SSRI Versus Bupropion Effects on Symptom Clusters in Suicidal Depression: Post Hoc Analysis of a Randomized Clinical Trial

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ABSTRACT

Objective: Identifying the depression symptoms most closely associated with suicidal thoughts and which medications provide the fastest depression relief may help suicide prevention.

Method: Post hoc analysis of data from a randomized, double-blind, 8-week clinical trial of the selective serotonin reuptake inhibitor paroxetine controlled release (n = 36) versus the norepinephrine-dopamine reuptake inhibitor bupropion extended release (n = 38) was conducted in patients with *DSM-IV* major depressive disorder and past suicide attempt or current suicidal thoughts. Treatment effects on Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory symptom clusters were compared. We hypothesized that paroxetine would demonstrate a superior effect on nonsuicidal, affective/cognitive depression symptom clusters that our prior work found to be associated with suicidal thoughts and attempts. Data were collected from February 2005 to January 2010.

Results: There was a treatment main effect on HDRS psychic depression (depressed mood, guilt, retardation, helpless, hopeless, worthless) (estimate = −2.2; 95% CI, −3.2 to −1.1; $t_{67.16} = -4.01$; $P < .001$), one of the clusters most strongly correlated to suicidal ideation. The net drug effect demonstrated that mean psychic depression score was 2.2 points lower after 1 week of paroxetine compared to bupropion treatment. The significance level of this effect was $P < .001$ at weeks 1 and 2, $P = .012$ at week 3 and $P = .051$ at week 4. Results for other depression scale factors were nonsignificant ($P > .05$).

Conclusions: The results require replication but suggest a pathway by which selective serotonin reuptake inhibitor treatment may exert a stronger effect compared with norepinephrine-dopamine reuptake inhibitor treatment on reduction of suicidal thoughts during initial weeks of pharmacotherapy in these higher risk patients.

Trial Registration: ClinicalTrials.gov identifier: NCT00429169.

J Clin Psychiatry 2013;74(9):872–879

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Submitted: *July 5, 2012; accepted December 19, 2012 (doi:10.4088/JCP.12m08000).*

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Suicide, which is most often associated with depressive disorders,[1,2] and suicide attempts cause substantial loss of life and suffering and cost an estimated $33 billion yearly in the United States.[3,4] Little change in the suicide rate, from 10 deaths per 100,000 persons in 1955 to 11 per 100,000 in 2005,[5] shows the lack of progress on prevention in the past half century.

Depression predicts suicide attempts via its effect on suicidal ideation.[6] Ninety percent of unplanned and 60% of planned first attempts are reported to occur within a year of ideation onset.[7] Clinicians assess suicidal ideation because it predicts attempts[8] and suicide.[9] Gibbons et al[10] reported that antidepressants reduce suicidal ideation in adults mainly by reducing depression severity. Better understanding of how depression leads to suicidal thoughts and which treatments provide the fastest relief may enhance suicide prevention.

The heterogeneity of depression and the suicidal phenotype is a challenge to research. Suicidal thoughts are a common depressive symptom, and scales like the Hamilton Depression Rating Scale (HDRS)[11] and Beck Depression Inventory (BDI)[12] contain suicide items. However, global depression severity relates only modestly to suicidal behavior, raising the question as to which aspects of depression psychopathology are most closely related to suicidal ideation and behavior.[13–15]

The HDRS and BDI are multidimensional scales comprising up to 7 symptom clusters or factors.[16–19] Antidepressant clinical trials[20–25] have investigated treatment effects on these factors. We found that depressed suicide attempters (N = 296) exhibited greater severity on a BDI self-blame factor compared to nonattempters.[26] Our study extracted 5 factors from the 24-item HDRS and 3 from the BDI.[26] In agreement with other reports,[16–18,27–30] both scales had a major affective/cognitive factor and minor factors representing somatic/vegetative or motivational symptoms.

In a follow-up study[32] of an overlapping but larger depressed sample (N = 400), the factors most correlated to suicidal thoughts, measured with the Scale for Suicide Ideation,[31] were psychic depression (HDRS), subjective depression (BDI), and self-blame (BDI), while somatic symptoms had little or no association. Assessment of symptom clusters in antidepressant clinical trials may reveal treatment effects on depression features related to the severity of suicidal thoughts.

