Efficacy of Risperidone Augmentation to Antidepressants in the Management of Suicidality in Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

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Objective: Major depressive disorder (MDD) is a severe mental illness with high risk of suicidality. Antidepressant treatment alone is not sufficient for the acute management of risk-taking symptoms of depression. This pilot study was designed to investigate the efficacy of risperidone augmentation to antidepressants in the acute management of suicidality and other core symptoms in MDD with suicidality.

Method: Twenty-four adult men and women diagnosed with MDD (DSM-IV), having a depressive episode with suicidality despite taking an antidepressant, were enrolled in an 8-week double-blind, placebo-controlled study. Subjects were randomly assigned to receive risperidone (0.25–2 mg/day) or placebo while continuing on their antidepressant therapy. Clinical efficacy in suicidality, depressive symptoms, and impulsivity were assessed after treatment with study drugs for 4 days, weekly for 4 weeks, then every other week for 4 weeks. Adverse events were also recorded at each visit. The study was conducted from June 2004 to April 2007.

Results: Risperidone significantly reduced suicidal ideations in MDD patients, and the overall effect of risperidone appeared to be superior to placebo. The effect of risperidone was rapid, with onset at 2 weeks' treatment, and was sustained along the course of 8 weeks' treatment. Furthermore, risperidone demonstrated superiority to placebo in improving other symptoms related to suicidality and having better trial completion rate, and the low dose risperidone was well tolerated by subjects in this study.

Conclusion: Data from this pilot study suggest that risperidone is beneficial as an augmenting treatment in MDD patients who have developed high-risk suicidal ideation during a depressive episode. The antisuicidality effect of risperidone is especially valuable in the acute management of severe depressive symptoms. Although the pilot study is limited by small sample size, the promising results warrant further larger scale investigation in the efficacy of atypical antipsychotics in the treatment of severe depression with suicidality.

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Suicidality is the most severe symptom and a frequent psychiatric emergency in patients with major depressive disorder (MDD). The reported prevalence of suicidal ideation in MDD is as high as between 51% to 60%, and the incidence of attempted suicide has been reported as 10% to 20%.[1–5] The treatment of acute suicidality often requires hospitalization to actively monitor and prevent emergent acts of self-harm. Most antidepressants have a 3- to 4-week delay before new therapeutic effects are noticeable and are less useful for the acute management of risk-taking symptoms of depression. Additionally, increased awareness of antidepressant treatment–emergent suicidal behavior[6] can also be a concern in the treatment of MDD patients. Thus, efficient pharmacologic management of suicidality in MDD remains to be established.

The psychopathological state of suicidality includes symptoms of severe depression with abnormal thought process, cognitive impairment, and behavioral disturbance. Suicidal patients often present with the "all or none" rigid thinking that results in poor problem solving abilities and lack of coping skills to adapt to stressful conditions, thereby developing hopelessness.[7] In patients

with MDD, distinctly higher neuropsychological impairment has been shown in those who attempt suicide when compared to those who do not attempt suicide.[8] The behavioral disturbance, such as impulsivity and aggression, is also a major contributing factor to the self-harm actions of suicidal patients.

The neurobiological models of suicidal behavior suggest dysfunction of serotonin and dopamine neurotransmission. Suicidal patients have high hydroxyindoleacetic acid in cerebrospinal fluid, and the threshold to act on suicidal thoughts has been correlated with decreased serotonin in brain.[9–13] The serotonin reuptake inhibitor antidepressants enhance synaptic availability of serotonin, which ameliorates depressive symptomatology through activation of serotonin receptors in the hippocampal and amygdalal regions of limbic septum.[14–16] On the other hand, activation of the serotonin 5-HT_{2A} receptor has been linked to the psychopathological components of suicidality as found in animal models, neuroimaging studies, and postmortem brains of suicidal patients.[17–19] Accumulating evidence from both preclinical and clinical studies suggests that blockade of 5-HT_{2A} receptors enhances the pharmacologic action of 5-HT_{1A} receptor activation or serotonin reuptake inhibition.[20,21] Furthermore, activation of the dopamine D_2 receptors in prefrontal cortex and nucleus accumbens is associated with aggression and is the therapeutic basis of antipsychotic use in the management of aggression in several psychiatric disorders.[22,23]

Clinical evidence has shown that atypical antipsychotics have additional psychotropic efficacy other than antipsychotics, such as mood stabilizing, antidepressant, antiaggression, and cognitive enhancing effects.[24–33] In addition to blocking the dopamine D_2 receptors, the extended therapeutic benefits of atypical antipsychotics may be explained partly by their 5-HT_{2A} receptor antagonism effect.[34,35] Emerging clinical trials have provided supportive data to the off-label use of atypical antipsychotics in MDD, especially for antidepressant treatment–resistant depression.[24,36–42] Additionally, clozapine and olanzapine were found to prevent suicide attempts in schizophrenia patients,[31,43] and a case report showed benefit of risperidone in decreasing suicidal ideation in patients with nonpsychotic depression,[44] suggesting a possible place for atypical antipsychotics as antisuicidal agents. However, formal evaluation of atypical antipsychotics in the treatment of MDD with suicidality is challenging, and data are still lacking.

