Antidepressants and Risks of Suicide and Suicide Attempts: A 27-Year Observational Study

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Objective: The 2007 revision of the black box warning for suicidality with antidepressants states that patients of all ages who initiate antidepressants should be monitored for clinical worsening or suicidality. The objective of this study was to examine the association of antidepressants with suicide attempts and with suicide deaths.

Method: A longitudinal, observational study of mood disorders with prospective assessments for up to 27 years was conducted at 5 US academic medical centers. The study sample included 757 participants who enrolled from 1979 to 1981 during an episode of mania, depression, or schizoaffective disorder, each based on Research Diagnostic Criteria. Unlike randomized controlled clinical trials of antidepressants, the analyses included participants with psychiatric and other medical comorbidity and those receiving acute or maintenance therapy, polypharmacy, or no psychopharmacologic treatment at all. Over follow-up, these participants had 6,716 time periods that were classified as either exposed to an antidepressant or not exposed. Propensity score–adjusted mixed-effects survival analyses were used to examine risk of suicide attempt or suicide, the primary outcome.

Results: The propensity model showed that antidepressant therapy was significantly more likely when participants' symptom severity was greater (odds ratio [OR] = 1.16; 95% CI, 1.12–1.21; $z = 8.22$; $P < .001$) or when it was worsening (OR = 1.69; 95% CI, 1.50–1.89; $z = 9.02$; $P < .001$). Quintile-stratified, propensity-adjusted safety analyses using mixed-effects grouped-time survival models indicate that the risk of suicide attempts or suicides was reduced by 20% among participants taking antidepressants (hazard ratio, 0.80; 95% CI, 0.68–0.95; $z = -2.54$; $P = .011$).

Conclusions: This longitudinal study of a broadly generalizable cohort found that, although those with more severe affective syndromes were more likely to initiate treatment, antidepressants were associated with a significant reduction in the risk of suicidal behavior. Nonetheless, we believe that clinicians must closely monitor patients when an antidepressant is initiated.

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On December 13, 2006, the Psychopharmacologic Drugs Advisory Committee of the US Food and Drug Administration (FDA) considered the risk of suicidality among adults who took antidepressants by reviewing results of 372 industry-sponsored randomized controlled clinical trials with 99,839 participants for a range of indications.[1] The FDA conducted its own meta-analyses that focused on the 77,382 adults from 295 randomized controlled clinical trials that evaluated treatments for major depressive disorder (MDD) and other psychiatric disorders.[1] The primary outcome in the meta-analyses was *suicidality*, defined as suicidal ideation, preparatory acts, attempts, or completions, and the trials evaluated the 11 antidepressants approved by the FDA since 1985. About 70% of the suicidality was suicidal thoughts, but there were 8 suicide deaths in the adult trials (5 in participants randomized to the investigational agent, 1 to an active comparator, and 2 to placebo). The meta-analyses showed a significant protective effect of antidepressants for ages ≥ 65 years and a marginal, yet nonsignificant, elevation in risk of suicidality for ages 18–25 years. The FDA briefing document[1] displayed these results superimposed on their earlier meta-analyses, which showed a significantly elevated risk of suicidality for children and adolescents randomized to antidepressants. Overall, the document portrayed decreasing antidepressant protection against and increasing risk of suicidality for younger patients.

On the basis of these analyses, the FDA issued a revised black box warning for all antidepressants on May 2, 2007, extending the coverage of the 2004 warning that applied to children and adolescents to include patients under 25 years of age.[2] The warning label[3] currently reads, "[A]ntidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders." It further warns that "[d]epression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide." Moreover, the warning is not entirely age-specific in that it says, "[P]atients 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."

One limitation of the data that the FDA analyzed is that those results do not generalize to most patients treated with antidepressants. The data primarily came from clinical trials lasting 4 to 8 weeks involving participants in episodes of major depression and other psychiatric disorders. However, a vast majority of patients with major depression, for

Clinical Points

- Patients with more severe affective syndromes were more likely to receive antidepressants.
- Antidepressants were associated with a significant reduction in the risk of suicide and suicide attempts.
- Clinicians must, however, closely monitor patients when an antidepressant is initiated.

example, are excluded from clinical trials.[4,5] This occurs because the inclusion criteria of those trials had thresholds for illness severity and exclusion criteria that usually excluded patients who were recently or currently suicidal or psychotic. In addition, the trials usually excluded patients with medical or psychiatric comorbidity or those taking concomitant medications. Therefore, the results of the FDA meta-analyses do not necessarily apply to patients with suicidality, psychosis, comorbid illnesses, or those receiving maintenance therapy or polypharmacy.

