Effect of Antidepressant Medication Treatment on Suicidal Ideation and Behavior in a Randomized Trial: An Exploratory Report From the Combining Medications to Enhance Depression Outcomes Study

Sidney Zisook, MD; Ira M. Lesser, MD; Barry Lebowitz, PhD; A. John Rush, MD; Gene Kallenberg, MD; Stephen R. Wisniewski, PhD; Andrew A. Nierenberg, MD; Maurizio Fava, MD; James F. Luther, MA; David W. Morris, PhD; and Madhukar H. Trivedi, MD

ABSTRACT

Objective: To explore relationships between baseline sociodemographic and clinical features and baseline suicidal ideation, and treatment effects on suicidal ideation and behavior, in depressed outpatients.

Method: From March 2008 to September 2009, the Combining Medications to Enhance Depression Outcomes study, a single-blind, 7-month randomized trial, enrolled outpatients with nonpsychotic chronic and/or recurrent major depressive disorder (*DSM-IV-TR* criteria) in primary and psychiatric care (N = 665). Participants received escitalopram plus placebo, bupropion sustained release (SR) plus escitalopram, or venlafaxine extended release (XR) plus mirtazapine. The primary outcome measure for this report is presence of suicidal ideation assessed by the Concise Health Risk Tracking Self-Report, which measures suicidal ideation and behaviors over the last 24 hours. Sociodemographic and clinical features were compared in those with versus without baseline ideation. At 4, 12, and 28 weeks, treatment effects on suicidality were assessed, and unadjusted and adjusted outcomes were compared among those with and without baseline ideation using linear, logistic, ordinal logistic, and negative binomial regression models.

Results: Baseline suicidal ideation was associated with greater depressive severity, childhood neglect, childhood abuse, early major depressive disorder onset, greater psychiatric comorbidity, and worse functioning and quality of life. After adjustment for treatment, gender, age at first depressive episode, obsessive-compulsive symptoms, and depressive severity, depressive symptom outcomes did not differ between ideation groups at 12 or 28 weeks or between treatments. Overall, 79% of participants with baseline suicidal ideation had none at week 4, 83% had none at week 12, and 86% had none at week 28. All treatments reduced ideation, with bupropion-SR plus escitalopram the most effective at week 12 ($P < .01$). In participants without baseline ideation, emergent ideation did not differ between treatments: 2.5% had ideation at 4 weeks, 1.3% had ideation at 12 weeks, and only 1.7% had ideation at 28 weeks. Four patients (all receiving venlafaxine-XR plus mirtazapine) attempted suicide ($P = .0162$).

Conclusion: Baseline ideation did not affect depressive symptom outcome. Bupropion-SR plus escitalopram most effectively reduced ideation. Ideation emergence was uncommon. Venlafaxine-XR plus mirtazapine may pose a higher risk of suicide attempts.

Trial Registration: clinicaltrials.gov Identifier: NCT00590863

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Corresponding author: *Sidney Zisook, MD, VA Healthcare System, 3350 La Jolla Village Dr, San Diego, CA 92161 (szisook@ucsd.edu).*

Suicide, the most serious consequence of untreated major depressive disorder (MDD), is responsible for more than 990,000 deaths annually worldwide.[1] Paradoxically, while the most reliable preventative strategy for suicide is the prompt diagnosis and treatment of MDD,[2] the most widely used treatments—antidepressant medications—have been implicated as possible precipitants of emergent or increased suicidal thoughts and behaviors, particularly in youths and young adults.[3–5] Furthermore, no antidepressant medication or combination of medications has yet been demonstrated to reliably decrease existing suicidal ideation and risk.

Most studies have not found robust differences among antidepressants regarding their effects on suicidality.[3,6,7] One study[8] found selective serotonin reuptake inhibitors (SSRIs) to be associated with an increased risk of suicidal behaviors compared with tricyclic antidepressants in the first month of treatment, while another[9] found venlafaxine (a serotonin-norepinephrine reuptake inhibitor) to be possibly associated with a higher rate of suicide attempts than SSRIs. No studies have assessed whether combination antidepressant medications differ from a standard monotherapy regarding effect on suicide risk.

The recently completed Combining Medications to Enhance Depression Outcomes (CO-MED) study used a cohort of 665 outpatients with nonpsychotic MDD to compare the efficacy of escitalopram to 2 antidepressant combinations. This current report uses the CO-MED data to evaluate the association between suicide risk and a broad range of clinical characteristics, and assess differential outcomes for the 3 treatment groups. The large sample enabled us to address the following questions:

1. What sociodemographic and clinical features are associated with baseline suicidal ideation?
2. Is baseline suicidal ideation related to treatment outcomes?
3. What are the effects of treatment with escitalopram monotherapy or with either combination on suicidal ideation for:
   a. Patients without baseline suicidal ideation?
   b. Patients with baseline suicidal ideation?

METHOD

Study Overview

CO-MED was a 7-month single-blind, randomized trial that compared the efficacy of monotherapy escitalopram plus placebo to 2 antidepressant combinations, escitalopram plus

Clinical Points

- Depressed patients with suicidal ideation can be effectively and safely treated with antidepressant medications.
- Effective antidepressant treatment reduces suicidal ideation.
- The substantial benefit of reducing suicidal ideation in depressed patients who are treated with antidepressant medications versus the small risk of emergent or worsening suicidal ideation with such treatment strongly favors treatment.
- For depressed outpatients with baseline suicidal ideation, there may be an advantage with the combination of bupropion-SR plus escitalopram compared to either escitalopram alone or the combination of venlafaxine-XR plus mirtazapine in terms of reducing suicidal ideation after 12 weeks of treatment.
- Suicide risk is a serious concern throughout the course of MDD, including before, during, and after treatment.

bupropion sustained release (SR) and venlafaxine extended release (XR) plus mirtazapine (1:1:1 ratio) in 12 weeks of first-step acute-phase MDD treatment.[10] The study recruited outpatients with nonpsychotic MDD from 6 primary care and 9 psychiatric care sites.