On the basis of the presented evidence, we hypothesize that atypical antipsychotic augmentation therapy is superior to antidepressant monotherapy in the reduction of acute suicidality in patients with MDD. In this pilot study, we tested the hypothesis by examining the efficacy of risperidone as an augmenting treatment to antidepressants in a small group of patients who had severe depression with suicidality.

STUDY DESIGN AND METHOD

A double-blind, placebo-controlled study was conducted from June 2004 to April 2007 at the University of Alabama at Birmingham (UAB). This study was registered at ClinicalTrials.gov (NCT00167154). The study protocol was approved by the UAB Institutional Review Board for Human Use. A written informed consent was obtained from all patients before undergoing baseline screen. Twenty-four participants fulfilling all inclusion criteria were enrolled from the UAB psychiatry research clinic.

The patients included were 19- to 60-year-old individuals with a DSM-IV diagnosis of MDD, currently experiencing a depressive episode with suicidal ideation despite treatment with up to 2 antidepressants for 3 or more weeks. For inclusion, the severity of depression and suicidality on the Montgomery-Asberg Depression Rating Scale (MADRS)[45] included a total score ≥ 25 and a suicidal subscore ≥ 4. The patients were in good general health and without any unstable medical conditions. Depressed patients without suicidality, with severe psychotic features, or with other major psychiatric diagnosis other than MDD, such as bipolar disorder, schizoaffective disorder, schizophrenia, substance abuse or dependence, or generalized anxiety disorder, were excluded from the study. Female patients who were pregnant or lactating were also excluded from the study.

After the baseline assessment, enrolled subjects were randomly assigned to risperidone or placebo treatment while their antidepressant treatment was continued. The initial dose of risperidone was 0.5 mg/day, which could be titrated up to a maximum of 2 mg/day or down to 0.25 mg/day based upon clinical judgment and reported adverse effects. However, the dosages of antidepressants were not changed during the study. During the 8-week study, all patients were reassessed at the end of treatment day 4 (week 0.5) and weeks 1, 2, 3, 4, 6, and 8.

The primary efficacy measure of the study was the severity of suicidality, which was assessed using the Beck Scale for Suicide Ideation (BSSI).[46] The other core symptoms of depression were assessed by the clinician-rated MADRS and the self-rated Profile of Mood States (POMS),[47] the impulsivity was assessed by the Barratt Impulsiveness Scale, Version 11 (BIS-11),[48] and the severity of clinical symptoms was assessed by the Clinical Global Impressions–Severity of Illness (CGI-S) scale. Safety measures were administered at each visit, including vital signs and weight, self-reported adverse events, the Abnormal Involuntary Movement Scale (AIMS), and the Simpson-Angus Scale (SAS). Prolactin levels were also measured at the baseline and the end of treatment.

Statistical analysis was undertaken to measure timely changes and overall effects. The within-group changes from baseline to each assessment point were analyzed

using a paired t test in which the mean change was adjusted for the treatment and baseline values. The between-group (risperidone vs. placebo) changes from baseline were analyzed using the analysis of covariance model at each assessment point and at the end of treatment using the last observation carried forward (LOCF) data. The overall effects between the treatment groups were analyzed using the repeated analysis of variance model including week 0.5 to week 8 data, in which changes from baseline were dependent variables, groups and visits were factors, and the baseline value was the covariate.

RESULTS

Among the 24 enrolled subjects, only 1 subject dropped out of the study before the first follow-up visit and thus data from this subject was not included in analysis. The entrance and exit information for the remaining 23 subjects is listed in Table 1. The participants included 7 men and 16 women, who had comparable age and education. Among the 23 subjects, risperidone and placebo were equally allocated, with 12 receiving risperidone treatment and 11 receiving placebo treatment. However, due to the small sample size, the gender distribution between treatment groups was uneven, with more women randomly assigned into the risperidone group (Table 1). Among all enrolled subjects, the MADRS total scores at screen (or baseline) visit were between 26 and 44, with a median of 34.5 and a mean ± SD of 35.5 ± 5.57. The screen MADRS scores in the risperidone and the placebo groups were within the same severity range. We used the MADRS suicidal thoughts subscore (item 10) as the primary inclusion criteria for suicidal ideation, which was a mean ± SD of 4.29 ± 0.46 among the enrolled subjects, and there was no difference between the 2 treatment groups (Table 1). All patients were enrolled from a UAB psychiatric outpatient clinic, and only 1 required hospitalization, during the second week of treatment. This event was not evaluated as an adverse event but was considered a necessary action to the severity of symptoms. Throughout the 8-week study, the overall completion rate in the risperidone group was higher, in that only 1 subject dropped out early from the risperidone treatment, whereas 4 subjects dropped out early from the placebo treatment, resulting in a low completion rate. Thus, the participation rate suggests that depressed suicidal patients who received risperidone augmentation treatment might have a better outcome than those who received placebo augmentation. The number of subjects assessed at each visit is listed in Table 2, which also indicates the sample size used for all data analysis.

The antidepressants used concurrently by subjects prior to and during the study were amitriptyline, bupropion, duloxetine, escitalopram, fluoxetine, nefazodone, paroxetine, sertraline, and venlafaxine. Antidepressants taken by subjects in each treatment group were similar except that amitriptyline, duloxetine, and nefazodone were only taken by 1 of 3 subjects in the placebo group (Table 2). Most subjects were taking 1 antidepressant at enrollment, with the exception of 1 subject in each group who was taking escitalopram plus bupropion. The doses of risperidone and placebo were initiated at 0.5 mg/day, and the mean ± SD dose at the final medication dispensation for risperidone was slightly lower than for placebo, but there was no significant difference (Table 2).