The objective of this article is to examine the risk of suicide attempts or suicide deaths associated with antidepressants in a broader range of participants that are more representative of the population of patients treated with antidepressants. Our goal was to focus exclusively on the FDA warning about antidepressant risk, not to examine the wide range of variables with hypothesized relationships to suicidality. The data come from the NIMH Collaborative Program on the Psychobiology of Depression—Clinical Studies (Collaborative Depression Study [CDS]), which began collecting prospective follow-up data in 1978.[6] The study provides a unique opportunity to examine risk of suicidality with antidepressants due to the combination of methodological strengths of the study, including direct participant interviews, standardized diagnostic and follow-up instruments, frequent follow-up assessments, and up to 27 years of prospective follow-up. We include all study participants whether in a mood disorder episode or in recovery. We hypothesized that, on the basis of the FDA findings, there would be an elevation in suicide attempts and suicide deaths among participants who received an antidepressant compared with those who did not.

METHOD

Participants

The CDS recruited patients from 1978 through 1981 who were treated for depressive disorders, bipolar disorder, or schizoaffective disorder at 1 of 5 academic medical centers in the United States (Boston, Massachusetts; Chicago, Illinois; Iowa City, Iowa; New York, New York; and St Louis, Missouri).[6] At intake, all participants were English speaking, at least 17 years of age, white (genetic hypotheses were tested), and all provided written informed consent. The study protocol was approved by the institutional review board at each site. The analyses described below involved 757 participants.

Classification of Antidepressant Exposure

For each week of follow-up, participants were classified into 1 of 2 categories depending on whether or not they received antidepressant medication for that particular week. The antidepressants examined include amitriptyline, amoxapine, bupropion, citalopram, clomipramine, deprenyl, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine. Dose had no bearing on classification of weekly exposure nor did the use of other medications. The unit of analysis in this study was *antidepressant exposure interval*, defined as a period of consecutive weeks during which antidepressant exposure classification remained unchanged. This unit of analysis differs from most studies in which the unit is the participant per se. A switch from one antidepressant to another did not initiate a new exposure interval but instead extended the length of the current interval. Exposure intervals varied in duration and represented the data examined in survival analyses of time until suicidal behavior. Each antidepressant exposure interval terminated in 1 of 3 ways: (1) a suicide attempt or suicide death, (2) a change in antidepressant exposure status, or (3) end of follow-up. A new exposure interval began in the week following each suicide attempt. During this 27-year follow-up study, most participants had several periods during which antidepressant medication treatment was used and other periods in which no such treatment was used.

Assessments

The Schedule for Affective Disorders and Schizophrenia[7] was used for diagnostic assessment based on Research Diagnostic Criteria.[8] The Longitudinal Interval Follow-up Evaluation (LIFE)[9] is a semistructured instrument that was administered, semiannually for the first 5 years of follow-up and annually thereafter, by trained, well-supervised raters. The LIFE was used to assess level of psychopathology, functional impairment, and dose and duration of somatic treatment. Raters received rigorous training before they were certified to conduct interviews. As a result, interrater reliability for the LIFE is excellent, with intraclass correlation coefficients (ICCs) for rating changes in symptoms (ICC = 0.92), recovery from mood episodes (ICC = 0.95), and reappearance of symptoms (ICC = 0.88).[9]

Information regarding antidepressants was collected during LIFE interviews. The severity of symptoms of major affective disorders was recorded in the LIFE with Psychiatric Status Ratings, which range from 1 (not present) to 6 (definite criteria, severe symptoms) and on a scale of 1 (no symptoms) to 3 (definite criteria) for minor depression and hypomania. The rater assigned Psychiatric Status Ratings values for each week that had elapsed since the prior interview. To do so, the rater identified chronological anchor points (eg, holidays) to

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assist the participant in recalling when significant clinical improvement or deterioration took place. Information on suicide attempts and deaths, including the date, method, and medical severity, was systematically recorded. Raters also wrote a narrative description after each interview. Clinical records and informants were used for corroboration when available.

