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Pilot Randomized Clinical Trial of an SSRI *vs* Bupropion: Effects on Suicidal Behavior, Ideation, and Mood in Major Depression

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Randomized controlled trials in depressed patients selected for elevated suicidal risk are rare. The resultant lack of data leaves uncertainty about treatment in this population. This study compared a serotonin reuptake inhibitor with a noradrenergic/dopaminergic antidepressant in major depression with elevated suicidal risk factors. We conducted a double-blind, randomized, clinical pilot trial of paroxetine ($N = 36$) or bupropion ($N = 38$) in DSM IV major depression with a suicide attempt history or current suicidal ideation. The effects during acute (8 weeks) and continuation treatment (up to 16 weeks) were measured. Main outcomes were suicidal behavior and ideation. The secondary outcome was modified 17-item Hamilton Depression Rating Scale score subtracting the suicide item (mHDRS-17). Treatment was not associated with time to a suicidal event and no treatment main effect or treatment × time interaction on suicidal ideation or mHDRS-17 was found. Exploratory model selection showed modest advantages for paroxetine on: (1) mHDRS-17 ($p = 0.02$); and (2) in a separate model adjusted for baseline depression, for suicidal ideation measured with the Beck Scale for Suicidal Ideation ($p = 0.03$), with benefit increasing with baseline severity. Depressed patients with greater baseline suicidal ideation treated with paroxetine compared with bupropion appeared to experience greater acute improvement in suicidal ideation, after adjusting for global depression. Given the lack of evidence-based pharmacotherapy guidelines for suicidal, depressed patients—an important public health population—this preliminary finding merits further study.
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INTRODUCTION

Suicide results in ~30 000 US deaths and costs an estimated $33 billion annually in addition to immeasurable suffering (Corso *et al*, 2007). Suicide is most often associated with a depressive disorder (Mann *et al*, 2005), but antidepressant clinical trials have generally excluded suicidal patients. Randomized antidepressant trials designed *a priori* to study depressed suicide attempters or ideators are rare, resulting in scant evidence to guide treatment for these elevated risk patients. Most antidepressant trials have not measured suicidal ideation and behavior systematically, leading, in some cases, to contradictory findings from analyses of spontaneously reported adverse events *versus* rating scale data (Hammad *et al*, 2006; Carpenter *et al*, 2011). Elevated risk samples may enhance detection in clinical trials of differential treatment effects on suicidal behavior or ideation, which could advance public health.

The antidepressant section of the American Psychiatric Association Practice Guideline on suicidal patients states, 'non-tricyclic, non-MAOI antidepressants are relatively safe…on overdose,' but offers no other advice (Jacobs *et al*, 2003). No published antidepressant randomized clinical trial, to our knowledge, has *a priori* sought to enroll patients at *elevated* suicidal risk. Suicide attempt history and ideation severity are risk factors for suicide (Meyer *et al*, 2010). Prospective studies show that suicidal ideation increases the risk of attempts and suicide in mood disorders (Oquendo *et al*, 2004a; Fawcett *et al*, 1990). Within 1 year of ideation onset, 90% of unplanned and 60% of planned first suicide attempts occur (Kessler *et al*, 1999).

There is clinical equipoise regarding the effects of predominantly serotonergic *versus* noradrenergic antidepressants on suicidal ideation. Of 10 studies, 5 suggested an advantage for serotonergic drugs (Gonella *et al*, 1990;

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Kasper *et al*, 1995; Sacchetti *et al*, 1991; Montgomery *et al*, 1978; Mahapatra and Hackett, 1997), 4 found similar efficacy (Lapierre, 1991; Judd *et al*, 1993; Möller and Steinmeyer, 1994; Tollefson *et al*, 1994), and 1 (Marchesi *et al*, 1998) suggested a noradrenergic advantage. Most of these relied on one scale item to measure suicidal ideation. None used a dedicated scale administered by independent, blinded raters and none specifically recruited patients with suicidality. Neurobiological depression research targets many putative mechanisms, but clinicians still tend to group antidepressants by predominant monoaminergic effects. Suicidal behavior is associated with serotonin system hypofunction (Mann, 2003); thus, we hypothesized that a serotonin reuptake inhibitor (SSRI) would be more beneficial for suicidal behavior and ideation than a predominantly nonserotonergic antidepressant.

SSRIs and bupropion comprise the five most prescribed US antidepressants (Drug Topics staff, 2010a, 2010b). SSRIs primarily enhance serotonin neurotransmission whereas bupropion is a norepinephrine–dopamine reuptake inhibitor (NDRI) with minimal (or no) direct effects on serotonin (Baldessarini, 2006). Similar antidepressant efficacy of these drugs (Thase *et al*, 2005; Gartlehner *et al*, 2008; Cipriani *et al*, 2009), and their relative safety on overdose, facilitates comparison of effects on suicidal ideation or behavior.

The primary aim of this study was to collect pilot data to explore if an SSRI antidepressant medication would be different from the NDRI, bupropion, for reducing suicidal behavior, ideation, and neuropsychological measures of impulsivity. A secondary outcome was global depression, measured using the 17-item Hamilton Depression Rating Scale after subtracting out the suicide item (mHDRS-17) (Hamilton, 1960). We enrolled depressed patients at elevated suicidal risk, specifically a history of a suicide attempt or current suicidal ideation. We hypothesized that suicidal behavior and ideation would improve more with the SSRI, paroxetine, compared with bupropion. We report here on suicidal behavior, ideation, and mHDRS-17 depressive symptoms. A follow-up paper will report neuropsychological outcomes.