Table 1. Demographic Information of 23 Subjects With MDD Randomly Assigned to Risperidone or Placebo

Variable	Risperidone (N = 12)	Placebo (N = 11)
Male, N	1	6
Female, N	11	5
Age, mean ± SD, y	46.5 ± 12.1	41.3 ± 12.6
Education, mean ± SD, y	14.25 ± 2.8	15.27 ± 1.7
MADRS at screen, mean ± SD		
Total score	36.42 ± 5.42	35.00 ± 3.38
Suicidal thoughts subscore	4.25 ± 0.45	4.36 ± 0.50
Completer, N (%)	11 (91.67)	7 (63.64)
Early withdrawal, N (%)	1 (8.33)	4 (36.36)

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder.

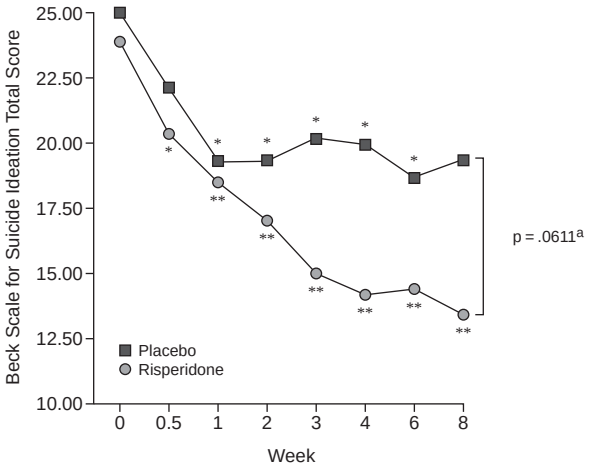
The primary objective of this study is to evaluate the efficacy of risperidone augmentation in suicidal ideation developed during a depressive episode in MDD patients. This was primarily assessed using the BSSI, which includes 21 items with a range of total scores between 0 and 49. The average baseline BSSI scores (mean ± SD) in the risperidone and the placebo groups were 23.92 ± 9.29 and 24.91 ± 9.21, respectively, confirming that subjects had suicidal ideations at enrollment (Figure 1). During the first week of treatment, there was a 22% reduction in the mean BSSI scores in both groups. However, after the initial period, only risperidone treatment further decreased suicidal ideation, resulting in an additional 20% reduction in the BSSI scores between week 1 and week 8. The mean change from baseline at each assessment point was statistically significant during weeks 2 through 8 ($p < .005$ at all time points) and at the end of treatment when the LOCF data were assessed ($p = .0004$). In contrast, the placebo effect reached plateau after week 1 treatment, with the mean ± SD BSSI scores of 19.27 ± 9.08 and 19.29 ± 10.77 at the end of week 2 and week 8, respectively. Although the LOCF change from baseline after placebo treatment also reached statistical difference ($p = .03$), the level of significance was lower than that for risperidone, and it was likely a result of an initial placebo effect during the first-week treatment. With an overall between-group p value of .0611 in a small sample size, the result of this pilot study suggests a trend toward risperidone being superior to placebo as an augmenting treatment in reducing suicidal ideation in MDD patients.

Table 2. Study Drug Administration, Sample Size, and Concomitant Antidepressants

	Risperidone		Placebo	
Week	Dosage, mean ± SD, mg/d	N	Dosage, mean ± SD, mg/d	N
0	0.00	12	0.00	11
0.5	0.46 ± 0.09	12	0.50 ± 0.00	11
1	0.67 ± 0.24	12	0.77 ± 0.25	11
2	1.02 ± 0.62	12	1.20 ± 0.40	10
3	1.36 ± 0.61	11	1.50 ± 0.63	10
4	1.32 ± 0.65	11	1.50 ± 0.58	9
6	1.20 ± 0.68	11	1.50 ± 0.58	9
8	1.25 ± 0.72	11	1.44 ± 0.58	7
End point (LOCF)	1.17 ± 0.74	12	1.50 ± 0.56	11
Concomitant antidepressants	Escitalopram 10–20 mg Escitalopram 40 mg + bupropion 150 mg Fluoxetine 20 mg Paroxetine 20–40 mg Sertraline 50 mg Venlafaxine 75–300 mg		Amitriptyline 25 mg Duloxetine 60 mg Escitalopram 10–20 mg Escitalopram 20 mg + bupropion 300 mg Fluoxetine 25 mg Nefazodone 200 mg Paroxetine 40 mg Sertraline 100 mg Venlafaxine 75 mg	

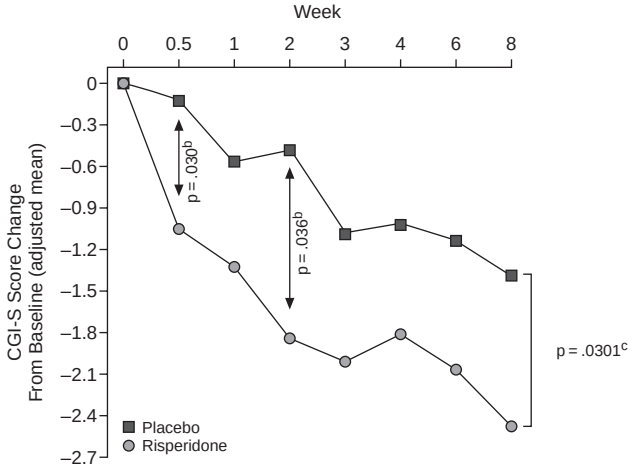
Abbreviation: LOCF = last observation carried forward.