In our prior report[33] on a randomized, double-blind, clinical trial of paroxetine (n = 36) versus bupropion (n = 38) in depressed patients with past suicide attempt or current suicidal ideation, we found that patients with greater baseline levels of suicidal ideation experienced greater acute improvement in suicidal thoughts and total depression score on paroxetine compared with bupropion. Selective serotonin reuptake inhibitors (SSRIs), including paroxetine, primarily enhance serotonin neurotransmission, while bupropion is a norepinephrine-dopamine reuptake inhibitor (NDRI) with minimal (or no) direct effects on serotonin.[34] Understanding the reasons for this differential drug effect on

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Clinical Points

- In higher suicidal risk patients with major depressive disorder (suicidal ideation or past attempt), change in suicidal ideation is more strongly associated with change in affective/cognitive symptoms as compared to somatic/neurovegetative symptoms.
- Controlled-release paroxetine appears to have a modest advantage, compared to extended-release bupropion, in reducing affective/cognitive depression symptoms, which are the symptoms most closely associated with suicidal ideation.
- The results require replication but suggest that selective-serotonin reuptake inhibitor therapy may have a modest advantage over norepinephrine-dopamine reuptake inhibitor therapy for reducing suicidal ideation via faster reduction of core affective/cognitive depression symptoms in the early weeks of treatment.

suicidal ideation could potentially enhance clinical care for suicidal patients.

In this study, we used these clinical trial data[33] to investigate the relationship of treatment to change in the HDRS and BDI depression factors examined in our prior work.[26,32] We hypothesized that differential drug effects would be observed on the depression factors most strongly associated with suicidal ideation,[32] ie, that the HDRS psychic depression, BDI subjective depression, and BDI self-blame factors would improve more with paroxetine compared to bupropion.

METHOD

Patients

Detailed trial methods and primary results of our prior study have been reported elsewhere.[33] Briefly, patients 18 to 75 years old with current *DSM-IV* major depressive disorder (MDD), a score of 16 or greater on the HDRS-17,[11] and a past suicide attempt, current suicidal ideation, or both were eligible. Minimum ideation for nonattempters was a score of 2 or greater on HDRS item 3 (suicide): "wishes to be dead or has any thoughts of possible death to self."[11] Exclusions were bipolar disorder, psychosis, anorexia or bulimia nervosa; current SSRI or bupropion use for other indications (eg, anxiety); drug or alcohol dependence within 6 months; unstable medical illness; contraindication to either drug; nonresponse to 3 other SSRIs, paroxetine, or bupropion in the last 2 years; pregnancy or lactation; and lack of capacity to consent.

The trial was conducted at Columbia University Medical Center-New York State Psychiatric Institute. Data were collected from February 2005 to January 2010. Participants were recruited via media, internet, and clinician referral. After complete description of the study to subjects, written informed consent was obtained. The study was registered on ClinicalTrials.gov (identifier: NCT00429169).

Treatment

Patients, treating psychiatrists, and clinical raters were blind to treatment assignment. Patients met weekly for 8 weeks with a psychiatrist for pharmacotherapy and a psychologist for ratings. Daily dose was (weeks 1–2) paroxetine controlled release 25 mg or bupropion extended release 150 mg; (weeks 3–4) paroxetine controlled release 37.5 mg or bupropion extended release 300 mg, and (weeks 5–8) optional increase to paroxetine controlled release 50 mg or bupropion extended release 450 mg, if clinically indicated. Concomitant benzodiazepine for anxiety or zolpidem for insomnia were allowed. Patients with inadequate response or intolerable side effects were switched to open treatment.

Outcome and Measures

Raters were PhD- or masters-level psychologists. Axis I and II diagnoses were made by using the Structured Clinical Interviews for *DSM-IV* Axis I and II Disorders (SCID-I and SCID-II).[35,36] Suicide attempts were assessed with the Columbia Suicide History Form.[37] Diagnostic and suicide attempt classifications were made in a weekly, interdisciplinary consensus conference. Depressive symptoms were assessed at baseline and weekly with the 24-item HDRS[11] and the BDI.[12] Suicidal ideation was assessed at baseline and weekly with the clinician-rated Scale for Suicide Ideation.[31]