PATIENTS AND METHODS

Patients

Patients 18 to 75 years old with a current episode of DSM IV major depressive disorder, scoring $\geqslant 16$ on the HDRS-17 (all items) (Hamilton, 1960), and who reported *either* a past suicide attempt *or* current suicidal ideation *or both* were eligible. Past attempters without current ideation were eligible. The first eight subjects were enrolled under inclusion criteria requiring a suicide attempt, after which eligibility was changed to include current ideation without past attempt because of challenges in recruitment. The ideation threshold for nonattempters was a score of $\geqslant 2$ on HDRS item 3 (suicide), 'wishes to be dead or has any thoughts of possible death to self' (Hamilton, 1960). Patients with suicide plan or intent were enrolled if they consented to voluntary admission to our research unit. Other risk mitigation strategies included a research psychiatrist on-call at all times, available between time points for consultations and emergencies, and careful ongoing assessment of mood, side effects, and review of procedures to follow if patients became acutely suicidal.

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 three other SSRIs, paroxetine, or bupropion in the past 2 years (at least 2/3 maximum approved dose for $\geqslant 6$ weeks), pregnancy or lactation, and lack of capacity to consent.

This single site trial was conducted at Columbia University Medical Center/New York State Psychiatric Institute. Participants were recruited via local media and internet advertising, and clinician referral. After complete description of the study to subjects, written informed consent was obtained.

Intervention

Patients were randomized to extended-release oral paroxetine or bupropion. Pills were identically over-encapsulated and each vial label had *both* medication names, so that patients did not know which one they were taking, but only whether to take 1, 2, or 3 pills daily.

Participants met with a study psychiatrist for pharmacotherapy and with a psychologist for ratings. Assessments were weekly for 8 weeks, and then monthly for an additional 16 weeks. Daily dose was paroxetine 25 mg or bupropion 150 mg in weeks 1 and 2 and paroxetine 37.5 mg or bupropion 300 mg in weeks 3 and 4. After 4 weeks, the protocol permitted an increase to paroxetine 50 mg or bupropion 450 mg daily, if indicated. Concomitant benzodiazepine (up to lorazepam 6 mg daily or its equivalent) for anxiety or zolpidem for insomnia were allowed. The 16-week continuation phase remained blinded if the patient had a satisfactory response to the randomized drug. Patients with an inadequate response or intolerable side effects were switched to open treatment.

Outcome and Measures

Research assessors were PhD or masters level psychologists. Axis I and II diagnoses were made using the Structured Clinical Interview for DSM-IV (SCID I and II) (Spitzer *et al*, 1990; First *et al*, 1996). Diagnostic and suicide attempt classifications were made in a weekly consensus conference including psychologists and psychiatrists. Suicidal events were assessed with the Columbia Suicide History Form (Oquendo *et al*, 2003), and were classified as major (an attempt) or minor (increase in ideation requiring clinical intervention, such as hospitalization) (Oquendo *et al*, 2004b).

The clinician-rated Scale for Suicidal Ideation (SSI) (Beck *et al*, 1979) was used weekly for 8 weeks, and then monthly. It has 19 items scaled 0 (least severe) to 2 (most severe) and total score is the sum, ranging from 0 to 38 (Beck *et al*, 1979). Items measure frequency, intensity, and attitudes toward suicidal thoughts, feelings of control over them, and suicide plans (Beck *et al*, 1979). Mean score in 90 inpatients hospitalized for suicidal ideation was 9.4 ± 8.4 *versus* 4.4 ± 5.8 in outpatients (Beck *et al*, 1979).

Global depressive symptoms, not hypothesized to differ by drug group, were assessed weekly for 8 weeks and then monthly with the HDRS-17 (Hamilton, 1960). Raters were trained by in-person observation and participated in weekly reliability monitoring using video and audio tapes. The intraclass correlation for the HDRS-17 was 94% and for the SSI was 97%.

Study psychiatrists measured treatment nonadherence since the last visit by asking patients to estimate proportion of missed doses. Side effects were assessed with the Treatment Emergent Symptom Scale (Vinar, 1971).

Sample Size

The study was powered for $N=50$ subjects per group based on naturalistic treatment data from our clinic showing more aggression, a correlate of suicidal behavior (Mann *et al*, 1999), using the Brown Goodwin Aggression Inventory (Brown *et al*, 1979), during 3-month follow-up of depressed subjects on bupropion ($N=5$) *vs* SSRI ($N=27$). An interim data analysis with $N=68$ subjects was performed to generate data for a grant application without identifying the treatment groups. This showed a main effect of treatment *and* an interaction of treatment with baseline suicidal ideation severity on follow-up ideation. After consulting with clinical colleagues, statisticians, and the IRB, a decision was made to stop enrollment. Here we report an analysis of the complete data set, which included $N=74$ subjects, as enrollment continued during the period of the interim analysis. The data set was considered complete when all subjects who enrolled at the time the recruitment was suspended had finished participation.