Figure 1. Efficacy of Risperidone in Suicidality



*p < .05, paired t test for change from baseline.
**p < .005, paired t test for change from baseline.
[a]Repeated analysis of variance of overall effects between 2 treatments using week 0.5–8 data; change from baseline is dependent variable, groups and visits are factors, and baseline value is covariate.

Figure 2. Effect of Risperidone in Symptom Severity[a]



[a]The baseline CGI-S scores in the risperidone- and placebo-treated groups were 5.75 ± 0.45 and 5.36 ± 0.50, respectively.
[b]Analysis of covariance model analyzing the effects between 2 treatment groups.
[c]Repeated analysis of variance of overall effects between 2 treatments using week 0.5–8 data; change from baseline is dependent variable, groups and visits are factors, and baseline value is covariate.
Abbreviation: CGI-S = Clinical Global Impressions–Severity of Illness.

The severity of clinical symptoms before and after treatment was evaluated by the CGI-S. The baseline CGI-S scores in the risperidone-treated and placebo-treated groups were 5.75 ± 0.45 and 5.36 ± 0.50, respectively. The clinical response to risperidone was rapid, because there was a significant separation on the CGI-S between risperidone and placebo at week 0.5 and week 2 (Figure 2). Although both risperidone and placebo reduced the symptom severity along the course of treatment, the LOCF reduction by risperidone was larger (2.38 ± 0.41) than that of placebo (1.23 ± 0.43), and the overall effect of risperidone was significantly superior to placebo (p = .0301). To evaluate if the superior effect of risperidone over placebo on the CGI-S was a combined result of reduced suicidality and an improvement in other symptoms related to suicidality, such as depression and impulsivity, these symptoms were further assessed using several secondary measurements.

The effects of risperidone augmentation on the core symptoms of depression were first assessed by measuring

Table 3. Effect of Risperidone and Placebo on Symptoms of Depression: MADRS Change From Baseline

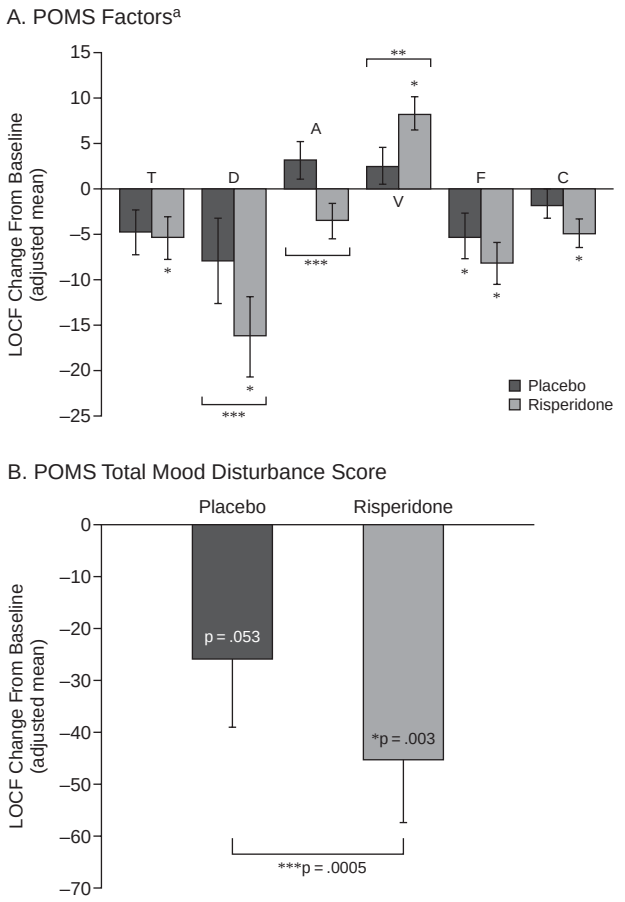
	Risperidone		Placebo		
Week	Mean Change[a]	SE	Mean Change[a]	SE	p Value[b]
0.5	–9.23	2.77	–6.84	2.89	.5585
1	–13.03	2.76	–10.46	2.89	.5296
2	–18.13	2.45	–7.84	2.69	.0111*
3	–20.03	2.83	–8.06	2.98	.0105*
4	–19.44	2.81	–11.29	3.12	.0742
6	–21.68	2.28	–11.39	2.53	.0087*
8	–22.09	3.29	–14.44	4.18	.1822

[a]Mean values were calculated using pooled baseline values from all samples in both groups.
[b]Between-group p values were analyzed using the analysis of covariance model.
*p < .05 was considered statistically significant.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

changes in MADRS scores. Along the course of treatment, the effect of risperidone appeared to be more prominent than placebo, as the MADRS scores between the 2 treatment groups were significantly different at week 2 (p = .0111), week 3 (p = .0105), and week 6 (p = .0087) (Table 3). At the end of treatment (LOCF), risperidone had a greater, although not statistically significant, decrease in MADRS score from baseline (mean ± SE change = 20.31 ± 3.31) than placebo (13.2 ± 3.46).