Main outcomes in this study were the 5 HDRS and 3 BDI factors analyzed in our prior study.[26] In this article, we use the terms "factor" and "symptom cluster" interchangeably. Because our goal was to investigate nonsuicide depression symptom clusters not including suicidal ideation, we excluded the suicide item from the HDRS psychic depression factor where it loaded in our prior study.[26]

Factor compositions with the HDRS are as follows: psychic depression—depressed mood, guilt, retardation, helplessness, hopelessness, and worthlessness; loss of motivated behavior—work and interests, appetite, libido, and weight loss; anxiety—agitation, psychic anxiety, somatic anxiety, and hypochondriasis; disturbed thinking—lack of insight, depersonalization, paranoia, and obsessions/compulsions; sleep disturbance—early, middle, and late insomnia items; and unassigned items—energy and diurnal variation.

Factor compositions with the BDI are as follows: subjective depression—sadness, pessimism, dissatisfaction, interest in others, indecisiveness, body image, work, energy, and libido; self-blame—sense of failure, guilt, feeling punished, self-dislike, and self-criticism; somatic complaint—early awakening, appetite, and weight loss; and unassigned items—suicidal thoughts, crying, irritability, and somatic concern.

Statistical Methods

We used SPSS version 18 (IBM Corp, Armonk, New York) for all analyses. We created plots of mean score on each HDRS and BDI factor by time and treatment group (Figures 1 and 2). Since this analysis involves correlated longitudinal data with repeated measures, we used mixed-effects regression models[38] to analyze each factor. Data were examined for influential or outlying data points. We adjusted for potential baseline differences in factor scores between treatment groups by including baseline severity of each factor as a predictor in the model of that factor. The time variable was the natural log of study week. Baseline

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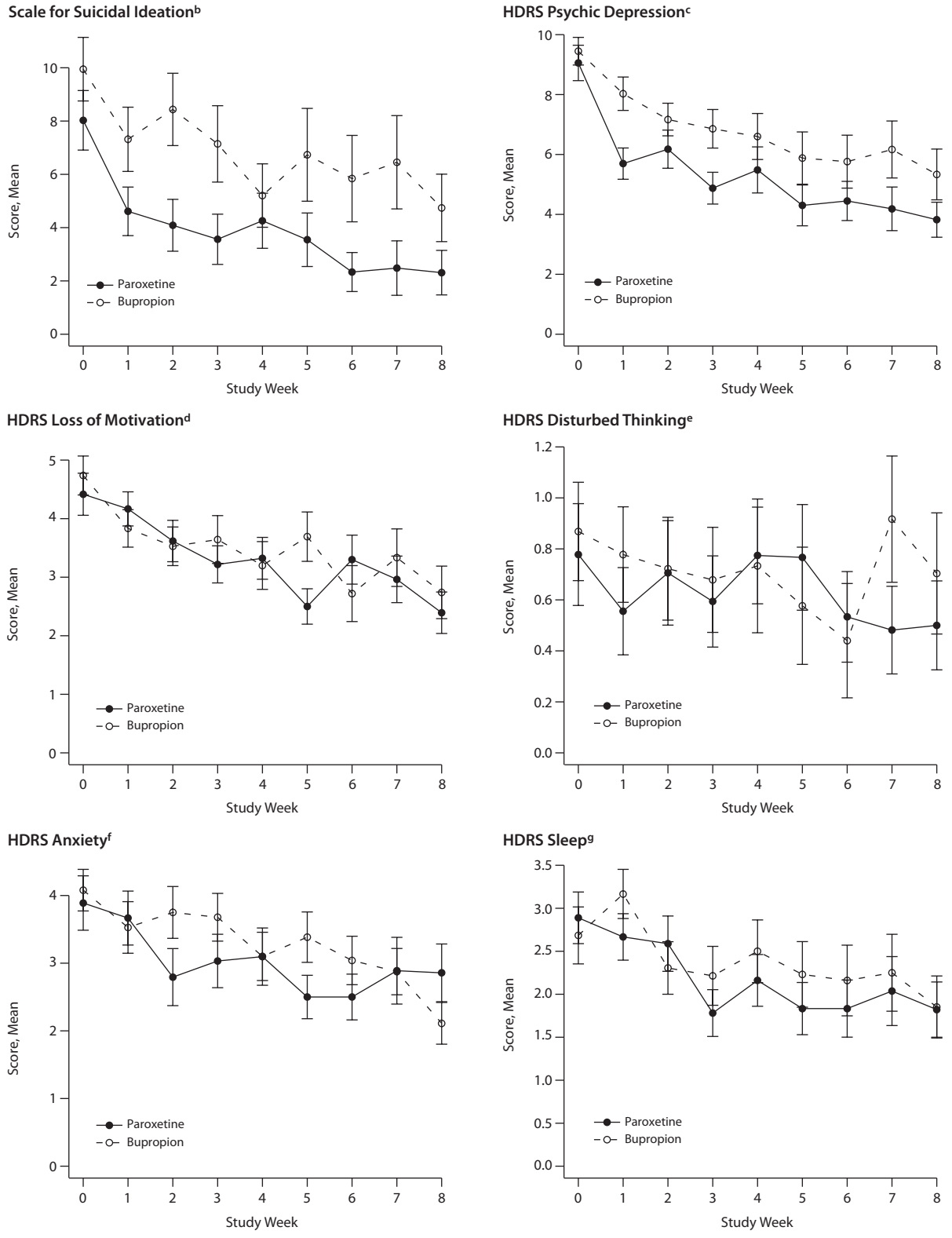
Figure 1. Depressed Patients' Mean Score of Suicidal Ideation and 24-Item Hamilton Depression Rating Scale (HDRS-24) Factors by Study Week and Treatment With Paroxetine Controlled Release Versus Bupropion Extended Release[a]