Randomization and Blinding

Patients, psychiatrists, and assessors were blind to treatment. The randomization sequence was generated by a pharmacist separate from the research team and was stratified on: (1) inpatient *versus* outpatient and (2) lifetime history of suicide attempt (yes/no). Random numbers were generated using Excel 5.0 Data Analysis ToolPak (Microsoft). Within each stratum, subjects were randomized in blocks of four (AABB, ABAB, BABA, and BBAA) so that allocation was 1 : 1 between groups. Unblinding occurred after all subjects had completed study treatment.

Statistical Methods

Our primary analysis investigated treatment effects on suicidal behavior and ideation. The analysis was modified intention to treat: (1) we excluded one patient from the paroxetine arm who was randomized and never returned for any assessment and (2) we excluded three other patients (two in the bupropion arm and one in the paroxetine arm) because of ineligibility discovered after randomization, which is justified under the intention-to-treat principle as ineligibility voided their enrollment (Figure 1). We used SPSS version 17 (SPSS) and SAS (SAS Institute, Cary, NC). Univariate tests compared groups on baseline characteristics, time in study, and concomitant medications. Kaplan–Meier survival analysis tested the association of treatment group with time to the first suicidal 'event' during the 24 weeks.

We modeled follow-up suicidal ideation using generalized least squares regression, a variant of mixed models, for correlated longitudinal data (Pinheiro and Bates, 2000). We modeled the acute and continuation phases separately. We anticipated smaller changes in suicidal ideation at later time points, and hence used a log transformation of time as a covariate. We compared and selected covariance structure using the Bayesian Information Criterion (BIC), which balances model fit and complexity (Rao and Wu, 2001). We examined residuals *vs* predicted values for influential data points.

Baseline suicidal ideation score ($SSI_{baseline}$) was a covariate in all models of follow-up ideation, a method used widely in longitudinal models for randomized trials (Fitzmaurice *et al*, 2004). We also adjusted for baseline mHDRS-17. Continuation phase suicidal ideation scores tended to be low (63% were 0), and hence we used a natural log transformation of the score after adding 1.

Exploratory model selection used backward elimination of interaction terms based on the BIC. Assuming other variables to be equal, we computed mean predicted differences in follow-up suicidal ideation by treatment. Standard errors used to compute p-values were confirmed with the bootstrap method (Efron and Tibshirani, 1993). Comparison of concomitant medication use between treatment groups was preplanned, but without a specific hypothesis.

RESULTS

Study Patients

The first patient enrolled in February 2005 and the last in July 2009 with follow-up completed in January 2010. Figure 1 summarizes patient flow. The analysis included 38 subjects randomized to bupropion and 36 to paroxetine. Treatment groups did not differ in baseline sociodemographic, clinical, or suicidal characteristics (Table 1).

Follow-Up and Exposure to Intervention

Week 1–8 attrition was 32% overall and did not differ by treatment. A total of 9/36 paroxetine and 15/38 bupropion subjects did not complete 8 weeks of randomized treatment ($\chi^2=1.77$, df $=1$, $p=0.18$). In addition, 29/38 (76%) on bupropion and 24/36 (67%) on paroxetine did not complete 24 weeks of randomized treatment. Some patients who had to be withdrawn into open treatment because of side effects or nonresponse switched to the drug from the other treatment arm, and consequently we emphasize results from the acute phase. Figure 1 lists reasons for attrition.

Time to last assessment during the 24 weeks did not differ between groups ($Mean_{paroxetine}=17.9\pm8.1$, $Mean_{bupropion}=16.8\pm8.8$ weeks; Wilcoxon $Z=-0.59$, $p=0.55$). The median dose of paroxetine was 37.5 mg (mean $=33.7\pm14.3$) and for bupropion was 300 mg (mean $=275.3\pm135.8$).

Suicidal Events

There were a total of 10 suicidal events during the 24-week follow-up: 1/10 was an acetaminophen overdose requiring