Recruitment

Participants were enrolled from March 2008 through September 2009. Potential participants were screened at each clinical site using each site's standard procedure (variable across sites), often using the Patient Health Questionnaire.[11,12] After screening, the site's clinical research coordinator explained the protocol and obtained written informed consent for the full 7-month study period before proceeding.

Participants

Broad inclusion and minimal exclusion criteria were used to ensure a reasonably representative participant sample. Outpatient enrollees, 18–75 years of age, met *DSM-IV-TR*[13] criteria for either recurrent or chronic MDD based on a clinical interview and confirmed using a *DSM-IV* MDD symptom checklist completed by the clinical research coordinator. Eligible participants had to be in the index episode for ≥ 2 months, to reduce the likelihood of placebo response, and have a score ≥ 16 on the 17-Item Hamilton Depression Rating Scale ($HDRS_{17}$).[14] Participants with and without current suicidal ideation were included as long as outpatient treatment was considered clinically appropriate. A full listing of exclusion criteria is available on the CO-MED Web site.[15]

The study protocol was developed according to the principles of the Declaration of Helsinki. The protocol and all consent and study procedures were approved by the institutional review boards at the National Coordinating Center (The University of Texas Southwestern Medical Center at Dallas), the University of Pittsburgh Data Coordinating Center, each participating Regional Center, and all relevant clinical sites.

Baseline Data

Sociodemographic and illness features were gathered at baseline. The anxiety subscale of the baseline $HDRS_{17}$ established the presence of anxious features.[16] The self-report Psychiatric Diagnostic Screening Questionnaire[17,18] established the presence of current Axis I disorders with 90% specificity.[19] The Concise Health Risk Tracking Self-Report (CHRT-SR) scale[20] established the presence of suicidal ideation, the Altman Self-Rating Mania Scale[21] established the presence of manic symptoms, the Concise Associated Symptoms Tracking Self-Rated scale[22] measured associated symptoms, and the Cognitive and Physical Functioning Questionnaire[23] measured functioning. The Self-Administered Comorbidity Questionnaire[24] established the presence, severity, and functional impact of a range of common general medical comorbidities.

Antidepressant Treatment

The aim of CO-MED was to test whether 2 different medications given in combination as the first treatment step, compared to 1 medication, would enhance remission rates, increase speed of remission, be tolerable, and provide better sustained benefits in the longer term. Thus, the medications selected included a commonly used and effective monotherapy with predominantly serotonergic effects (escitalopram plus placebo) and 2 frequently used combinations: one with predominantly serotonergic and noradrenergic effects (venlafaxine-XR plus mirtazapine) and the other with serotonergic, noradrenergic, and dopaminergic effects (escitalopram plus bupropion-SR).

A 12-week study period was chosen for the primary analysis so that (1) maximal doses (if needed) could be delivered for at least 4 weeks, (2) most participants whose depression could remit would do so without an excessively long trial,[25] and (3) attrition might be minimized. Treatment visits were planned at baseline and weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, and 28.[10] Measurement-based care provided personally tailored and vigorous dosing,[25–27] with dosage adjustments based on the 16-item Quick Inventory of Depressive Symptomatology–Clinician-rated ($QIDS\text{-}C_{16}$)[28–30] and the Frequency, Intensity and Burden of Side Effects Rating (FIBSER)[31] obtained at each treatment visit, and was guided by the CO-MED Operations Manual.[15]

Treatment was randomly assigned, stratified by clinical site using a Web-based randomization system.[32] Dosing schedules, shown in Table 1, were based on prior reports.[33–36] Doses were increased only in the context of acceptable side effects and tolerability and only if the $QIDS\text{-}C_{16}$ score was > 5. Participants could exit the study if unacceptable or intolerable side effects occurred that could not be resolved with dose reduction or medication treatment of side effects.

Table 1. Dosing Schedule

Escitalopram Plus Placebo
Escitalopram
Baseline (week 0): 1 tablet (10 g)/d
Week 4: 2 tablets (20 mg)/d (maximum dose)
Placebo
Week 2: 1 pill per day
Week 4: 2 pills per day
Escitalopram Plus Bupropion-SR
Bupropion-SR
Baseline: 150 mg/d
Week 1: 300 mg/d
Week 6+: 400 mg/d (200 mg bid) (maximum dose)
Escitalopram
Week 2: 10 mg/d
Week 4+: 20 mg/d
Venlafaxine-XR Plus Mirtazapine
Venlafaxine-XR
Baseline: 37.5 mg/d
Day 4: 75 mg/d
Week 1: 150 mg/d
Week 4: 225 mg/d
Week 8: 300 mg/d (maximum dose)
Mirtazapine
Week 2: 30 mg/d
Week 6: 45 mg/d (maximum dose)

Abbreviations: SR = sustained release, XR = extended release.

Medication Blinding

The first medication given in each treatment group was open label (both participant and study personnel unblinded), while each second medication was blinded (participant only). A full description of blinding methodology and concurrent treatments allowed has previously been provided.[10]

Research Outcomes

Outcome assessments were collected at baseline and all subsequent treatment visits. The primary outcome for this report is the presence of suicidal ideation, defined as a participant's having a rating of either "agree" or "strongly agree" to item 10 ("I have been having thoughts of killing myself"), item 11 ("I have thoughts of how I might kill myself"), or item 12 ("I have a plan to kill myself") on the CHRT-SR, which is applicable to the preceding 24 hours.[20] The possible range of the measure is from 0 to 28, with higher scores indicating higher ideation. The internal consistency (Cronbach α) was 0.77, with a consistent factor structure and 3 independent factors (current suicidal thoughts and plans, perceived lack of social support, and hopelessness).