[a]Error bars represent standard error of the mean. Paroxetine (n = 36) and bupropion (n = 38) sample sizes decreased over time because of drop-out (see Table 1). [b]Suicidal ideation was measured by using the Scale for Suicide Ideation. [c]Factor content for psychic depression includes depressed mood plus guilt plus retardation plus helplessness plus hopelessness plus worthlessness. [d]Factor content for loss of motivation includes work/activities plus appetite plus libido plus weight loss. [e]Factor content for disturbed thinking includes lack of insight plus depersonalization/derealization plus paranoia plus obsessions/compulsions. [f]Factor content for anxiety includes agitation plus psychic anxiety plus somatic anxiety plus hypochondriasis. [g]Factor content for sleep includes insomnia early plus insomnia middle plus insomnia late.

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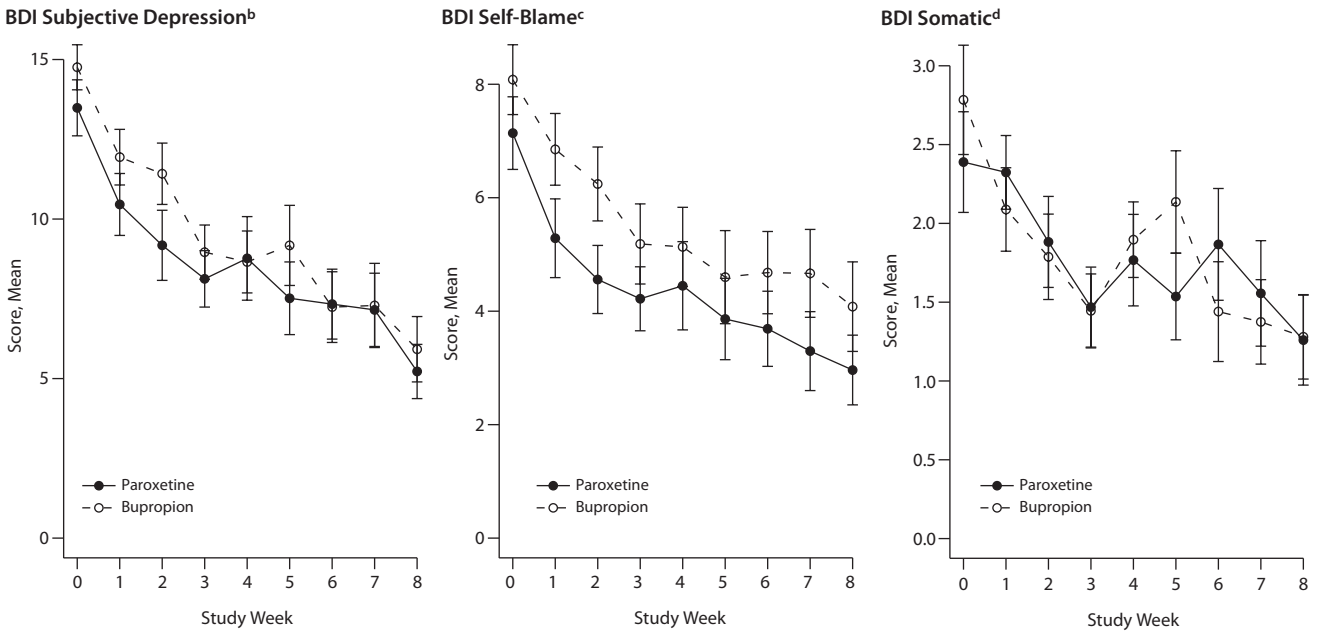
Figure 2. Depressed Patients' Mean Score on Beck Depression Inventory (BDI) Factors by Study Week and Treatment With Paroxetine Controlled Release Versus Bupropion Extended Release[a]