In addition to the MADRS, the mood states were also evaluated using the self-rated POMS, which is composed of 6 mood factors and a summarizing total score.[49] The POMS has been used often to test the short-term treatment response to therapeutic intervention in an outpatient psychiatric population. When the LOCF changes from baseline were assessed, risperidone had a divergent effect on each POMS factor (Figure 3A). Among all 6 factors, risperidone had the most significant effect on the depression-dejection factor, in which risperidone not only caused a significant reduction in depression but also had a significantly better overall effect than placebo. The anger-hostility factor was slightly reduced in risperidone-treated patients while it was slightly increased in placebo-treated patients, and the small opposite changes resulted in an overall significant difference between risperidone and placebo treatments. Furthermore, risperidone significantly increased vigor-activity, a factor that is negatively related to the other factors, whereas placebo had no effect on this factor. Risperidone, but not placebo, also slightly but significantly reduced tension-anxiety and confusion-bewilderment. Among the 6 factors, only fatigue-inertia was indifferently reduced by both risperidone and placebo. A total mood disturbance (TMD) score was also obtained by summing the scores across all 6 factors (weighing vigor-activity negatively). Risperidone significantly reduced the LOCF TMD score (p = .003), whereas placebo treatment had no significant effect (p = .053) (Figure 3B). Moreover, the overall effects of risperidone and placebo treatments were also different, showing that risperidone augmentation was significantly more effective than placebo in improving mood states.

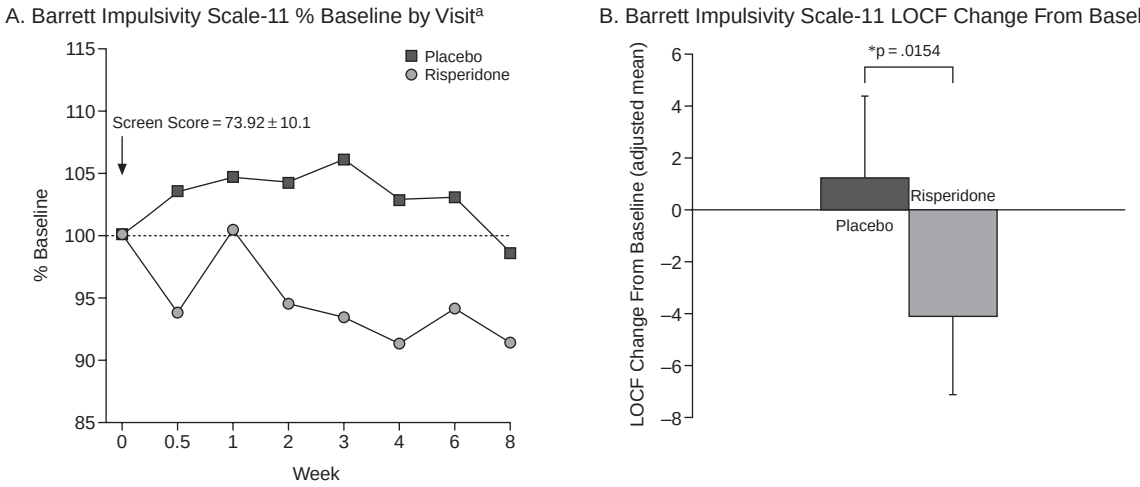
Figure 3. Effect of Risperidone on Profile of Mood States (POMS)



[a]POMS factors: T = tension-anxiety, D = depression-dejection, A = anger-hostility, V = vigor-activity, F = fatigue-inertia, C = confusion-bewilderment.
*p < .05, paired t test comparing the LOCF change from baseline.
**p < .05, analysis of covariance of LOCF effects between 2 treatments.
***p < .05, repeated analysis of variance of overall effects between 2 treatments using week 0.5–8 data, change from baseline is dependent variable, groups and visits are factors, and baseline value is covariate.
Abbreviation: LOCF = last observation carried forward.

Since suicidal ideation is associated with impulsivity and aggression, the trait impulsivity component of suicidality was also assessed using the BIS-11, a self-administered, 30-item questionnaire. Neither risperidone nor placebo treatment significantly changed the BIS-11 scores along the course of treatment (Figure 4A and B). However, patients treated with risperidone tended to have lower impulsivity throughout the 8-week treatment (overall mean ± SE = 94.2% ± 1.7% of baseline) except for a

Figure 4. Effect of Risperidone on Impulsivity



[a]Screen score reported as mean ± SD.
*p < .05 repeated analysis of variance of overall effects between 2 treatments using week 0.5–8 data; change from baseline is dependent variable, groups and visits are factors, and baseline value is covariate.
Abbreviation: LOCF = last observation carried forward.