Determination of symptom remission was made using the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR_{16})[37,38] and was based on the last 2 consecutive measurements obtained during the 12-week acute trial to ensure that a single "good week" was not falsely signaling remission. At least 1 of these ratings had to be < 6, while the other had to be < 8. If participants exited before 12 weeks, their last 2 consecutive QIDS-SR_{16} scores were used to ascribe remission. Those who exited before having 2 post-baseline measures were considered not remitted.

Participants could exit the study if they had received maximally tolerated dose(s) for ≥ 4 weeks by week 8 without showing a ≥ 30% reduction in baseline QIDS-C_{16} score. They could enter continuation treatment (weeks 12–28) if they had received an acceptable benefit (defined as a QIDS-C_{16} score ≤ 9 by week 12) or if they reached a QIDS-C_{16} score of 10–13 with clinician and participant judging the benefit to be substantial enough to indicate a treatment continuation. Thus, virtually all participants entering the continuation phase had at least a 40% reduction in baseline QIDS-C_{16} score.

Additional outcomes included attrition, anxiety as measured by the anxiety subscale of the 30-item Inventory of Depressive Symptomatology–Clinician-rated (IDS-C_{30}),[29,37,38] function as measured by the Work Productivity and Activity Impairment scale[39] and the Work and Social Adjustment Scale,[40] quality of life as measured by the Quality of Life Inventory,[41,42] side effect burden as measured by the FIBSER, and specific side effects as measured by the Systematic Assessment for Treatment Emergent Events–Systematic Inquiry.[43,44]

Statistical Analyses

Descriptive statistics, including measures of central tendency and dispersion, were computed for continuous data. Frequency distributions were estimated for categorical data. The appropriate parametric (eg, *t* test) or nonparametric (eg, χ^2, Wilcoxon) tests were used to evaluate the comparability of the sociodemographic, psychiatric, and medical characteristics among those with and without suicidal ideation.

At 12 and 28 weeks, unadjusted and adjusted outcomes were compared among those with and without suicidal ideation using regression models. The type of regression models varied by outcome and included linear regression, logistic regression, ordinal logistic regression, and negative binomial regression models. Potential confounders were identified using a stepwise logistic regression model with an indicator of suicidal ideation as the outcome and all other baseline characteristics as independent variables. Those variables that remained in the final stepwise model were considered as potential confounders in the adjusted models. The moderating effect of suicidal ideation on treatment was evaluated on 2 outcomes at 12 and 28 weeks, severity of depression (QIDS-SR_{16}) and side effect burden (FIBSER Burden). For severity of depression, a linear regression model was fit, and for side effect burden, an ordinal logistic regression model was fit. Both models included main effects for treatment and suicidal ideation, and the 2-way interaction between treatment and suicidal ideation.

For the 110 participants with baseline suicidal ideation, decreases in suicidal ideation were measured in 3 ways: percentage decrease in CHRT-SR items 10–12 total scores, percentage of participants with a decrease in CHRT-SR items 10–12, and percentage of participants with no suicidal ideation at weeks 12 or 28. For the 555 participants with no baseline suicidal ideation, emergent ideation was measured by 12- and 28-week total CHRT-SR items 10–12 scores and the percentage of participants with suicidal ideation at weeks 12 and 28. All analyses are considered to be exploratory.

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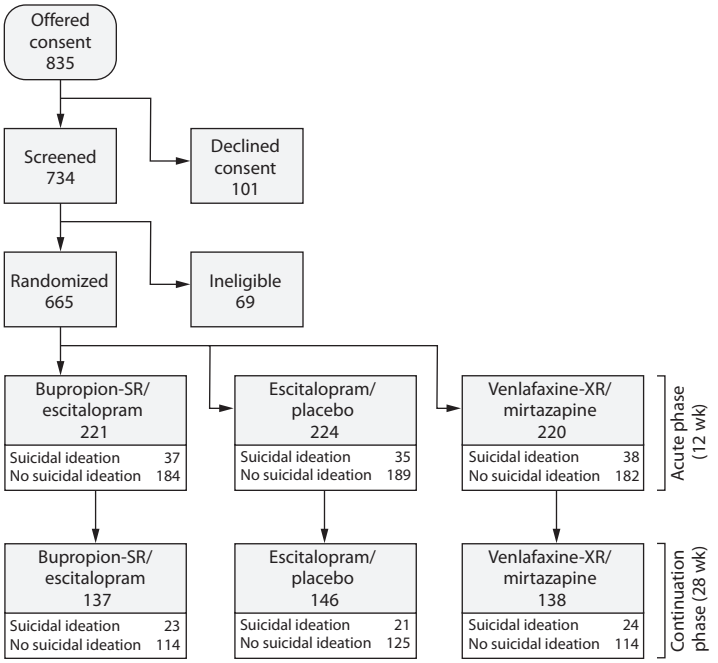
Figure 1. Flow of Participants With and Without Suicidal Ideation Through the Study



Abbreviations: SR = sustained release, XR = extended release.

A type I error or a *P* value of < .05 was used as a threshold to identify statistical significance. No adjustments were made for multiple comparisons, so results should be interpreted accordingly.

RESULTS

Of the 665 enrolled participants (Figure 1), 110 (16.5%) met the definition for suicidal ideation. Of these, 32 (4.8%) endorsed "thoughts of killing myself" *only*, 14 (2.1%) endorsed "thoughts of how" *only*, and 1 (0.2%) endorsed "I have a plan to kill myself" *only*. Fifty (7.5%) endorsed "thoughts of killing myself" *and* "thoughts of how." Thirteen (1.9%) endorsed "thoughts of killing myself," "thoughts of how," *and* "I have a plan to kill myself."

Participants with baseline suicidal ideation were more likely than those without to be unemployed; to have MDD onset before age 18 years; to have a history of suicide attempts; to have a history of emotional neglect and/or emotional, physical, or sexual abuse before age 18 years; to have a lower body mass index; to be seen in a psychiatric care setting; and to have substantial psychiatric comorbidity, melancholic features, or more severe depressions as measured by higher total QIDS-C_{16}, $HDRS_{17}$, and IDS-C_{30} scores (Tables 2 and 3). When the analyses were run again, controlling for severity of baseline depression and excluding the suicidal ideation item, the results regarding the significance of findings remained unaltered. Compared to participants without suicidal ideation, those with ideation endorsed more irritability, anxiety, panic, loneliness, and despair; had more cognitive and physical dysfunction; and had worse quality of life and poorer work and social function.