[a]Error bars represent standard error of the mean. Paroxetine (n = 36) and bupropion (n = 38) sample sizes decreased over time because of drop-out (see Table 1). [b]Factor content for subjective depression includes sadness plus pessimism plus lack of satisfaction plus loss of interest plus indecisiveness plus appearance plus work plus tiredness plus libido. [c]Factor content for self-blame includes failure plus guilt plus feel punished plus disappointed in self plus self-blame. [d]Factor content for somatic includes disturbed sleep plus appetite plus weight loss.

inpatient and attempter status were terms in all models, since randomization was stratified on those variables. The model for each factor included fixed effects for treatment, inpatient status at randomization (yes/no), history of past suicide attempt (yes/no), baseline severity of the factor, natural log(study week), and an interaction term of treatment × natural log(study week). The model tested for each factor was

$$\text{Factor}_{\text{during treatment}} = \text{treatment} + \text{inpatient} + \text{attempt} + \text{factor}_{\text{baseline}} + \log(\text{study week}) + \text{treatment} \times \log(\text{study week}).$$

To estimate the effect of treatment on each factor, we calculated predicted differences in factor scores between drug groups at each time point, assuming other variables were constant. These point estimates represent the net effect of the drug on each depression factor. Differences in predicted scores between treatment groups were tested.

We next analyzed the entire sample (N = 74), combining the drug groups, to explore whether change in suicidal ideation, irrespective of treatment, was associated with change in either the symptom clusters or the overall HDRS or BDI scores. We computed Spearman correlations between change (final minus baseline score) in suicidal ideation (Scale for Suicide Ideation) and change in score on the depression factors or total HDRS and BDI scales.

RESULTS

As previously reported, the treatment groups did not differ in baseline sociodemographic, clinical, or suicidal characteristics.[33] The treatment groups did not differ in study attrition rate, medication adherence, side effects, or frequency of concomitant benzodiazepine or zolpidem, although benzodiazepine dose was higher in the bupropion-treated group.[33] Figures 1 and 2 illustrate the trajectories of Scale for Suicide Ideation score and the HDRS and BDI depression factors by treatment during the trial.

Table 1. 24-Item Hamilton Depression Rating Scale Psychic Depression Factor Score at Baseline and Clinical Trial Weeks 1–8

	Paroxetine Controlled Release			Bupropion Extended Release		
Study Week Completed	n	Mean	SD	n	Mean	SD
Baseline	36	9.1	3.5	38	9.4	2.8
Week 1	36	5.7	3.1	36	8.0	3.3
Week 2	34	6.2	3.7	36	7.2	3.3
Week 3	32	4.9	3.0	28	6.9	3.4
Week 4	31	5.5	4.3	30	6.6	4.2
Week 5	30	4.3	3.7	25	5.9	4.4
Week 6	29	4.4	3.5	25	5.8	4.4
Week 7	27	4.2	3.8	24	6.2	4.7
Week 8	28	3.8	3.1	27	5.3	4.4

HDRS Psychic Depression

Table 1 summarizes the sample size, mean score, and SD for this factor at each time point. The mixed-effects model of the 8-week treatment showed a main effect on the psychic depression factor (estimate = −2.2; 95% CI, −3.2 to −1.1; $t_{67.16} = -4.01$; $P < .001$). Compared to bupropion, paroxetine treatment was, on average, associated with greater improvement in psychic depression symptoms (depressed mood,