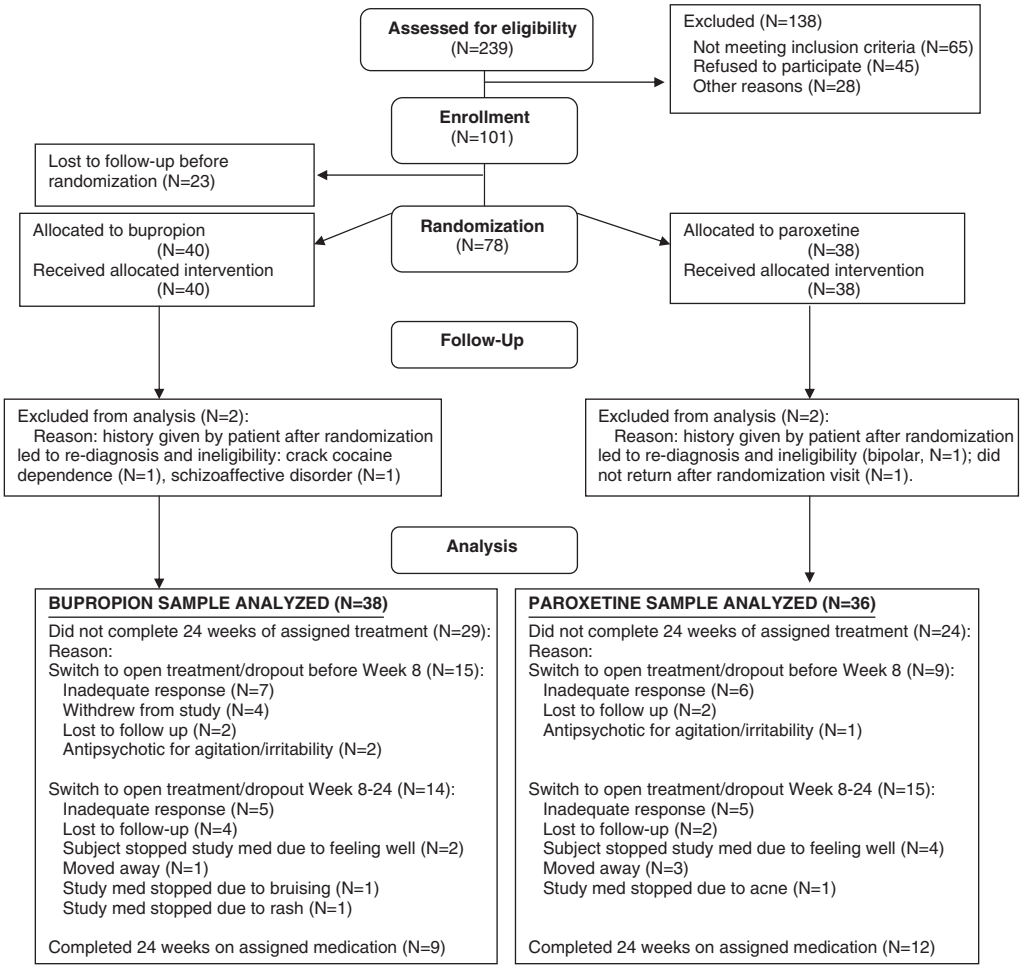

Figure 1 Flow diagram of progress through phases of the parallel randomized trial of two groups (enrollment, intervention allocation, follow-up, and data analysis) (Schulz *et al*, 2010).

medical admission for treatment of a hepatotoxic blood level followed by transfer to a psychiatric unit; 3/10 involved increased ideation or behavior by inpatients prompting initiation of close observation or withdrawal from the protocol with prescription of quetiapine for agitation; 6/10 were increased ideation of which 4 led to inpatient admission. In the paroxetine arm, four subjects accounted for one event each. In the bupropion arm, one subject had three events (but was counted only once in the survival analysis of time to the first event) and three subjects had one event each. Treatment was not associated with time to the first suicidal event during the week 1–8 acute phase (log rank $\chi^2 = 1.03$, df $= 1$, $p = 0.31$) or the complete 24-week follow-up (log rank $\chi^2 = 0.17$, df $= 1$, $p = 0.68$).

Suicidal Ideation: Acute Phase (Weeks 1–8)

Baseline suicidal ideation severity (mean $= 9.0$, SD $= 7.1$) did not differ by treatment (Table 1). Suicidal ideation during acute treatment had high variability, making interpretation difficult (Figures 2 and 3). The means (SD) for suicidal ideation and for mHDRS-17 at each time point are provided in Table 2.

To assess traditional RCT outcomes, we tested a model of follow-up SSI with main effects of treatment, randomization strata, time, $SSI_{baseline}$, $mHDRS\text{-}17_{baseline}$, and a treatment $\times$ time interaction. The treatment main effect ($p = 0.07$) and treatment $\times$ time interaction ($p = 0.27$) were not significant.

More generally, we performed exploratory model selection to determine the best fitting model of acute suicidal ideation. We tested a model with main effects as above and interactions of treatment $\times$ time, treatment $\times$ $SSI_{baseline}$, time $\times$ $SSI_{baseline}$, and a three-way interaction of treatment $\times$ time $\times$ $SSI_{baseline}$. We used the BIC to select the best model from the group that included the full model, models without the three-way interaction but with all combinations of two-way interactions, and the model with no interaction (data available on request). The model with the best (smallest) BIC included interactions of treatment $\times$ time and treatment $\times$ $SSI_{baseline}$ (Table 3). This model had a lower BIC, indicating a better fit, than the traditional model without the treatment $\times$ $SSI_{baseline}$ interaction.

The treatment $\times$ $SSI_{baseline}$ interaction effect on follow-up ideation was significant (Table 3). For each point that $SSI_{baseline}$ was more severe, follow-up ideation was 0.29 points lower, favoring paroxetine at every time point. Figures 2 and 3 illustrate change in suicidal ideation over time in subgroups divided by treatment and median split of $SSI_{baseline}$.

In order to ascertain the robustness for the finding regarding the treatment $\times$ $SSI_{baseline}$ interaction effect, we

Table 1 Demographic and Baseline Characteristics of Study Participants by Treatment ($N = 74$)