Table 2. Demographic Measures by Baseline Suicidal Ideation

	Baseline Suicidal Ideation[a]					
	Yes (n = 110)		No (n = 555)		Analyses[b]	
Measure	n	%	n	%	Test Statistic	*P*
Age					$\chi^2_2 = 3.9654$	.1377
18–29 y	29	26.4	107	19.3		
30–54 y	63	57.3	322	58.0		
55–75 y	18	16.4	126	22.7		
Sex					$\chi^2_1 = 3.0183$	.0823
Male	43	39.1	170	30.6		
Female	67	60.9	385	69.4		
Race					$\chi^2_2 = 0.2122$	.8993
White	71	67.6	360	66.9		
Black	27	25.7	147	27.3		
Other	7	6.7	31	5.8		
Hispanic	11	10.0	90	16.2	$\chi^2_1 = 2.754$	.0970
Employed	45	40.9	286	51.5	$\chi^2_1 = 4.1436$	**.0418**
Clinical setting					$\chi^2_1 = 4.5701$	**.0325**
Primary care	47	42.7	299	53.9		
Psychiatric care	63	57.3	256	46.1		
	Mean	SD	Mean	SD		
Age, y	41.3	13.4	43.0	12.9	$t_{663} = \lvert 1.28 \rvert$	.2014
Education, y	13.9	2.9	13.7	3.0	$t_{639} = \lvert 0.4 \rvert$	.6902
Monthly household income, US $	2,336	3,981	2,740	5,568	$\chi^2_1 = 0.9145$	.3389

[a]Percentages based on available data.
[b]Chi-square for continuous measures indicates Kruskal-Wallis test. *P* values in bold indicate that the threshold for statistical significance has been reached.

At 12 weeks, in the unadjusted analysis, participants with baseline suicidal ideation had lower remission rates (26.6% vs 38.6%, OR = 0.569, *P* = .0310), greater depressive severity on the QIDS-SR_{16} (10.1 ± 6.5 vs 7.8 ± 5.1, β = 1.972, *P* = .0018), and worse work and social adjustment (OR = 1.540, *P* = .0432) than those without ideation (for work and social adjustment,

Table 3. Clinical Measures by Baseline Suicidal Ideation

	Baseline Suicidal Ideation[a]					
	Yes (n = 110)		No (n = 555)		Analyses[b]	
Measure	n	%	n	%	Test Statistic	*P*
Body mass index					$\chi^2_3 = 6.2657$	.0994
Normal/underweight (< 25)	36	33.0	133	24.1		
Overweight (25–29.9)	29	26.6	158	28.6		
Obese I (30–34.9)	24	22.0	109	19.7		
Obese II and III (35+)	20	18.3	153	27.7		
Menopausal[c]	15	25.4	125	33.2	$\chi^2_1 = 1.4292$	.2319
Age at first depressive episode < 18 y	68	61.8	228	41.2	$\chi^2_1 = 15.737$	**< .0001**
At least 1 depressive episode prior to current depressive episode	85	77.3	432	78.1	$\chi^2_1 = 0.0383$	.8448
Ever attempted suicide	22	21.8	37	6.8	$\chi^2_1 = 22.849$	**< .0001**
Lifetime severity of suicidality					$\chi^2_6 = 131.32$	**< .0001**
None			198	36.5		
Thoughts of dying	10	9.9	167	30.8		
Suicidal thoughts	23	22.8	75	13.8		
Specific method	25	24.8	34	6.3		
Plan	15	14.9	23	4.2		
Preparation	6	5.9	8	1.5		
Attempt	22	21.8	37	6.8		
Neglected before age 18 y	54	49.5	186	33.5	$\chi^2_1 = 10.14$	**.0015**
Emotionally abused before age 18 y	57	52.3	204	36.8	$\chi^2_1 = 9.2186$	**.0024**
Physically abused before age 18 y	29	26.6	102	18.4	$\chi^2_1 = 3.8939$	**.0485**
Sexually abused before age 18 y	33	30.3	112	20.2	$\chi^2_1 = 5.393$	**.0202**
Any abuse before age 18 y	67	61.5	243	43.9	$\chi^2_1 = 11.339$	**.0008**
PDSQ disorders						
Agoraphobia	16	14.5	53	9.5	$\chi^2_1 = 2.464$	.1165
Alcohol abuse	14	12.7	53	9.6	$\chi^2_1 = 1.0105$	.3148
Bulimia	19	17.3	59	10.6	$\chi^2_1 = 3.9119$	**.0479**
Drug abuse	11	10.0	24	4.3	$\chi^2_1 = 5.9311$	**.0149**
Generalized anxiety	38	34.5	93	16.8	$\chi^2_1 = 18.365$	**< .0001**
Hypochondriasis	7	6.4	22	4.0	$(P) = .0993$	.3025
Obsessive-compulsive	22	20.0	57	10.3	$\chi^2_1 = 8.302$	**.0040**
Panic	19	17.3	46	8.3	$\chi^2_1 = 8.4028$	**.0037**
Posttraumatic stress	24	21.8	57	10.3	$\chi^2_1 = 11.445$	**.0007**
Social phobia	41	37.3	137	24.7	$\chi^2_1 = 7.4212$	**.0064**
Somatoform	5	4.5	16	2.9	$(P) = .1408$	.3693
Substance abuse	21	19.1	66	11.9	$\chi^2_1 = 4.1527$	**.0416**
No. of PDSQ psychiatric disorders					$\chi^2_4 = 20.458$	**.0004**
0	36	32.7	260	46.9		
1	24	21.8	135	24.4		
2	15	13.6	77	13.9		
3	13	11.8	37	6.7		
4+	22	20.0	45	8.1		
No. of treated SCQ health problems					$\chi^2_3 = 5.0068$	.1713
0	60	55.0	268	48.4		
1	19	17.4	139	25.1		
2	20	18.3	78	14.1		
3+	10	9.2	69	12.5		
SCQ heart	5	4.5	35	6.3	$\chi^2_1 = 0.5035$	.4780
SCQ neuropsychological	5	4.5	13	2.3	$(P) = .101$	.1984
Current episode duration 2+ y	63	57.3	305	55.2	$\chi^2_1 = 0.1668$	.6830
Chronic/recurrent depression					$\chi^2_2 = 0.1668$	.9200
Chronic only	25	22.7	121	21.9		
Recurrent only	47	42.7	248	44.8		
Both	38	34.5	184	33.3		
QIDS-SR_{16} depressive severity					$\chi^2_3 = 55.17$	**< .0001**
0–10 (None/mild)	3	2.8	78	14.5		
11–15 (Moderate)	30	28.0	208	38.6		
16–20 (Severe)	43	40.2	217	40.3		
21–27 (Very severe)	31	29.0	36	6.7		
IDS-C_{30} lethargic depression	81	73.6	371	66.8	$\chi^2_1 = 1.9439$	.1632
Anxious features ($HDRS_{17}$)	82	74.5	415	74.8	$\chi^2_1 = 0.0026$	.9597
Atypical features (IDS-6_{30})	21	19.1	82	14.8	$\chi^2_1 = 1.3065$	.2530
Melancholic features (IDS-6_{30})	32	33.3	92	18.1	$\chi^2_1 = 11.54$	**.0007**
IDS-C_{30} sleep disturbance	98	89.1	489	88.1	$\chi^2_1 = 0.0856$	.7698