Data Analytic Procedures

Analyses compared the rates of suicide attempts and suicide deaths (hereafter referred to as "suicidal behavior") during periods in which participants took an antidepressant with the rates during periods in which no antidepressant was taken. These analyses were conducted in 2 stages (described in detail below): (1) a model of propensity for antidepressant exposure and (2) a model of treatment safety, which focused exclusively on suicidal behavior. The unit of analysis in both the propensity and safety models was the antidepressant exposure interval (as defined above). The longitudinal approach to data analyses accounted for the multiple correlated exposure intervals within participant and the variability in the duration of treatment, and it allowed for within-participant variation in exposure status and propensity scores over time.[10,11]

Propensity for antidepressant exposure. The data come from an observational study in which clinician decision and self-selection played a key role in determining treatment assignment. Randomized treatment assignment was not used, and, therefore, it is quite possible that antidepressants were initiated for the more symptomatic participants. In such cases, comparison of suicidality in the exposed and unexposed intervals would be influenced by pretreatment confounding variables unless an appropriate adjustment was implemented. For that reason, the propensity score, which represents the conditional probability of exposure to antidepressants, was used as an adjustment for comparisons of exposure intervals.[12] The propensity for antidepressant exposure model involved mixed-effects logistic regression analyses that examined the association of clinical and demographic characteristics with receiving antidepressant treatment, the binary dependent variable. On the basis of our earlier work,[13] independent variables included those hypothesized to be associated with receiving treatment: gender, marital status, socioeconomic status, education level, study site, presence of major depressive symptoms at intake, age at start of the exposure interval, number of affective episodes prior to the exposure interval (1, 2, 3, 4, and 5 or more), suicide attempt from study intake to the start of the interval, level of psychopathology (mean Psychiatric Status Ratings in the 8 weeks prior to the interval), and trajectory of psychopathology in those 8 weeks (ie, whether the affective syndrome was worsening, stable, or improving based on Psychiatric Status Ratings severity). A participant-specific intercept was included as a random effect, which accounted for differences between the overall sample probability of exposure and that of each participant. A linear combination of these variables, called the propensity score, was derived based on logistic model parameter estimates. The propensity score represents the probability of antidepressant exposure, ranging from 0 to 1. A propensity score close to 1 represents an interval with characteristics associated with antidepressant exposure, whereas a score close to 0 denotes an exposure interval with features not associated with exposure. Each participant's propensity score could vary during the course of follow-up because the scoring algorithm included several time-varying variables; yet the propensity score for each exposure interval was based on variables assessed prior to that interval. The analyses did not include antidepressant exposure intervals that commenced in the first 8 weeks after study intake because the propensity score included 2 predictors of antidepressant exposure that reflected psychopathology in the 8 weeks prior to each treatment change. All other exposure intervals over 27 years of follow-up were included in the analyses.

Primary analyses: safety models. Safety analyses examined the number of weeks from the start of an antidepressant exposure interval until suicidal behavior using a mixed-effects, grouped-time survival model with a complementary log-log function.[14] Survival time represented "time until suicidal behavior" during which consecutive weeks of treatment remained at the initial status, either receiving or not receiving an antidepressant. A new survival interval (ie, antidepressant exposure interval) commenced with each change in treatment exposure status. In addition, a new exposure interval began immediately after each suicide attempt to correspond with the new period of risk. In this way, each participant accumulated intervals over time. Survival intervals that terminated either with a change in antidepressant exposure status or due to the end of follow-up were classified as censored. Censoring due to end of follow-up was assumed to be unrelated to suicidal behavior. The longitudinal application of the propensity adjustment with repeated survival data has been shown to reduce bias in the estimate of the treatment effect with observational data.[11]

The safety analyses included 1 fixed effect, binary treatment, and 1 random effect, the participant-specific intercept. These analyses were stratified by the propensity score quintile.[12,15] That is, separate safety analyses were conducted for those least likely to receive antidepressants (quintile 1), those somewhat more likely to receive antidepressants (quintile 2), and so on. It is possible that multiple exposure intervals from 1 participant were classified in different quintiles because time-varying variables were included in the propensity score. For example, if a participant's affective syndrome worsened, that participant's propensity for treatment would become elevated. The rationale for quintile stratification is as follows: although there are demographic and clinical differences between the exposed and unexposed when examining all exposure intervals, the differences become inconsequential within a quintile that is delineated based on a linear combination of those demographic and clinical variables. These stratified results were then pooled using the Mantel-Haenszel procedure[16] and implemented as described by Fleiss.[17] Prior to pooling the quintile-specific results, the assumption of no propensity by treatment interaction was examined.[11] If statistically

significant, such an interaction would indicate that antidepressant risk varied across quintiles and pooling would be contraindicated. All mixed-effects models were analyzed with the SuperMix software.[18] A 2-tailed α level of .05 was used for each statistical test described in this report.