Demographics	Bupropion ($N = 38$), no. (%)[a]	Paroxetine ($N = 36$), no. (%)[a]	χ^2	df	*p*-value
Female	21 (55.3)	21 (58.3)	0.07	1	0.79
White race	26 (68.4)	26 (72.2)	0.13	1	0.72
Employed	16 (42.1)	17 (47.2)	0.19	1	0.66
Inpatient at randomization	5 (13.2)	4 (11.1)			>0.99[b]
Cluster B personality disorder[c]	7 (18)	7 (19)	0.01	1	0.91
Lifetime substance use disorder	16 (42)	13 (36)	0.28	1	0.59
History of past suicide attempt at randomization	22 (57.9)	21 (58.3)	0.001	1	0.97
			***t* or (z)**	**df**	***p*-value**
Age, mean (SD), years	37.9 (11.9)	35.2 (12.8)	0.98	72	0.33
Education, mean (SD), years	15.6 (3.1)	15.3 (2.3)	0.52	67.4	0.60
Depression severity at baseline, mean (SD)[d]	19.5 (5.5)	18.7 (6.4)	0.60	72	0.55
Suicidal ideation severity at baseline, mean (SD)[e]	9.9 (7.4)	8.0 (6.7)	(−1.17)		0.24
			z		***p*-value**
Number of past major depressive episodes, median (IQR)[f]	4.0 (1.8–12.0)	3.0 (2.0–12.3)	−0.34		0.74
Length (weeks) of current major depressive episode, median (IQR)[g]	36 (8.0–104.0)	36 (11.0–104.0)	−0.01		0.99
Number of past antidepressant medication trials, median (IQR)	2 (0–3.3)	1 (0–2)	1.64		0.10

[a]Except where otherwise noted.
[b]Fisher's exact test.
[c]Cluster B personality disorder = borderline, antisocial, narcissistic, or histrionic.
[d]17-item Hamilton Depression Rating Scale (Hamilton, 1960).
[e]Scale for Suicidal Ideation score (Beck *et al*, 1979).
[f]Truncated at 50.
[g]Truncated at 104 weeks.

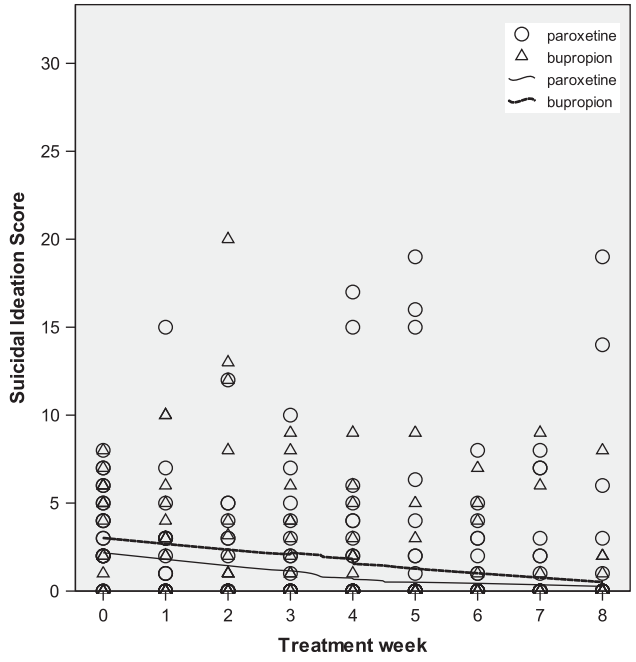

Figure 2 Scatter-plot of Scale for Suicidal Ideation (SSI) (Beck *et al*, 1979) score *vs* time, by treatment, in patients with baseline SSI ⩽8. Locally weighted polynomial regression lines for scatter-plot smoothing (Cleveland, 1979) use 80% of points to fit and Epanechnikov kernel. Data points may represent more than one patient.

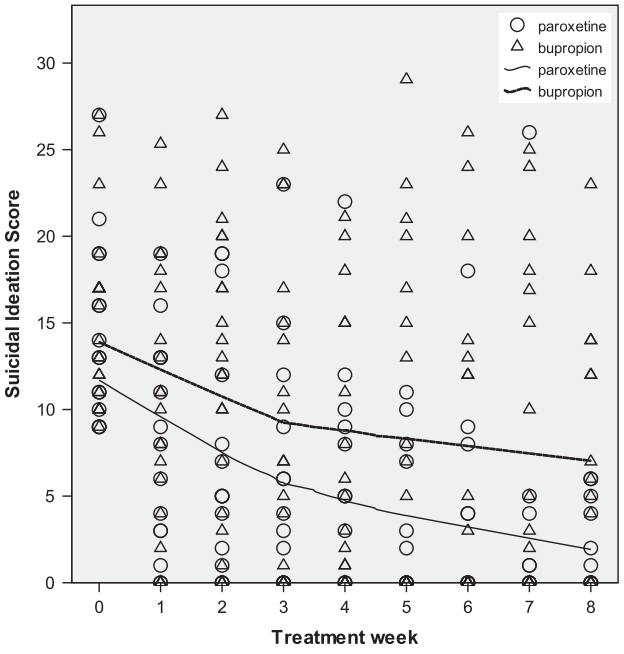

Figure 3 Scatter-plot of Scale for Suicidal Ideation (SSI) (Beck *et al*, 1979) score *vs* time, by treatment, in patients with baseline SSI ⩾9. Locally weighted polynomial regression lines for scatter-plot smoothing (Cleveland, 1979) use 80% of points to fit and Epanechnikov kernel. Data points may represent more than one patient.