(continued)

Table 3 (continued). Clinical Measures by Baseline Suicidal Ideation

	Baseline Suicidal Ideation[a]					
	Yes (n = 110)		No (n = 555)		Analyses[b]	
Measure	Mean	SD	Mean	SD	Test Statistic	*P*
Body mass index	28.9	7.3	31.4	9.1	$\chi^2_1 = 6.9457$	**.0084**
Systolic blood pressure, mm Hg	125	19	125	17	$t_{656} = \lvert 0.28 \rvert$	.7781
Diastolic blood pressure, mm Hg	79.2	12.1	79.1	11.6	$t_{656} = \lvert 0.07 \rvert$	.9445
Pulse, bpm	74.7	13.1	73.2	11.1	$t_{141.0} = \lvert 1.13 \rvert$	.2596
Age at first depressive episode, y	20.2	13.9	24.8	14.0	$\chi^2_1 = 13.976$	**.0002**
Time since first depressive episode, y	21.1	14.8	18.2	13.4	$\chi^2_1 = 3.2204$	.0727
No. of depressive episodes prior to current depressive episode	7.5	16.6	9.3	20.5	$\chi^2_1 = 0.0091$	.9242
No. of suicide attempts	0.66	2.62	0.16	0.88	$\chi^2_1 = 22.771$	**<.0001**
Age neglected, y	6.7	4.0	7.3	4.3	$t_{236} = \lvert 0.96 \rvert$	.3363
Age emotionally abused, y	6.7	3.6	8.1	4.2	$t_{255} = \lvert 2.3 \rvert$	**.0224**
Age physically abused, y	7.2	3.3	7.6	4.0	$t_{126} = \lvert 0.51 \rvert$	.6077
Age sexually abused, y	7.9	3.9	9.3	4.0	$t_{143} = \lvert 1.78 \rvert$	.0766
SCQ	3.2	3.3	3.4	3.6	$\chi^2_1 = 0.182$	.6697
No. of treated SCQ health problems	0.92	1.31	0.99	1.26	$\chi^2_1 = 0.8246$	.3638
No. of antidepressants prior to current treatment	1.7	1.9	1.5	1.7	$\chi^2_1 = 0.0256$	.8728
No. of concomitant medications	2.8	2.5	3.0	2.9	$\chi^2_1 = 0.1846$	.6674
Current depressive episode duration, mo	87.4	142	56.6	94.9	$\chi^2_1 = 0.8672$	.3517
$HDRS_{17}$	26.1	5.4	23.4	4.5	$t_{140.8} = \lvert 4.83 \rvert$	**<.0001**
$IDS\text{-}C_{30}$	42.2	9.2	37.2	8.9	$t_{663} = \lvert 5.35 \rvert$	**<.0001**
$QIDS\text{-}C_{16}$	17.5	3.0	15.5	3.4	$t_{663} = \lvert 5.79 \rvert$	**<.0001**
$QIDS\text{-}SR_{16}$	17.9	4.3	15.0	4.1	$t_{644} = \lvert 6.68 \rvert$	**<.0001**
ASRMS	1.6	2.2	1.5	2.3	$\chi^2_1 = 0.0897$	.7646
CAST-SR						
Irritability	13.4	3.4	12.1	3.8	$t_{662} = \lvert 3.34 \rvert$	**.0009**
Anxiety	6.9	2.9	6.1	3.0	$\chi^2_1 = 5.4872$	**.0192**
Mania	3.2	2.5	3.7	2.8	$\chi^2_1 = 1.9803$	**.1594**
Insomnia	5.5	2.4	5.0	2.3	$t_{662} = \lvert 2.16 \rvert$	**.0309**
Panic	3.3	2.4	2.5	2.1	$\chi^2_1 = 9.5046$	**.0020**
CHRT-SR						
Loneliness	4.4	2.0	3.2	2.0	$t_{662} = \lvert 5.78 \rvert$	**<.0001**
Despair	5.6	1.9	4.1	2.2	$t_{663} = \lvert 6.83 \rvert$	**<.0001**
CPFQ	29.5	5.7	27.3	5.8	$t_{663} = \lvert 3.62 \rvert$	**.0003**
Quality of Life Inventory	−1.8	2.0	−1.1	1.9	$t_{659} = \lvert 3.93 \rvert$	**<.0001**
Work and Social Adjustment Scale	30.7	7.9	26.2	8.8	$\chi^2_1 = 29.509$	**<.0001**