Secondary analyses: age-specific models. In an effort to more closely parallel the FDA analyses, age-specific analyses of risk were conducted because the FDA meta-analyses of short-term trials found clear differences in the magnitude and direction of antidepressant safety, with higher risk of suicidality among those randomized to antidepressants in the youngest group (< 25 years) and a protective effect of antidepressants in the oldest group (65+ years).[1]

RESULTS

Study Sample

The study sample of 757 participants had a mean (SD) age at intake into the CDS of 38.1 (14.0) years and included 468 (61.8%) women. Their intake diagnoses were schizoaffective-manic (n = 26, 3.4%), mania (119, 15.7%), schizoaffective-depressed (n = 24, 3.2%), and depression (n = 588, 77.7%). The mean (SD) 17-item Hamilton Depression Rating Scale[19] at intake was 20.2 (7.9). The median follow-up time was 20 years (mean = 16.4; SD = 8.5; range, 0.3–27). Additional demographic and clinical characteristics of the sample are presented in Table 1.

Table 1. Demographic and Clinical Characteristics of Study Sample at Intake Into Collaborative Depression Study (CDS) (N = 757)

Characteristic	n	%	
Gender			
Women	468	61.8	
Men	289	38.2	
Marital status			
Never married	249	32.9	
Married	338	44.6	
Divorced/separated/widowed	170	22.5	
Hollingshead SES[20,a]			
1	33	4.4	
2	125	16.5	
3	229	30.3	
4	223	29.5	
5	147	19.4	
Intake site			
New York, New York	104	13.7	
St Louis, Missouri	202	26.7	
Boston, Massachusetts	122	16.1	
Iowa City, Iowa	181	23.9	
Chicago, Illinois	148	19.6	
Intake status			
Inpatient	602	79.5	
Outpatient	155	20.5	
No. of major depressive episodes prior to CDS intake			
0	206	27.2	
1	177	23.4	
2	103	13.6	
3	72	9.5	
4	43	5.7	
5 or more	156	20.6	
History of suicide attempt	375	49.5	
	Mean	Median	SD
Global Assessment Scale score	35.6	35	10.8
17-Item Hamilton Depression Rating Scale (extracted)	20.2	21	7.9
Age, y	38.1	35	14.0
Follow-up duration, y	16.4	20	8.5

[a]Holingshead SES score ranges from 1 (higher socioeconomic status) to 5 (lower socioeconomic status).

Antidepressant Exposure

The analyses included 6,716 exposure intervals observed among the 757 participants over the course of follow-up. Table 2 shows that nearly half of the intervals involved antidepressant exposure (3,283 exposed intervals [48.9%]; 3,433 unexposed intervals [51.1%]). On average, participants spent 42.1% (median = 37.6; SD = 34.3) of follow-up on antidepressants. The participants' affective syndrome severity at the commencement of intervals exposed to antidepressants was significantly higher than for the unexposed intervals (Psychiatric Status Ratings: [exposed] mean = 3.59, SD = 1.40; [unexposed] mean = 3.33, SD = 1.43; $z = 8.79$, $P < .001$). Of the exposed intervals, 85.7% began when the participant was in a mood episode; whereas 72.5% of the unexposed intervals began when in a mood episode.

Propensity for Antidepressant Exposure

The propensity model shows that participants with more severe affective syndromes were significantly more likely to initiate antidepressants (odds ratio [OR] = 1.16; 95% CI, 1.12–1.21; $z = 8.22$; $P < .001$; severity was measured on the 6-point Psychiatric Status Ratings scale). Similarly, those whose trajectory of illness severity was worsening in the 8 weeks prior to the exposure interval were 69% more likely to receive antidepressants (OR = 1.69; 95% CI, 1.50–1.89; $z = 9.02$; $P < .001$) than those with stable severity, whereas those with improvement in trajectory of illness severity were 26% less likely to receive antidepressants (OR = 0.74; 95% CI, 0.64–0.85; $z = -4.08$; $P < .001$). There were no other significant associations identified in the propensity model.