Table 2 Mean (SD) of Scale for Suicidal Ideation (SSI)[a] Score; and mHDRS-17[b] at Each Time Point During Treatment with Paroxetine ($N=36$) *vs* Bupropion ($N=38$)

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Month 3	Month 4	Month 5	Month 6
Scale for Suicidal Ideation score													
Bupropion	9.9 (7.4)	7.3 (7.2)	8.4 (8.3)	7.1 (7.6)	5.2 (6.5)	6.7 (8.9)	5.8 (8.1)	6.5 (8.6)	4.7 (6.6)	2.2 (3.8)	1.1 (2.4)	3.5 (4.7)	4.2 (8.0)
Paroxetine	8.0 (6.7)	4.6 (5.5)	4.1 (5.7)	3.6 (5.3)	4.3 (5.8)	3.5 (5.5)	2.3 (4.0)	2.5 (5.3)	2.3 (4.5)	2.8 (4.6)	0.7 (1.6)	1.3 (3.1)	3.4 (6.1)
mHDRS-17 (subtracting suicide item)													
Bupropion	17.6 (5.2)	15.3 (5.5)	14.5 (6.1)	13.8 (5.5)	12.7 (6.3)	12.8 (5.9)	11.3 (6.8)	12.3 (6.6)	10.1 (6.5)	10.2 (7.8)	7.6 (4.6)	9.5 (6.5)	9.5 (6.1)
Paroxetine	16.9 (5.8)	14.3 (4.8)	13.2 (5.5)	11.5 (5.5)	12.5 (6.5)	9.8 (5.9)	11.3 (7.1)	10.8 (6.8)	9.8 (5.8)	7.7 (5.5)	7.8 (6.7)	6.4 (5.1)	9.3 (7.1)

[a]Scale for Suicidal Ideation (Beck *et al*, 1979).
[b]17-item Hamilton Depression Rating Scale score after subtracting suicide item (Hamilton, 1960).

Table 3 Selected Exploratory Model of Suicidal Ideation During Acute Treatment (Weeks 1–8) with Paroxetine ($N=36$) *vs* Bupropion ($N=38$)[a]

Variable	Estimate (95% CI)	t	df	p-value
Treatment	0.25 (−3.23 to 3.74)	0.14	99.51	0.89
Inpatient status at randomization	0.26 (−2.80 to 3.32)	0.17	61.02	0.87
Past suicide attempt at randomization[b]	0.44 (−1.49 to 2.37)	0.46	60.64	0.65
Baseline mHDRS-17[c]	0.15 (−0.04 to 0.33)	1.56	62.63	0.13
Time	−1.49 (−2.52 to −0.48)	−2.89	153.97	0.004
Baseline suicidal ideation[d]	0.58 (0.39 to 0.78)	5.97	63.97	<0.001
Treatment × time	0.82 (−0.60 to 2.25)	1.14	149.93	0.26
Treatment × baseline suicidal ideation	−0.29 (−0.57 to −0.023)	−2.17	59.99	0.03

[a]Generalized least squares regression model selected using Bayesian Information Criterion (BIC); first-order autoregressive moving average covariance; outcome = Scale for Suicidal Ideation (Beck *et al*, 1979) score during treatment.
[b]Subject had history of a past suicide attempt (lifetime) at baseline (yes/no).
[c]The 17-item Hamilton Depression Rating Scale score after subtracting suicide item (Hamilton, 1960).
[d]Baseline score on Scale for Suicidal Ideation (Beck *et al*, 1979).

conducted various sensitivity analyses. A test of the model including an indicator variable for the eight subjects enrolled under the initial attempter-only criteria gave the same results (estimate = −0.29, $p=0.035$). A test of the model after removing one possibly influential data point gave similar results (estimate = −0.32, $p=0.02$). Restricting the model to weeks 4–8, when doses of both drugs were optimal, strengthened the interaction effect favoring paroxetine (estimate = −0.45, $p=0.003$).

Suicidal Ideation Model Predictions

For subjects at the 75th percentile of $SSI_{baseline}$ (score = 13.3), the fitted model predicts that follow-up ideation would be 3.7 points lower after 1 week ($p=0.009$) and 2.5 points lower after 4 weeks of treatment ($p=0.03$) on paroxetine relative to bupropion (Table 4). Predicted treatment differences at weeks 8, 16, and 24 were not significant according to the model ($p=0.65$, 0.14, and 0.08, respectively).

Worsening of Ideation

To assess possible deleterious treatment effects on suicidal ideation, we tested a mixed logistic regression model of worsening (increase of $\geqslant 5$ points over $SSI_{baseline}$) during the acute phase. Among patients at the 75th percentile of $SSI_{baseline}$, there was a trend for bupropion treatment having 5.9 times higher odds of worsening SSI after 1 week compared with paroxetine (estimate = 1.77, $t=1.89$, df = 121.4, $p=0.06$, OR = 5.9, 95% CI = 0.94–36.70). A treatment × time interaction showed that this effect diminished over time (estimate = 1.06, $t=2.02$, df = 84.11, $p=0.05$).

Acute Depressive Symptoms without Suicide Item

To investigate the effects of acute treatment on depressive symptoms other than suicidality, we modeled mHDRS-17 at each time point. Predictors were treatment, randomization strata, time, $SSI_{baseline}$, $mHDRS\text{-}17_{baseline}$, and interaction terms for treatment × time and treatment × $mHDRS\text{-}17_{baseline}$. The latter interaction was significant favoring paroxetine (estimate = −0.46, 95% CI = 0.83 to 0.08, $t=2.41$, df = 67.56, $p=0.02$). For each point more severe $mHDRS\text{-}17_{baseline}$, these symptoms were 0.46 point lower with paroxetine compared with bupropion at every acute follow-up time point. Treatment × time was not significant ($p=0.74$).