[a]Values based on available data.
[b]Chi-square for continuous measures indicates Kruskal-Wallis test; (*P*) indicates Fisher exact. *P* values in bold indicate that the threshold for statistical significance has been reached.
[c]Denominator is number of women (see Table 2).
Abbreviations: ASRMS = Altman Self-Rating Mania Scale, CAST-SR = Concise Associated Symptoms Tracking Self-Rated, CHRT-SR = Concise Health Risk Tracking Self-Report, CPFQ = Cognitive and Physical Functioning Questionnaire, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, $IDS\text{-}C_{30}$ = 30-item Inventory of Depressive Symptomatology–Clinician-Rated, PDSQ = Psychiatric Diagnostic Screening Questionnaire, $QIDS\text{-}C_{16}$ = 16-item Quick Inventory of Depressive Symptomatology–Clinician-Rated, $QIDS\text{-}SR_{16}$ = 16-item Quick Inventory of Depressive Symptomatology–Self-Report, SCQ = Self-Administered Comorbidity Questionnaire.

an extremely nonnormal distribution required binning). These outcomes no longer differed after adjustment for treatment, gender, age at first depressive episode, obsessive-compulsive symptoms, and depressive severity. At 28 weeks, participants who had baseline suicidal ideation had greater depressive severity on the $QIDS\text{-}SR_{16}$ (9.1 ± 6.3 vs 7.3 ± 5.4, β = 1.235, *P* = .0418) (unadjusted only) and worse work and social adjustment (OR = 1.604, *P* = .0268) (unadjusted only) than those without ideation.

There was no significant baseline suicidal ideation–by-treatment interaction for week 12 or week 28 regarding remission or relapse rates or percentage reductions in $QIDS\text{-}SR_{16}$ depressive severity (Table 4).

Participants with suicidal ideation at baseline were significantly more likely than those without to have suicidal ideation at week 4 (20.8% [21/110] vs 2.5% [13/527], *P* < .0001), at week 12 (17.3% [18/104] vs 1.3% [7/525], *P* < .0001) and at week 28 (14.4% [15/104] vs 1.7% [9/527], *P* < .0001). Over 96% of participants without suicidal ideation at baseline continued without suicidal ideation at weeks 4, 12, and 28.

For the 110 participants with pretreatment suicidal ideation, all 3 treatment groups were associated with decreases in suicidal ideation, with the bupropion-SR plus escitalopram combination showing significantly greater improvement than the other medications (Table 5). At week 12, 100% (35/35) of participants taking bupropion-SR plus escitalopram had a decrease in total CHRT-SR scores (mean 83% decrease), and 97.1% (34/35) of these participants no longer had suicidal ideation. Results were similar at week 28, with 100% (35/35) of participants receiving bupropion-SR plus escitalopram continuing to show improvement from baseline, although differences between treatment groups were no longer statistically significant.

Table 4. Selected Outcomes by Baseline Suicidal Ideation, Treatment, and Study Phase

	Baseline Suicidal Ideation[a]												
	Yes						No						
	Bupropion-SR + Escitalopram (n = 37)		Escitalopram + Placebo (n = 35)		Venlafaxine-XR + Mirtazapine (n = 38)		Bupropion-SR + Escitalopram (n = 184)		Escitalopram + Placebo (n = 189)		Venlafaxine-XR + Mirtazapine (n = 182)		P[b]
Acute phase	n	%	n	%	n	%	n	%	n	%	n	%	
Early termination	11	29.7	9	25.7	11	28.9	59	32.1	46	24.3	46	25.3	.8669
Last QIDS-SR_{16} < 6	9	25.0	8	22.9	12	31.6	73	39.9	73	38.6	67	37.2	.6214
% QIDS-SR_{16} reduction ≥ 50	17	47.2	15	46.9	17	44.7	94	52.5	98	52.7	93	54.1	.9432
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Last QIDS-SR_{16}	10.2	6.2	9.6	6.4	10.6	7.0	7.7	5.0	7.6	4.9	8.0	5.3	.8620
% QIDS-SR_{16} reduction	−44	31.3	−44	35.4	−42	36.5	−45	35.3	−47	32.7	−47	35.0	.9096
Continuation phase	n	%	n	%	n	%	n	%	n	%	n	%	
Early termination	14	37.8	14	40.0	14	36.8	70	38.0	64	33.9	68	37.4	.8309
Last QIDS-SR_{16} < 6	16	43.2	13	37.1	12	32.4	85	47.0	88	46.8	78	43.3	.8177
% QIDS-SR_{16} reduction ≥ 50	22	59.5	19	59.4	16	43.2	103	58.2	110	59.5	104	60.5	.2799
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Last QIDS-SR_{16}	9.1	6.4	8.1	6.0	10.2	6.5	6.9	5.1	7.2	5.3	7.7	5.7	.5725
% QIDS-SR_{16} reduction	−50	32.1	−51	32.7	−43	34.1	−50	37.3	−51	32.9	−49	36.5	.7682

[a]Values based on available data.
[b]Probability value associated with baseline suicidal ideation–by-treatment interaction term.
Abbreviations: QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology–Self-Report, SR = sustained release, XR = extended release.