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Table 2. Predicted Differences[a] Between Treatment Groups[b] in Hamilton Depression Rating Scale (HDRS) Psychic Depression Factor Score During Clinical Trial Weeks 1–8[c]

Study Week Completed	Predicted Difference in HDRS Psychic Depression Score	95% CI	Standard Error	*z*	*P*
Week 1	−2.2	−3.3 to −1.1	0.54	−4.01	<.001
Week 2	−1.6	−2.6 to −0.6	0.49	−3.30	<.001
Week 3	−1.3	−2.3 to −0.3	0.53	−2.52	.012
Week 4	−1.1	−2.2 to 0.0	0.58	−1.95	.051
Week 5	−0.9	−2.1 to 0.3	0.63	−1.55	.122
Week 6	−0.8	−2.1 to 0.5	0.67	−1.25	.213
Week 7	−0.7	−2.1 to 0.7	0.71	−1.02	.309
Week 8	−0.6	−2.1 to 0.8	0.74	−0.83	.404

[a]Predicted difference (paroxetine group – bupropion group) is based on the model equation:

$Factor_{during\ treatment}$ = treatment + inpatient + attempt + $factor_{baseline}$ + log(study week) + treatment × log(study week).

[b]Paroxetine controlled release (n = 36) versus bupropion extended release (n = 38).

[c]HDRS psychic depression factor includes depressed mood plus guilt plus retardation plus helplessness plus hopelessness plus worthlessness item sum.

guilt, retardation, helplessness, hopelessness, worthlessness). There was a treatment-by-time interaction, but the effect size was two-thirds smaller than the main effect (estimate = 0.74; 95% CI, 0.005 to 1.5; $t_{61.01} = 2.01$, $P = .048$). The net treatment effect (main effect plus interaction) on this symptom cluster showed greater improvement on paroxetine during the first month of treatment (Table 2). Predicted psychic depression scores were lower for patients randomized to paroxetine compared to bupropion, with the difference largest after 1 week (2.2 points) and statistically significant through week 3, with a strong trend at week 4 (Table 2).

Other Depression Factors

The net treatment effect on the BDI self-blame factor (sense of failure, guilt, feeling punished, self-dislike, self-criticism/blame) was not significant at week 1 (estimate = −1.1; 95% CI, −2.4 to 0.22; SE = 0.68; $z = -1.64$; $P = .101$), with larger *P* values at subsequent time points. For HDRS loss of motivation (work/interests, appetite, libido, weight loss), the treatment main effect was not significant ($P = .37$) and the treatment-by-time interaction showed a trend toward greater improvement on paroxetine compared to bupropion (estimate = −0.49; 95% CI, −0.98 to 0.001; $t_{62.13} = -1.99$; $P = .051$). Models of the other factors (HDRS anxiety, disturbed thinking, or sleep disturbance and BDI subjective depression or somatic complaint) showed no differential treatment effects ($P > .1$).

Baseline Inpatient and Past Attempter Status

Inpatient status at baseline was not significant in any model ($P > .05$). Past suicide attempt was not significant in any model, except for BDI somatic complaint (early awakening, appetite loss, weight loss), where past attempters, on average, had a 0.71 point higher (worse) score than non-attempters during treatment (estimate = −0.71; 95% CI, −1.2 to −0.3; $t_{61.65} = -3.13$; $P = .003$).

Suicidal Ideation Change: Correlations With Change in Depression Scales and Factors

Irrespective of treatment, change in suicidal ideation (Scale for Suicide Ideation score) correlated comparably with change in total score on the 24-item HDRS (Spearman $\rho = 0.44$, $P < .001$) and BDI (Spearman $\rho = 0.43$, $P < .001$). Change in suicidal ideation correlated with change in factor scores in decreasing order of strength as follows: BDI subjective depression ($\rho = 0.42$, $P < .001$), BDI self-blame ($\rho = 0.36$, $P = .002$), HDRS psychic depression ($\rho = 0.29$, $P = .012$), BDI somatic complaint ($\rho = 0.28$, $P = .02$), HDRS disturbed thinking ($\rho = 0.27$, $P = .02$), and HDRS sleep (ρ 0.26, $P = .03$). Suicidal ideation change did not correlate with change in the HDRS loss of motivation ($\rho = 0.15$, $P = .19$) or anxiety factors ($\rho = 0.17$, $P = .16$).