Table 4. Assessment of Tolerability to Risperidone (N = 23)

	Risperidone		Placebo	
Variable	Total Event (N)	% of Total Subjects	Total Event (N)	% of Total Subjects
Reported adverse events[a]				
Nausea	2	8.70	3	13.04
Heartburn	1	4.35	2	8.70
Diarrhea	2	8.70	3	13.04
Increased appetite	1	4.35	2	8.70
Dry mouth	7	30.43	0	0.00
Bad taste	3	13.04	0	0.00
Somnolence	2	8.70	1	4.35
Insomnia	1	4.35	3	13.04
Delayed ejaculation	0	0.00	3	13.04
Headache	2	8.70	11	47.83
Dizziness	2	8.70	1	4.35
	Incidence (N)	Severity	Incidence (N)	Severity
Movement scales				
AIMS	1	1	2	1–9
SAS	2	1–9	1	1–4
	Baseline	End Point (CFB)	Baseline	End Point (CFB)
Body weight				
Mean, lb	187.17	191.5 (4.33)	203.64	208.95 (5.32)
SD	36.91	37.05 (3.75)	37.73	40.16 (9.09)
N	12	12	11	11
	Baseline	End Point	Baseline	End Point
Prolactin levels				
Mean, ng/mL	10.06	52.06	8.49	11.64
SD	4.55	61.58	5.75	8.05
N	8	8	7	7

[a]Adverse events reported by ≥ 3 subjects.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, CFB = change from baseline, SAS = Simpson-Angus Scale.

transient return to baseline impulsivity at week 1, whereas patients treated with placebo tended to have an overall higher than baseline impulsivity (103.6% ± 1.6%) from week 0.5 to week 6, with a return to baseline only at week 8. The pattern of impulsivity between the 2 treatment groups was found to be statistically different (p = .0154) (Figure 4B).

The tolerability to the study drugs was assessed by self-reported adverse events, rating scales for extrapyramidal movement (AIMS and SAS), weight, and plasma prolactin levels (Table 4). The most reported adverse events were gastrointestinal symptoms, among which only dry mouth and bad taste were reported by more subjects taking risperidone than taking placebo. No other

symptoms were reported more often by subjects on risperidone treatment. In fact, more subjects in the placebo group reported sexual side effects and headache. Throughout the 8-week study, only 1–2 subjects from each treatment group experienced extrapyramidal side effects when rated on the AIMS and SAS, in which all cases had a low score of 1–9 on a maximal scale of 40. There was no major difference in LOCF change in body weight between the risperidone and placebo treatments. Prolactin levels were increased after risperidone treatment; however, relevant symptoms, such as menstrual disturbances, galactorrhea, impotence, oligospermia, and decreased libido, were not reported.

DISCUSSION

The primary objective of this pilot study was to target the pharmacologic management of suicidality, the most severe and risk-taking symptom of depression. Although the mood stabilizer lithium and the atypical antipsychotics clozapine and olanzapine have shown clinical efficacy in long-term suicide prevention, with the former mostly investigated in bipolar disorder and the later two in schizophrenia,[31,50] acute pharmacologic management of suicidal risk in MDD remains underinvestigated.[51] We therefore initiated a pilot study investigating the efficacy of risperidone, a representative atypical antipsychotic, as an augmenting treatment to antidepressants in the acute management of suicidal ideations in patients with MDD.

In order to obtain details in most aspects of suicidal ideation, we used the BSSI, which has a range of scores from 0 to 49. The initial decrease in BSSI scores in both groups may be attributable to the well-known placebo response in depressed patients. The reduction in BSSI scores in the first week may also reflect the unusual amount of time and attention directed to the subject by the research staff in the first week (3 visits in an 8-day period). When the placebo group began weekly office visits, there was no further improvement, whereas the risperidone group continued to improve on the BSSI throughout the 8-week treatment. Also important, the onset of the therapeutic effect of risperidone was rapid, with a significant reduction of BSSI at treatment day 4. This observation is further supported by a rapid reduction in the CGI-S scores on treatment day 4. Therefore, data from this pilot study suggest that the atypical antipsychotic risperidone is likely an effective add-on treatment option in MDD patients whose symptoms include high-risk suicidality.

To balance the subjective and objective outcomes in suicidality, we evaluated the depressive symptoms using both the clinician-rated MADRS and the patient-rated POMS. The overall impression is that risperidone is superior to placebo in reducing depressive symptoms, a consistent finding from the previously reported effect of atypical antipsychotics in MDD.[40–42] Interestingly, the patient-rated POMS appeared to be more sensitive than the clinician-rated MADRS in detecting changes in depressive symptoms. The significant changes were especially noticeable when individual aspects of mood states were analyzed separately. This observation may be a considerable factor when evaluating patients with suicidality whose cognitive and psychological impairments may limit their communicating skills with clinicians.

Suicide action has been considered as an impulsive behavior,[52] and there is no well-established treatment to prevent the risk-taking impulsive behavior. Risperidone was reported to be beneficial for aggressive behaviors in autistic children[25,53,54] and dementia.[28,55] In this study, neither risperidone nor placebo treatment caused a significant change in impulsivity, but a significant between-group difference suggests that risperidone may have a potential effect toward reducing the impulsive suicidal attempts. However, such a significant effect will require a larger sample size to confirm.

In this 8-week study, the observed clinical efficacy of risperidone was identified at a low dose range (0.5–2 mg/day) that was well tolerated by patients with MDD. Interestingly, more risperidone-treated patients completed the entire 8-week study, providing additional evidence that MDD patients with suicidality may have therapeutic benefit from risperidone. Pharmacologically, as risperidone is more potent on serotonin 5-HT_2 receptors than on dopamine D_2 receptors,[56] we speculate that the low-dose therapeutic effect of risperidone in MDD with suicidality may involve regulation of both serotonin and dopamine receptors.

