvulsants or sedatives.[43,44] Several variables of clinical interest, such as anxiety and psychosis, could not be captured on all participants at the beginning of treatment interval. The assessments for severity of mood symptoms and treatments received were carried out annually and semiannually and have the potential for recall bias. All clinical raters were carefully trained, certified for the assessment procedures, and the evaluations were monitored on an ongoing basis throughout the study.[45] Antidepressant dose did not play a role in classification of exposure. This was done to replicate the approach used in the FDA meta-analyses,[1] which didn't investigate a dose-response relationship. Also akin to the FDA paradigm, our analyses did not separately examine each of the antidepressants, and we would have been underpowered to assess any specific medication by group interactions. We, in fact, could not assess the interaction between diagnosis and antidepressant exposure, due to the need for diagnosis-specific propensity scores and subsequent separate analyses. Thus, our findings suggest but do not demonstrate moderation by diagnosis. While lithium use was captured in our propensity score, concurrent lithium

treatment could still result in residual confounding if lithium exposure was not present at onset of the treatment interval. Similarly, prior suicide attempts were associated with a lower likelihood of antidepressant use in bipolar I disorder. While our diagnosis-specific propensity scores are a notable strength of the analysis, residual confounding could persist following propensity adjustment. Our comparator involved no exposure to antidepressants, which, unlike placebo, does not capture the expectation of a therapeutic intervention.[46] Information regarding the lack of antidepressant treatment during the comparator periods was obtained from the participants, their providers, and medical records when available. The majority of our participants were recruited as inpatients, which may lead to some selection bias for higher acuity of illness, although our sample most likely generalizes better to clinical practice than much of the clinical trial literature. Follow-up extended beyond initial hospitalization for these participants, and individuals with bipolar disorder are commonly hospitalized at some point over their course of illness.[47] There is also the potential for sampling bias associated with the selection of participants with bipolar disorder over long-term follow-up.

In conclusion, contrary to our hypotheses, we found significant protective antidepressant effects for suicidal behavior in bipolar I and II disorders, wherein the potential benefit on clinical symptoms is controversial and not established,[48] but no significant effect in unipolar disorder. Future study is warranted to confirm these findings and to identify if specific classes of antidepressants may have protective effects. Nevertheless, clinicians must closely monitor patients for clinical worsening when administering somatic antidepressant treatment.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Silenor, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), isocarboxazid (Marplan), lithium (Lithobid and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), protriptyline (Vivactil and others), selegiline (Eldepryl and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), trazodone (Oleptro and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

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Author contributions: All authors had full access to all the data in the study. Dr Solomon takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study participants: The Collaborative Depression Study has been conducted with current participation of the following investigators: M. B. Keller, MD (Chairperson, Providence), W. Coryell (Co-Chairperson, Iowa City); D. A. Solomon, MD (Providence); W. A. Scheftner, MD (Chicago); W. Coryell, MD (Iowa City); J. Endicott, PhD; A. C. Leon, PhD†; J. Loth, MSW (New York); J. Rice, PhD (St Louis). Other current contributors include: H. S. Akiskal, MD; J. Fawcett, MD; L. L. Judd, MD; and J. D. Maser, PhD. The Collaborative Program was initiated in 1975 to investigate nosologic, genetic, family, prognostic, and psychosocial issues of Mood Disorders and is an ongoing, long-term multidisciplinary investigation of the course of Mood and related affective disorders. The original Principal and Co-Principal investigators were from 5 academic centers and included Gerald Klerman, MD† (Co-Chairperson); Martin Keller, MD; Robert Shapiro, MD† (Massachusetts General Hospital, Harvard Medical School); Eli Robins, MD†; Paula Clayton, MD; Theodore Reich, MD†; Amos Wellner, MD† (Washington University Medical School); Jean Endicott, PhD; Robert Spitzer, MD (Columbia University); Nancy Andreasen, MD, PhD; William Coryell, MD; George Winokur, MD† (University of Iowa); and Jan Fawcett, MD, and William Scheftner, MD (Rush-Presbyterian-St. Luke's Medical Center). The NIMH Clinical Research Branch was an active collaborator in the origin and development of the Collaborative Program with Martin M. Katz, PhD, Branch Chief as the Co-Chairperson and Robert Hirschfeld, MD, as the Program Coordinator. Other past contributors include: J. Croughan, MD; P. W. Lavori, PhD; M. T. Shea, PhD; T. I. Mueller, MD; R. Gibbons, PhD; M. A. Young, PhD; and D. C. Clark, PhD.

Potential conflicts of interest: **Dr Solomon** serves as Deputy Editor of Psychiatry at UpToDate.com. **Dr Endicott** has received research support from New York State Department of Mental Health and Cyberonics. She has served as a consultant or advisory board member to Amgen, AstraZeneca, Bayer Health Care, CHID Foundation, and NY University. **Dr Keller** receives grant or research support from Pfizer. **Dr Leon**† was on the Safety Data Monitoring Boards of Pfizer, AstraZeneca, Merck, and Sunovian. He was a consultant for the US Food and Drug Administration, National Institute of Mental Health, and MedAvante. **Drs Fiedorowicz, Coryell,** and **Fawcett** and **Mr Li** have no conflicts of interests to disclose.

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†Deceased.

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