DISCUSSION

Depressed patients with past suicide attempt or current suicidal thoughts treated with paroxetine had a superior response compared to bupropion on the HDRS psychic depression factor during the first month of treatment. Response of other HDRS and BDI factors did not differ by treatment.

The results partially support our hypothesis that an SSRI, which appears potentially advantageous compared to bupropion for reducing suicidal ideation among those most suicidal at baseline,[33] would also be superior for nonsuicide depression symptoms that are more closely associated with suicidal ideation.[32] If confirmed, this finding would help guide treatment choice for more suicidal patients in whom faster reduction of suicidal risk would be a major clinical advantage.[10]

Our prior studies[26,32] suggest that suicide attempts and ideation are more strongly associated with core affective/cognitive depression symptoms than with somatic/neurovegetative symptoms. The results from this independent clinical trial sample, irrespective of treatment, are consistent with our prior work. Beck et al[39] reported that suicidal thoughts are more strongly associated with psychological compared to somatic symptoms in inpatients with a recent suicide attempt (N = 247) and inpatients without an attempt but with suicidal thoughts (N = 188).[27] They found similar factor structures for the BDI in both samples, suggesting that the association of suicidal thoughts with nonsuicide depressive symptoms is independent of past attempt history.[27]

While the above observational studies[26,27,32,39] and this clinical trial suggest a stronger association of suicidal thoughts with affective/cognitive symptoms relative to somatic symptoms of depression, a simple dichotomy would be overstated. The HDRS psychic depression factor contains 5 affective/cognitive items plus retardation, a psychomotor feature.[26] It is noteworthy that, along with guilt, 2 of these 6 items are features of melancholia, which, we reported, is associated with more lethal past suicide attempts and greater prospective attempt risk than nonmelancholic depression.[40] In the present study, attempters had higher scores for BDI somatic complaint, which comprises 3 melancholic features

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(early awakening, appetite loss, weight loss), but there was no differential drug effect on this cluster. The treatment effect for the HDRS sleep factor, including early awakening, appeared to favor paroxetine but was not statistically significant ($P = .103$), possibly because of insufficient power. Sleep disturbance, especially insomnia, is a risk factor for suicidal ideation and suicide.[9,41–44]

Symptom clusters within depression rating scales may be useful in the identification and treatment of depressed patients at higher risk for suicidal behavior. Evidence that severity of these symptom clusters is associated with relative regional activity in discrete brain regions[45] may explain why only some factors are related to suicidal behavior in depressed patients. Our results suggest superior response of affective/cognitive depression symptoms with SSRI as compared to NDRI treatment. The findings require replication, but suggest a possible mechanism for the reported advantage of SSRI for suicidal ideation.[33]

We did not find evidence to support our hypotheses that the BDI subjective depression and self-blame factors would improve more with paroxetine relative to bupropion. The lack of a differential treatment effect for these factors may be partly explained by the self-report nature of the BDI, whereas the HDRS was rated by clinicians blind to treatment group. Several studies found the HDRS to be more sensitive than the BDI to change during treatment (reviewed in Bagby et al[17]). It is noteworthy that the HDRS psychic depression factor contains the "hopelessness" and "guilt" items, which overlap, respectively, with the BDI subjective depression and self-blame factors.

The lack of a differential treatment effect on HDRS anxiety is surprising, given the common use of SSRIs to treat anxiety disorders. The relationship of anxiety to suicidal ideation and behavior is complex. Anxiety predicted suicidal behavior in some studies.[6,9,46,47] Others, including ours, failed to find such an association or found a protective effect after adjusting for other psychiatric disorders.[26,48–54]

Our results are strongest for the first month of treatment. However, Trivedi et al[24] noted the "crucial early stage (first 4 weeks)" of MDD treatment in a 12-week nefazodone trial. They demonstrated that the pattern of change in 17-item HDRS symptom clusters during the first month discriminated late responders from nonresponders better than total HDRS score.[24] These findings have particular relevance for suicidal patients in whom it is important to relieve suicidal ideation quickly, and early signs of treatment efficacy would aid clinicians.