The major limitation of this study is a small sample size and a high placebo dropout rate. The small sample size limits the power of statistical analysis; thus, data reported here are as observed, and multiple analyses among different measurements with corrections were not conducted. Another limitation of the study is the uneven gender distribution during randomization, which is likely a result of small sample size. Since gender is known as a social-demographic correlate associated with suicide behavior,[57,58] the uneven gender distribution may affect the outcome of this study. Thus, larger scale studies are needed to confirm findings reported in this study. Nevertheless, the trend of effect observed in this pilot study conducted in a challenging patient population highly suggests that risperidone is likely an effective treatment in the acute management of emerging or prolonged suicidality and other related symptoms. These results elucidate the importance of using atypical antipsychotics to target the high-risk symptoms in depression in a timely manner and encourage extended studies in pharmacologic management of suicidality.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), clozapine (Clozaril, FazaClo, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), lithium

(Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), risperidone (Risperdal), sertraline (Zoloft and others), venlafaxine (Effexor and others).

REFERENCES

1. Hoyer EH, Mortensen PB, Olesen AV. Mortality and causes of death in a total national sample of patients with affective disorders admitted for the first time between 1973 and 1993. Br J Psychiatry 2000;176:76–82
2. Chen YW, Dilsaver SC. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. Biol Psychiatry 1996;39:896–899
3. Gladstone GL, Mitchell PB, Parker G, et al. Indicators of suicide over 10 years in a specialist mood disorders unit sample. J Clin Psychiatry 2001;62:945–951
4. Oquendo MA, Galfalvy H, Russo S, et al. Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. Am J Psychiatry 2004;161:1433–1441
5. Sokero TP, Melartin TK, Rytsala HJ, et al. Prospective study of risk factors for attempted suicide among patients with DSM-IV major depressive disorder. Br J Psychiatry 2005;186:314–318
6. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63:332–339
7. Marzuk PM, Hartwell N, Leon AC, et al. Executive functioning in depressed patients with suicidal ideation. Acta Psychiatr Scand 2005; 112:294–301
8. Keilp JG, Sackeim HA, Brodsky BS, et al. Neuropsychological dysfunction in depressed suicide attempters. Am J Psychiatry 2001;158:735–741
9. Cremniter D, Jamain S, Kollenbach K, et al. CSF 5-HIAA levels are lower in impulsive as compared to nonimpulsive violent suicide attempters and control subjects. Biol Psychiatry 1999;45:1572–1579
10. Faustman WO, King RJ, Faull KF, et al. MMPI measures of impulsivity and depression correlate with CSF 5-HIAA and HVA in depression but not schizophrenia. J Affect Disord 1991;22:235–239
11. Nordstrom P, Asberg M. Suicide risk and serotonin. Int Clin Psychopharmacol 1992 Jun;6(suppl 6):12–21
12. Nordstrom P, Samuelsson M, Asberg M, et al. CSF 5-HIAA predicts suicide risk after attempted suicide. Suicide Life Threat Behav 1994;24: 1–9
13. Samuelsson M, Jokinen J, Nordstrom AL, et al. CSF 5-HIAA, suicide intent and hopelessness in the prediction of early suicide in male high-risk suicide attempters. Acta Psychiatr Scand 2006;113:44–47
14. Ressler KJ, Nemeroff CB. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress Anxiety 2000;12(suppl 1):2–19
15. Ichikawa J, Ishii H, Bonaccorso S, et al. 5-HT(2A) and D(2) receptor blockade increases cortical DA release via 5-HT(1A) receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. J Neurochem 2001;76:1521–1531
16. Celada P, Puig M, Amargos-Bosch M, et al. The therapeutic role of 5-HT1A and 5-HT2A receptors in depression. J Psychiatry Neurosci 2004;29:252–265
17. Pandey GN, Dwivedi Y, Rizavi HS, et al. Higher expression of serotonin 5-HT(2A) receptors in the postmortem brains of teenage suicide victims. Am J Psychiatry 2002;159:419–429
18. Meyer JH, McMain S, Kennedy SH, et al. Dysfunctional attitudes and 5-HT2 receptors during depression and self-harm. Am J Psychiatry 2003; 160:90–99
19. Arango V, Ernsberger P, Marzuk PM, et al. Autoradiographic demonstration of increased serotonin 5-HT2 and beta-adrenergic receptor binding sites in the brain of suicide victims. Arch Gen Psychiatry 1990;47: 1038–1047
20. Li X, Zhu W, Roh MS, et al. In vivo regulation of glycogen synthase kinase-3beta (GSK3beta) by serotonergic activity in mouse brain. Neuropsychopharmacology 2004;29:1426–1431
21. Marek GJ, Carpenter LL, McDougle CJ, et al. Synergistic action of 5-HT2A antagonists and selective serotonin reuptake inhibitors in neuropsychiatric disorders. Neuropsychopharmacology 2003;28:402–412
22. de Almeida RM, Ferrari PF, Parmigiani S, et al. Escalated aggressive behavior: dopamine, serotonin and GABA. Eur J Pharmacol 2005;526:51–64
23. Miczek KA, Faccidomo S, de Almeida RM, et al. Escalated aggressive behavior: new pharmacotherapeutic approaches and opportunities. Ann N Y Acad Sci 2004;1036:336–355
24. Blier P, Szabo ST. Potential mechanisms of action of atypical antipsychotic medications in treatment-resistant depression and anxiety. J Clin Psychiatry 2005;66(suppl 8):30–40
25. McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med 2002;347: 314–321
26. Greenberg WM, Citrome L. Ziprasidone for schizophrenia and bipolar disorder: a review of the clinical trials. CNS Drug Rev 2007;13:137–177
27. Chengappa KN, Suppes T, Berk M. Treatment of bipolar mania with atypical antipsychotics. Expert Rev Neurother 2004;4:S17–S25
28. Katz IR, Jeste DV, Mintzer JE, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. J Clin Psychiatry 1999;60:107–115
29. Buckley PF. Second-generation antipsychotic medications in the treatment of mood disorders: focus on aripiprazole. Drugs Today (Barc) 2005;41:5–11
30. Forsthoff A, Grunze H, Seemuller F, et al. Risperidone monotherapy in manic inpatients: an open label, multicentre trial. World J Biol Psychiatry 2007;8(4):256–261
31. Barbee JG, Conrad EJ, Jamhour NJ. The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major depressive disorder. J Clin Psychiatry 2004;65: 975–981
32. Keck PE Jr, Calabrese JR, McIntyre RS, et al. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry 2007;68:1480–1491
33. Sachs GS, Gaulin BD, Gutierrez-Esteinou R, et al. Antimanic response to aripiprazole in bipolar I disorder patients is independent of the agitation level at baseline. J Clin Psychiatry 2007;68:1377–1383
34. Li X, Rosborough KM, Friedman AB, et al. Regulation of mouse brain glycogen synthase kinase-3 by atypical antipsychotics. Int J Neuropsychopharmacol 2007;10:7–19
35. Meltzer HY. The role of serotonin in antipsychotic drug action. Neuropsychopharmacology 1999;21:106S–115S
36. Shelton RC. Augmentation strategies to increase antidepressant efficacy. J Clin Psychiatry 2007;68(suppl 10):18–22
37. Papakostas GI, Shelton RC, Smith J, et al. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. J Clin Psychiatry 2007;68:826–831
38. Rapaport MH, Gharabawi GM, Canuso CM, et al. Effects of risperidone augmentation in patients with treatment-resistant depression: results of open-label treatment followed by double-blind continuation. Neuropsychopharmacology 2006;31:2505–2513
39. Li X, May RS, Tolbert LC, et al. Risperidone and haloperidol augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder: a crossover study. J Clin Psychiatry 2005;66:736–743
40. Mahmoud RA, Pandina GJ, Turkoz I, et al. Risperidone for treatment-refractory major depressive disorder: a randomized trial. Ann Intern Med 2007;147:593–602
41. Thase ME, Corya SA, Osuntokun O, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. J Clin Psychiatry 2007;68:224–236
42. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2007;68:843–853
43. Keck PE Jr, Strakowski SM, McElroy SL. The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. J Clin Psychiatry 2000;61 (suppl 3):4–9
44. Viner MW, Chen Y, Bakshi I, et al. Low-dose risperidone augmentation of antidepressants in nonpsychotic depressive disorders with suicidal ideation. J Clin Psychopharmacol 2003;23:104–106
45. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
46. Beck AT, Weishaar ME. Suicide risk assessment and prediction. Crisis 1990;11:22–30
47. McNair DM, Heuchert JP. In: Profile of Mood States-Technical Update.