Primary Results: Safety Model

The results indicate that the risk of suicidal behavior was reduced by 20% among participants exposed to antidepressants (hazard ratio = 0.80; 95% CI, 0.68–0.95; $z = -2.54$; $P = .011$; Table 2) controlling for variables in the propensity score through stratification. These results are derived from pooled quintile-specific estimates of suicidality risk. Pooling was implemented because the treatment by propensity quintile interaction was not statistically significant ($\chi^2_4 = 1.90$, $P = .755$). Unadjusted rates of suicidal behavior were 11.3% among unexposed intervals (370 attempts [10.8%] and 17 suicides [0.50%]) and 10.1% among exposed intervals (321 suicide attempts [9.8%] and 9 suicides [0.27%]) (Table 2). During the first 4 weeks of exposure, a period generally deemed to be at high risk of suicidality, the rates were 1.0% among exposed intervals and 0.7% among unexposed intervals.

Of the 3,433 unexposed intervals, 1,851 (54.9%) had no contemporaneous exposure to mood stabilizers (including lithium, anticonvulsants, antipsychotics, and ECT). Among

Table 2. Suicidal Behavior by Antidepressant Exposure Status

Antidepressant Exposure Status	Antidepressant Exposure Intervals, No. (%)	Suicidal Behavior, No. of Events	Unadjusted Rate/Interval, %	Propensity-Adjusted Hazard Ratio	95% CI	*z*	*P*
Not exposed	3,433 (51.1)	387[a]	11.3	1.00			
Exposed	3,283 (48.9)	330[b]	10.1	0.80	0.68–0.95	−2.54	.011

[a]370 suicide attempts; 17 suicide deaths.
[b]321 suicide attempts; 9 suicide deaths.

Table 3. Suicidal Behavior by Age and Antidepressant Exposure Status

Age, y	Antidepressant Exposure Status	No. of Antidepressant Exposure Intervals	Suicide Deaths, n	Suicidal Behavior,[a] No. of Events	Suicidal Behavior Rate/Interval, %	Propensity-Adjusted Hazard Ratio	95% CI	*z*	*P*
<25	Not exposed	239	2	53	22.2				
	Exposed	176	1	24	13.6	1.09	0.62–1.92	0.28	.777
25–29	Not exposed	362	3	74	20.4				
	Exposed	293	0	34	11.6	0.67	0.42–1.06	−1.71	.087
30–64	Not exposed	2,502	10	249	10.0				
	Exposed	2,481	7	247	10.0	0.86	0.71–1.05	−1.49	.136
65+	Not exposed	330	2	11	3.3				
	Exposed	333	1	25	7.5	2.00	0.91–4.37	1.73	.083

[a]Suicide attempts or suicide deaths.

intervals not exposed to antidepressants, those with no mood stabilizers had higher unadjusted rates of suicidal behavior (12.6%) than the intervals with mood stabilizers (9.7%).

Secondary Analyses: Age-Specific Models

Age-specific analyses adopted the age categories applied in the FDA meta-analyses (<25, 25–29, 30–64, 65+ years).[1] Separate propensity models were estimated for each age-specific analysis. The association between antidepressant exposure and suicidal behavior was nonsignificant for any age group in age-specific, propensity-adjusted, mixed-effects survival analyses (see hazard ratios in Table 3). In part, this is due to the reduced power from smaller *n*'s in the age-specific strata.

DISCUSSION

The risk of suicidal behavior among those taking antidepressants was examined in a 27-year observational study. The propensity model indicates that more severely ill participants were significantly more likely to initiate antidepressant treatment. Nevertheless, antidepressants significantly reduced the risk of suicide attempts and deaths by 20%.

Secondary analyses examined safety of antidepressants, separately for each of 4 age groups. Unlike the primary analyses, the association of antidepressants and suicidal behavior was nonsignificant, in part due to the reduced statistical power in age-specific subsets of data.