The main limitation of this study is the relatively small sample size. However, depressed suicide attempters and ideators are a selected population often excluded from clinical trials. The study is a post hoc analysis in that the regression model was not prespecified, although investigation of depression scale factors was a preplanned exploratory aim. The 8-week treatment is typical for a short-term study and more than covered the differential drug effect for HDRS psychic depression, which was modest and statistically significant until week 4.

An asymmetric drug titration schedule may have contributed to the results. Paroxetine controlled release, the formulation used in our study, showed antidepressant efficacy for some patients at 12.5 mg daily in one 8-week trial (N = 447), though the customary dose range is 25–62.5 mg daily.[55] Many clinicians do not consider bupropion 150 mg daily to be a minimally effective dose, though an 8-week randomized controlled trial found bupropion sustained release 150 mg (N = 121) versus 300 mg (N = 120) daily to have equal antidepressant efficacy in moderate to severely depressed patients and, both were superior to placebo (N = 121).[56] A meta-analysis by Papakostas and Fava[57] suggests that placebo-like effects, a proxy for expectation of improvement, may be greater in trials without a placebo arm. While nonspecific effects could partly explain our findings, their meta-analysis suggests it is more likely these would have biased our results toward the null, making the differences that were found more convincing.

Antidepressant treatment effect sizes appear to be smaller in routine clinical practice than in efficacy trials.[58] Our study may be considered an effectiveness trial in that the sample was selected for increased suicidal risk, and comorbidities, such as substance abuse and anxiety disorders, were permitted, making it more applicable to community practice. Given the lack of evidence-based treatments to reduce suicidal risk, even a modestly greater reduction of suicidal ideation,[33] and of the depression symptoms most strongly associated to it, even for 1 month, would be meaningful for suicidal, depressed patients. It also raises hope for other treatments that may outperform those in the current study in reducing key components of depression related to suicidal ideation.

In summary, the results suggest that, in depressed patients with suicidal thoughts or past attempt, paroxetine treatment, more than bupropion, reduced the depression symptoms most strongly associated with suicidal ideation for up to 1 month of follow-up. The findings require replication but may point to a mediating pathway for the potential advantage of SSRI over NDRI therapy in depressed patients with greater levels of suicidal ideation.[33] Our analysis also suggests possible symptom targets—namely, the subjective mood symptoms of depression—for the development of additional treatments that are advantageous for reducing suicidal thoughts.

Drug names: bupropion (Aplenzin, Wellbutrin, and others); paroxetine (Paxil, Pexeva, and others); zolpidem (Ambien, Edluar, and others).

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Potential conflicts of interest: **Dr Burke** receives royalties for use of the Columbia-Suicide Severity Rating Scale (C-SSRS). **Dr Oquendo** receives royalties for use of the C-SSRS; has received financial compensation from Pfizer for the safety evaluation of a clinical facility unrelated to this study; has received a grant from Eli Lilly to support a year's salary for a Lilly Suicide Scholar; and has received unrestricted educational grants and/or lecture fees from Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Otsuko, Pfizer, Sanofi-Aventis, and Shire. Her family owns stock in Bristol-Myers Squibb. **Dr Mann** received past research grants for unrelated brain imaging studies from GlaxoSmithKline and Novartis and receives royalties from the Research Foundation for Mental Hygiene for use of the C-SSRS, which was not used in this study. **Drs Grunebaum**, **Keilp**, and **Ellis**; **Ms Sudol**; and **Mr Bauer** have no conflicts of interest related to this study.

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Funding/support: This work received support from a NARSAD Young Investigator grant (Dr Grunebaum) and National Institute of Mental Health (NIMH) grant K23 MH076049 (Dr Grunebaum). Other support was received from grants MH48514 and MH62185. Paroxetine controlled release and bupropion extended release pills were donated by GlaxoSmithKline in the study's first 3 years and then purchased with grant funds. Dr Grunebaum received no personal direct support from GlaxoSmithKline for this study.
Role of sponsor: NARSAD, NIMH, and GlaxoSmithKline had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. No pharmaceutical company was involved in the design or conduct of the study, had access to the data, or had any role in its analysis or presentation.

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