Table 4 Mean Predicted Difference in Scale for Suicidal Ideation (SSI) (Beck *et al*, 1979) Score During Acute Treatment with Paroxetine ($N = 36$) *vs* Bupropion ($N = 38$)

Number of treatment weeks completed	Mean predicted difference in SSI score (95% CI) between treatment groups at follow-up time point[a]	z	*p*-value
Subjects at 75th percentile of baseline SSI score = 13.3			
Week 1	−3.7 (−6.4 to −0.9)	−2.62	0.009
Week 4	−2.5 (−4.7 to −0.3)	−2.23	0.03
Week 8	−1.9 (−4.5 to −0.6)	−1.49	0.14
Subjects at median of baseline SSI score = 7.5			
Week 1	−1.9 (−4.5 to 0.6)	−1.53	0.13
Week 4	−0.8 (−2.8 to 1.1)	−0.82	0.41
Week 8	−0.2 (−2.6 to 2.1)	−0.21	0.84
Subjects at 25th percentile of baseline SSI score = 2.8			
Week 1	−0.6 (−3.5 to 2.4)	−0.37	0.71
Week 4	0.6 (−1.9 to 3.1)	0.45	0.65
Week 8	1.2 (−1.7 to 4.0)	0.79	0.43

[a](Scale for Suicidal Ideation)$_{\text{paroxetine}}$ − (Scale for Suicidal Ideation)$_{\text{bupropion}}$. Positive number favors bupropion; negative number favors paroxetine.

Treatment Adherence and Side Effects

Subjects reported taking 'all/nearly all doses' since their last visit for 75% of bupropion ratings ($N = 379$) and 79% of paroxetine ratings ($N = 399$). Using a generalized least squares model, adjusted for randomization strata, drug group was not associated with adherence during the 8-week acute phase ($t = -0.42$, df = 47.1, $p = 0.68$) or the entire 24 weeks ($t = 0.48$, df = 164.2, $p = 0.43$). Using a similar model, drug group was not associated with overall side effect intensity ($t = 0.77$, df = 62.5, $p = 0.44$).

Concomitant Medication

Of the patients, 7/38 (18%) on bupropion received zolpidem for insomnia *vs* 8/36 (22%) on paroxetine ($\chi^2 = 0.17$, df = 1, $p = 0.68$). In addition, 15/38 (40%) on bupropion received a benzodiazepine *versus* 14/36 (39%) on paroxetine ($\chi^2 = 0.003$, df = 1, $p = 0.96$). Maximum dose of benzodiazepine (mg lorazepam) in the bupropion group was double that in the paroxetine group ($\text{Mean}_{\text{bupropion}} = 3.6 \pm 2.8$; $\text{Mean}_{\text{paroxetine}} = 1.8 \pm 1.4$; Mann–Whitney $U = 153.0$, $p = 0.03$).

DISCUSSION

This pilot randomized clinical trial comparing paroxetine with bupropion treatment in depressed suicide attempters and ideators tested our hypotheses that suicidal behavior and ideation would improve more with paroxetine. Basic treatment main effects and treatment by time interactions were not found in support of these hypotheses.

Exploratory model selection analysis of acute treatment suggests that compared with bupropion: (1) patients with more severe global depressive symptoms apart from suicidality improved more in terms of depression on paroxetine, while controlling for $\text{SSI}_{\text{baseline}}$; and (2) patients with more severe $\text{SSI}_{\text{baseline}}$ improved more in terms of suicidal ideation on paroxetine, controlling for baseline depression. The model predicted that suicidal ideation was lower with paroxetine than bupropion treatment in patients with the highest $\text{SSI}_{\text{baseline}}$ (75th percentile, score = 13.3) by 3.7 points at week 1 and 2.5 points at week 4. For comparison, the difference on the SSI between 'weak' *vs* 'moderate to strong' desire to attempt suicide (item 4) is 1 point and between no plans and 'definite plans' for suicide (item 18) is 2 points (Beck *et al*, 1979). The nearly two-point difference between treatment groups in $\text{SSI}_{\text{baseline}}$ does not explain these results as all models adjusted for $\text{SSI}_{\text{baseline}}$.

In patients presenting with the most severe suicidal ideation, the odds of worsening by $\geqslant 5$ points after 1 week were 5.9 times greater on bupropion compared with paroxetine ($p = 0.06$). This trend-level finding raises the question of whether bupropion-related activation may have contributed to early worsening of suicidal ideation in some patients. This hypothesis would be consistent with our finding that the bupropion group received twice the dose of benzodiazepine compared with the paroxetine group. Reported associations of anxiety (Fawcett *et al*, 1990), but not (Placidi *et al*, 2000), insomnia (Wojnar *et al*, 2009), and sedative–hypnotics (Brower *et al*, 2011) to suicidal ideation and behavior suggest complex relationships between these variables.

Our findings for suicidal ideation are consistent with studies reporting that more suicidal depression is associated with a better response to predominantly serotonergic antidepressants (Gonella *et al*, 1990; Kasper *et al*, 1995; Sacchetti *et al*, 1991; Montgomery *et al*, 1978; Mahapatra and Hackett, 1997). However, the neurobiological significance of our results is limited by serotonergic–noradrenergic interactions and neurotransmitter nonspecificity of both drugs (Baldessarini, 2006; Owens *et al*, 2008). Paroxetine is predominantly serotonergic, but in a novel assay of human serum samples, it showed potential norepinephrine transporter inhibition (hypothetically 10–20% at the doses used in our study) (Owens *et al*, 2008).