Toronto, Ontario, Canada: Multi-Health Systems Inc; 2003
48. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt Impulsiveness Scale. J Clin Psychol 1995;51:768–774
49. McNair DM, Lorr M, Droppleman LF. Manual for the Profile of Mood States. San Diego, Calif: Educational and Industrial Testing Service; 1988
50. Cipriani A, Pretty H, Hawton K, et al. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry 2005;162: 1805–1819
51. Ernst CL, Goldberg JF. Antisuicide properties of psychotropic drugs: a critical review. Harv Rev Psychiatry 2004;12:14–41
52. Roggenbach J, Muller-Oerlinghausen B, Franke L. Suicidality, impulsivity and aggression: is there a link to 5-HIAA concentration in the cerebrospinal fluid? Psychiatry Res 2002;113:193–206
53. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. Am J Psychiatry 2005;162: 1361–1369
54. Villeneuve E, Lemelin S. Open-label study of atypical neuroleptic quetiapine for treatment of borderline personality disorder: impulsivity as main target. J Clin Psychiatry 2005;66:1298–1303
55. Herrmann N, Rivard MF, Flynn M, et al. Risperidone for the treatment of behavioral disturbances in dementia: a case series. J Neuropsychiatry Clin Neurosci 1998;10:220–223
56. Schotte A, Janssen PF, Gommeren W, et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology (Berl) 1996;124:57–73
57. Zhang J, McKeown RE, Hussey JR, et al. Gender differences in risk factors for attempted suicide among young adults: findings from the Third National Health and Nutrition Examination Survey. Ann Epidemiol 2005;15:167–174
58. Qin P, Agerbo E, Westergard-Nielsen N, et al. Gender differences in risk factors for suicide in Denmark. Br J Psychiatry 2000;177:546–550