Table 5. CHRT-SR Suicidality and Ideation Subscale Measures by Treatment and Study Phase for Those With or Without Baseline Suicidal Ideation

	Treatment						Analyses[a]				
									Pairwise Comparisons		
Measure	Bupropion-SR + Escitalopram (n = 35)		Escitalopram + Placebo (n = 33)		Venlafaxine-XR + Mirtazapine (n = 36)		Test Statistic	P	B + E vs E + P	B + E vs V + M	E + P vs V + M
Participants with baseline suicidal ideation											
Acute phase	n	%	n	%	n	%					
Suicidal ideation (exit)	1	2.9	8	24.2	9	25.0	$\chi^2_2 = 7.7$	**.0212**	.012[b]	.014[b]	.942
Ideation improvement	35	100	30	90.9	29	80.6	$(P) = .001$	**.0124**	.109	.011[b]	.311
	Mean	SD	Mean	SD	Mean	SD					
Ideation (baseline)	6.6	2.0	6.6	1.7	6.7	2.1	$F_{2,101} = 0.01$	0.9897			
Ideation (exit)	1.1	1.9	2.9	3.0	2.8	3.0	$\chi^2_2 = 10.1$	**.0065**	.003[b]	.010[b]	.838
% Ideation change	−83	25.0	−58	43.2	−51	58.5	$\chi^2_2 = 9.74$	**.0077**	.004[b]	.009[b]	.887
Continuation phase	n	%	n	%	n	%					
Suicidal ideation (exit)	2	5.7	6	18.2	7	19.4	$\chi^2_2 = 3.263$	.1956			
Ideation improvement	35	100	31	93.9	31	86.1	$(P) = .009$	**.0440**	.232	.054	.431
	Mean	SD	Mean	SD	Mean	SD					
Ideation (exit)	1.7	2.1	2.9	2.7	2.5	2.5	$\chi^2_2 = 4.605$	.1000			
% Ideation change	−76	26.5	−58	41.4	−55	56.4	$\chi^2_2 = 4.453$	.1079			
Participants without baseline suicidal ideation											
	n = 174		n = 180		n = 173						
Acute phase	n	%	n	%	n	%					
Suicidal ideation (exit)	2	1.2	2	1.1	3	1.7	$(P) = .096$	.8970			
	Mean	SD	Mean	SD	Mean	SD					
Ideation (baseline)	1.2	1.7	0.9	1.5	1.4	1.7	$\chi^2_2 = 8.54$	**.0140**	.024	.583	.006[b]
Ideation (exit)	0.78	1.53	0.84	1.39	0.93	1.61	$\chi^2_2 = 0.916$	.6327			
Continuation phase	n	%	n	%	n	%					
Suicidal ideation (exit)	2	1.1	2	1.1	5	2.9	$(P) = .037$	.4508			
	Mean	SD	Mean	SD	Mean	SD					
Ideation (exit)	0.81	1.47	0.81	1.58	1.02	1.68	$\chi^2_2 = 1.871$	.3924			

[a]Chi-square for continuous measures indicates Kruskal-Wallis test; (P) indicates Fisher exact. P values in bold indicate that the threshold for statistical significance has been reached.
[b]Significant after Bonferroni correction ($P < .0166$).
Abbreviations: B = bupropion sustained release, CHRT-SR = Concise Health Risk Tracking Self-Report, E = escitalopram, M = mirtazapine, P = placebo, SR = sustained release, V = venlafaxine extended release, XR = extended release.

For the 555 participants without pretreatment suicidal ideation, emergent ideation was a rare event. Only about 1% of the participants taking either escitalopram or bupropion-SR plus escitalopram had emergent ideation at week 12 (2/180 and 2/174, respectively) and week 28 (2/180 and 2/174, respectively). About 2% (3/173) of participants taking venlafaxine-XR plus mirtazapine had emergent ideation at week 12, and about 3% (5/173) of this group had emergent ideation at week 28 (Table 5). Differences were not statistically significant between treatment groups on any suicidal ideation measure.

During the 28-week study period, 7 participants (1.05%) were hospitalized for serious ideation (n = 3) or suicide attempts (n = 4), and no participant completed suicide. Thus, there were very few events for an MDD patient sample of this size, and no statistically significant differences between groups at 12 weeks or 28 weeks. More events occurred during the continuation treatment period (5 of the 7 hospitalizations and 2 of the 4 attempts). Over the 28-week study period, more participants receiving the venlafaxine-XR plus mirtazapine combination attempted suicide (4/173) than participants receiving the other treatments (escitalopram plus placebo: 0/180; bupropion-SR plus escitalopram: 0/174) ($P = .0162$).

DISCUSSION

Participants with baseline suicidal ideation were severely depressed and impaired with high levels of comorbidity and dysfunction. Those with baseline ideation were as likely as those without to tolerate the medications and have a positive outcome in terms of depressive symptoms and function after 12 and 28 weeks of treatment. After adjusting for gender, age at first depressive episode, obsessive-compulsive symptoms, and depressive severity, there were no interactions between treatment group and baseline suicidal ideation regarding MDD treatment outcome. However, all 3 treatments resulted in improvements in suicidal ideation, and none were likely to be associated with emergent suicidal ideation. The 4 participants who attempted suicide were taking venlafaxine-XR plus mirtazapine.

What Sociodemographic and Clinical Features Were Associated With Baseline Suicidal Ideation?

Our study confirms previous findings of associations between baseline suicidal ideation and unemployment, early-onset MDD, past suicide attempts, anxious features, and severity of MDD.[2,45-48] Two features deserve special mention. Although the mechanism is unclear, there is an extensive literature linking lower body mass index to increased risk for suicide.[49–52] Similarly, there is a growing literature linking a history of childhood adversity to a variety of adult mental health consequences,[53–55] including the development of MDD[56] and suicidal behaviors.[57] More recognition and research on these important links may ultimately provide opportunities for vitally needed primary prevention.[58]

Is Baseline Suicidal Ideation Related to Treatment Outcomes?

Participants with baseline suicidal ideation responded as well to antidepressant treatment as did participants without ideation. Only 1 small, retrospective analysis of 63 MDD patients with or without suicidal ideation at antidepressant treatment initiation has studied this issue, finding no differences in remission between groups.[59] Our confirmation of these findings takes on special clinical importance in light of a reluctance among some clinicians to prescribe antidepressants when suicidal risk is present for fear of exacerbating this risk.[60,61]

In addition, antidepressant response and tolerability were equally robust for participants with and without suicidal ideation for all 3 treatments. We are not aware of any published studies that previously assessed this issue.