Our results for suicidal ideation are also consistent with the greater percentage of depressed paroxetine-treated patients with 'declining suicidal ideation' as compared with placebo in a recent meta-analysis (Carpenter *et al*, 2011). Seemingly contradictory to this latter result based on rating scale data, the meta-analysis of adverse events found more frequent suicidal behavior in depressed patients treated with paroxetine as compared with placebo, which appeared because of more events in young adults (Carpenter *et al*, 2011). Our study differs from this meta-analysis in several ways: (1) we compared paroxetine with bupropion, not placebo; (2) our study is a prospective, randomized clinical trial whereas meta-analysis is retrospective; (3) we selected for depressed attempters and ideators, whereas the meta-analysis mainly comprised trials that excluded suicidal patients; (4) our study randomization was stratified by the preexisting suicide risk factors of past attempt and current inpatient status; and (5) we did not analyze adverse events, which can be reported unsystematically (Carpenter *et al*, 2011).

We find different effects of treatment in patients who were more depressed or more suicidal at presentation.

These are consistent with previous reports that greater baseline severity increases the ability to detect treatment differences in clinical trials (Khan *et al*, 2002; Kirsch *et al*, 2008; Fournier *et al*, 2010).

The relatively low base rate of suicidal behavior is a challenge for clinical trials and forces a focus on proxy outcomes with higher base rates such as suicidal ideation. Clinicians assess suicidal ideation in part to evaluate need for hospitalization because of its predictive validity for risk of suicide attempts (Oquendo *et al*, 2004a) and suicide (Fawcett *et al*, 1990; Beck *et al*, 1999). Depression appears to predict suicide attempts via its effect on suicidal ideation (Nock *et al*, 2010). Most published antidepressant randomized clinical trials excluded suicidal patients and did not assess ideation and behavior systematically. Our pilot study, in a sample with clinically significant suicidal ideation and nearly 60% with past attempt, shows that such a randomized clinical trial is feasible and can yield useful results.

There has been a concern that some antidepressants may, on average, lead to improvement, but also possibly worsen ideation or trigger an attempt in vulnerable patients. We found 5.9 times greater odds of worsening suicidal ideation with bupropion compared with paroxetine and a statistical trend level of significance, which if confirmed would be important clinically. That result is also consistent with the reported lower rate of rating scale-based treatment-emergent suicidal behavior or ideation found in paroxetine-treated patients compared with placebo across all indications (Carpenter *et al*, 2011).

The main study limitations are the small sample and exploratory nature of the analyses. However, the week 1 model prediction of 3.7 points lower suicidal ideation with paroxetine relative to bupropion treatment ($p = 0.009$) would survive correction for several statistical tests. Bupropion had a slower titration schedule, but restricting the analysis to weeks 4–8 strengthened the treatment $\times$ $SSI_{baseline}$ interaction effect, suggesting that it was not simply because of an early dose advantage for paroxetine. We increased the initial dose after 2 weeks to give patients a longer accommodation period, because of concern about a hypothesized 'activation syndrome.' The trend toward more worsening suicidal ideation, in those with the severest $SSI_{baseline}$, after 1 week on bupropion raises questions about possible noradrenergic effects on a putative 'activation syndrome.' The latter is consistent with a reported higher rate of suicide attempts despite less depressive relapse in remitted depressed patients maintained for one year on maprotiline, a norepinephrine reuptake inhibitor, compared with placebo ($N = 1141$; $p = 0.03$) (Rouillon *et al*, 1989). Our analyses of follow-up suicidal ideation adjusted for baseline mHDRS-17, suggesting that these results are at least partly independent of baseline depression severity.

The 32% acute-phase attrition rate is in line with the average 33% rate found in four other 8-week bupropion *vs* SSRI randomized trials in MDD ($N = 1011$) (Thase *et al*, 2005). The lack of differential drug effects that we observed during the continuation phase may be explained by the high cumulative 6-month attrition, and low variance in ideation because of robust acute improvement. Clearly, all of these findings must be replicated in an adequately powered randomized clinical trial, but if confirmed would have importance for practice.

We did not exclude substance use disorder, because it is a risk factor for suicidal behavior, and that made the findings more generalizable. It also did not explain the treatment findings because the rate of lifetime substance use disorder was the same in both study arms. We did not measure plasma drug levels; however, adherence self-report correlates with antidepressant prescription refills (Saunders *et al*, 1998) and did not differ by treatment.

Data on prior treatment resistance, which can affect outcome, were limited. The drug arms did not differ in number of past major depressive episodes, length of current episode, or number of prior antidepressant medication trials. This makes it unlikely that an imbalance in treatment resistance explains the findings.

Our exploratory results suggest that an adequately powered trial is warranted to determine whether SSRIs have clinically meaningful advantages *vs* nonserotonergic antidepressants on suicidal behavior and ideation in depressed patients presenting with more severe suicidal ideation.

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DISCLOSURE

To defray costs, Paxil CR and Wellbutrin XL pills were donated by GlaxoSmithKline in the first 3 years of this study and were purchased with grant funds thereafter. Dr Mann received research grant support for unrelated brain imaging studies from GlaxoSmithKline and Novartis. Dr Duan received research support from Pfizer for unrelated health services research. The other authors declare no conflict of interest.

Disclaimer

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