Although on the surface it may seem that these results contradict those of the FDA meta-analyses, there are several reasons that they do not. First, we did not look at suicidal ideation, which accounted for about 70% of suicidality in the FDA data set. Suicidal ideation was not included in our analyses because it was not assessed in the study with the frequency required to correspond with the timing of treatment. Second, our data included a much broader range of participants, one that better reflects patients who receive antidepressants—those with comorbidity, patients with illness severity ranging from euthymia to severe mood episodes, and those treated with polypharmacy. Third, the study design did not include a placebo control. However, the use of a "no antidepressant" control seems to be more clinically applicable, yet we acknowledge that, unlike placebo, it fails to account for the expectations of a therapeutic intervention.[21]

Our results are consistent with other observational studies of antidepressants. A meta-analysis[22] of 8 observational studies (265,889 depressed patients) found that use of an SSRI was associated with a 40% decrease in risk of suicide attempt or death, compared with no antidepressant treatment in controls. Another observational study of patients in a large health plan found that risk of suicide attempts was higher in the month before antidepressant medication initiation and declined after initiation.[23,24] A similar pattern was found in a cohort of 226,866 depressed patients in the Veterans Administration health care system.[25]

Strengths of our analysis include the generalizable sample, a clinically relevant outcome variable, development of a propensity score based on detailed demographic and timely clinical data, and examination of full epochs of exposure, whether antidepressant positive or negative. However, there are several limitations to our findings. First, the differential risk of individual antidepressants was not examined. Instead, an effort was made to parallel the FDA analyses, and, for that reason, we evaluated the risk of antidepressants as a class of medications. Second, randomized treatment assignment was not used in this study, and, as a result, the exposed group had greater illness severity and a worsening trajectory when antidepressants were initiated. Randomized controlled trial data would have been preferable, but no antidepressant randomized controlled clinical trial had such a widely generalizable study sample or 27 years of follow-up. In the present article, the propensity adjustment was applied to make causal inferences with these observational data. The adjustment assumes

that no confounding variable was omitted from the respective propensity models, whether measured or unmeasured. We believe that our models were comprehensive enough to detect important correlates of antidepressant exposure. Yet we acknowledge that the assumption cannot be verified because unmeasured confounding variables, by their very nature, are not in our data set and that a misspecified propensity model can yield biased results.[26,27]

A third limitation is that we did not collect serum levels of the antidepressants. Instead, determination of antidepressant exposure was based on the structured interviews and available clinical records. Finally, the classification of antidepressant exposure ignored both dose and concomitant medications.

In conclusion, we found no evidence that treatment with antidepressants elevated the risk of suicidality. Instead, treatment reduced the risk and provided a protective effect. However, the risk was only reduced, not eliminated. Therefore, clinicians must monitor patients for suicidality when initiating an antidepressant. Mood disorder patients not receiving antidepressants, who are at higher risk for suicidality, should also be monitored.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Zonalon, Silenor, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), isocarboxazid (Marplan), lithium (Lithobid and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil and others), protriptyline (Vivactil 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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Potential conflicts of interest: **Dr Leon** has been a member of the Psychopharmacologic Drugs Advisory Committee of the US Food and Drug Administration that examined antidepressants and suicidality; has received research support from the National Institute of Mental Health (NIMH); has served on independent data and safety monitoring boards for AstraZeneca, Pfizer, and Sunovion; has been a consultant to NIMH, MedAvante, and Roche; and has equity in MedAvante. **Dr Solomon** is employed by UpToDate, Inc. **Dr Fiedorowicz** currently serves on colleagues' studies which are supported by Neurosearch, Vitalin/Enzymatic Therapy, the National Center for Complementary and Alternative Medicine, and the US Food and Drug Administration Orphan Products division. **Dr Endicott** is an employee of New York State Psychiatric Institute; has received research support from the NIMH and Cyberonics; and has served as a consultant or advisory board member to AstraZeneca, Bayer Shering, Cyberonics, Forest, GlaxoSmithKline, Eli Lilly, Otsuka, and Wyeth-Ayerst. **Dr Keller** has received consulting/honoraria fees from Medtronic and Sierra Neuropharmaceuticals and research funding from Pfizer. **Dr Coryell** and **Mr Li** report no financial or other relationships relevant to the subject of the article.

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Additional information: This article has been reviewed by the Publication Committee of the Collaborative Depression Study and has its endorsement. The data for this article came from the NIMH Collaborative Program on the Psychobiology of Depression-Clinical Studies (Katz and Klerman, 1979[6]). 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 five 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); 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; M. T. Shea, PhD; R. Gibbons, PhD; M. A. Young, PhD; and D. C. Clark, PhD.

†Deceased.

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