What Are the Effects of Treatment With Escitalopram Monotherapy or With Either Combination on Suicidal Ideation?

For participants without baseline suicidal ideation, we found no substantial differences among treatment groups regarding their likelihood of having emergent suicidal ideation, which is consistent with most other studies.[3,62] It should be noted that this study was not powered to find differences in emergent suicidal ideation and the numbers with emergent ideation in each treatment group were small. We previously reported that such cases of emergent suicidal ideation may be more a function of factors other than medications, such as the inherent ebb and flow of suicidal thoughts in patients with severe or melancholic MDD, intercurrent psychosocial stressors, or the presence of other comorbid conditions.[63]

For participants with baseline suicidal ideation, we found that all 3 treatments substantially reduced suicidal ideation, with bupropion-SR plus escitalopram significantly more likely to reduce ideation at week 12 than either of the other treatments. Although the numerical values continued to favor bupropion-SR plus escitalopram at 28 weeks, differences no longer reached statistically significant levels. Due to the design of the study, we cannot say whether the additional anti-ideation effect over escitalopram plus placebo or venlafaxine-XR plus mirtazapine was due to the bupropion-SR or to a unique interaction of the combination of bupropion-SR and escitalopram. The differential effects on ideation reduction cannot be attributed to antidepressant effects alone, as all treatments were equally likely to relieve depressive symptoms, including in participants with baseline ideation. From a theoretical perspective, the bupropion-SR plus escitalopram combination was the only treatment to have dopaminergic effects as well as serotonergic and noradrenergic effects (venlafaxine-XR plus mirtazapine) or predominantly serotonin effects (escitalopram plus placebo). All 3 neurotransmitters have been implicated in suicide risk,[64] and it is possible that interactions between neurotransmitters may be critical.[65] One recent study postulated that increases in suicidal ideation in men taking the pronoradrenergic agent nortriptyline were related to polymorphisms in the

α_{2A}-adrenergic receptor gene.[66] Whatever the mechanism, our finding has important public health implications if confirmed in a prospective, randomized, controlled clinical trial.

When we looked at suicidal behaviors, 3 findings stood out. First, there were no completed suicides during the study, and only 4 attempts were made. This is remarkable, especially in the context of all the publicity and fear regarding the potential suicide-inducing effects of antidepressants.[3–5] While we cannot be certain of the reason for so few suicide events, we believe that the frequency of visits, the use of measurement-based practice, the contributions of very involved research coordinators, the close monitoring of suicidal ideation, and the overall effectiveness of the treatments all contributed.[2,25,63] Second, suicide events were more likely to occur during the continuation period, which contrasts with the notion that suicide risk is greatest in the immediate aftermath of initiating treatment.[8] The decreased frequency of visits during continuation treatment may have been a factor, and treatment adherence may lessen with longer treatment durations.[67] Whatever the reason, this finding should be a reminder that suicide risk is a serious concern throughout the course of MDD, including before, during, and after treatment. Third, the venlafaxine plus mirtazapine combination was associated with a greater risk of suicide attempts than the other treatments. Some studies have suggested that venlafaxine may be more associated with "emergent" suicide ideation than other antidepressants,[9] but the data are not consistent.[3,7] This finding requires further study, as the combination of venlafaxine and mirtazapine is often reserved for very severely depressed patients who may already be at high risk for suicidal behaviors.

Study limitations include the use of a relatively small sample for some of the questions asked. Answers regarding differential medication effects on such low-frequency events as completed suicide will require huge samples collected over long timeframes. The preliminary suggestion of a possible increased risk of suicide attempts with the venlafaxine-XR and mirtazapine combination must be interpreted cautiously, as the study was not powered to detect differences in suicide attempt rates between treatments. In addition, caution should be exercised before generalizing the results to other antidepressants or to patient groups excluded from this trial. Because we did not have data on fluctuations of participant suicidal ideation prior to study entry, we could not distinguish newly emergent suicidal ideation from continued fluctuations. The primary suicide scale assessed ideation over the previous 24 hours only, which amounts to a very small percentage of the overall time of exposure to each treatment; thus, other important recent alterations in suicidal ideation or behaviors may be missed. The study also had several notable strengths: participants recruited from a variety of primary and psychiatric care settings, limited exclusion criteria, inclusion of participants with suicidal histories and current ideation, minority representation, assessments of multiple risk factors over several key psychosocial and clinical domains, and carefully monitored measurement-based care with 3 well-established treatment arms.

In conclusion, the treatment of adults with nonpsychotic, chronic, and/or recurrent MDD was as effective and well tolerated in participants with or without suicidal ideation. For participants with baseline ideation, treatment with any of the 3 therapies was much more likely to be associated with decreases than increases in ideation. The combination of bupropion-SR and escitalopram had a particularly robust effect on reducing suicidal ideation. This novel finding begs for replication with a hypothesis-driven, prospective, large, randomized, controlled study. This study's findings argue for an overall protective effect of antidepressant medications that alleviates depressive symptoms and reduces suicidal thoughts.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), escitalopram (Lexapro and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), venlafaxine (Effexor and others).

Author affiliations: Department of Psychiatry, University of California San Diego and VA Healthcare System, La Jolla, California (Dr Zisook); Department of Psychiatry and Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California (Dr Lesser); Department of Psychiatry (Dr Lebowitz) and Department of Family and Preventive Medicine (Dr Kallenberg), University of California, San Diego; Duke-National University of Singapore, Singapore (Dr Rush); Epidemiology Data Center, Graduate School of Public Health, University of Pittsburgh, Pennsylvania (Dr Wisniewski and Mr Luther); Depression Clinical and Research Program, Massachusetts General Hospital, Boston (Drs Nierenberg and Fava); and Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas (Drs Morris and Trivedi).

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