# Risperidone and Paroxetine Given Singly and in Combination for Bipolar Depression

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***Background:*** Bipolar depression is a major clinical problem that remains under-researched. The current study was intended to evaluate the effects of the novel antipsychotic risperidone, the selective serotonin reuptake inhibitor (SSRI) paroxetine, and the combination in patients with bipolar disorder.

***Method:*** Thirty patients with DSM-IV bipolar (I or II) disorder, depressed phase, who were receiving a stable dose of a mood stabilizer were randomly assigned to 12 weeks of double-blind treatment with risperidone (plus placebo), paroxetine (plus placebo), or the combination of risperidone and paroxetine. Data were gathered from August 1999 to September 2001.

***Results:*** All 3 groups experienced significant reductions in depression ratings from baseline to endpoint; there were no significant differences in outcome between groups. There were statistically significant differences in paroxetine dose contrasting paroxetine plus placebo against the combined condition. The switch rate into mania or hypomania was very low, with only 1 patient in the paroxetine plus placebo condition experiencing mild hypomania.

***Conclusion:*** These results suggest that risperidone, paroxetine, and the combination of risperidone and paroxetine are equally but modestly effective when added to a mood stabilizer in bipolar depression. The paroxetine dose differed between groups, possibly because of drug-drug interactions. Using another SSRI in the combined condition could have produced a more robust effect and should be tested.

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The management of bipolar disorder, particularly bipolar depression, remains a challenge for clinicians.[1,2] Whereas bipolar mania has received a great deal of research attention over the last half-century, bipolar depression is a relatively neglected entity. Treatments for acute mania and mood stabilization have proliferated: lithium, valproic acid, and olanzapine have established effectiveness, while data support the effects of lamotrigine, risperidone, clozapine, and others.[1,2] However, Frankle et al.[3] have concluded that, in spite of advances in pharmacotherapy in the last 20 years, little progress has been made to reduce the length of depressive episodes in bipolar disorder. As an example, Judd and colleagues,[4] reporting data from the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression, found that over an average of 13.4 years, bipolar patients spent 50.3% of weeks with significant depressive symptoms (12.9% in a major depressive episode), against only 1.3% with mania and 2.3% with mixed symptoms. Clearly, bipolar depression is a major problem and represents an area that needs attention.

Recently, there has been some progress. For example, the anticonvulsant lamotrigine was shown to be effective as compared with placebo in a 7-week trial.[5] In this study, Clinical Global Impressions-Improvement scale (CGI-I) response rates were 51% for lamotrigine 200 mg/day, 41% for lamotrigine 50 mg/day, and 26% for placebo. In a second study,[6] recently manic or hypomanic patients were stabilized on lamotrigine treatment, then randomly assigned to continuation treatment with lamotrigine or discontinuation of lamotrigine and treatment with either placebo or lithium carbonate for up to 18 months. Lamotrigine significantly prolonged time to the next depressive episode relative to placebo, whereas lithium did not. Conversely, lithium but not lamotrigine significantly prolonged time to the next manic or hypomanic episode. Together, these studies suggest that lamotrigine may well be an effective short- and long-term treatment for bipolar depression. Although relatively rare, the most significant limitation of the treatment is the potential for serious adverse effects, including severe rash or Stevens-Johnson syndrome.[7]

Olanzapine, a novel antipsychotic, may also be effective for bipolar depression. In a large-scale study,[8] bipolar depressed patients were randomly assigned to receive olanzapine alone, olanzapine plus fluoxetine, or placebo

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for 8 weeks. Both monotherapy olanzapine and the combination were superior to placebo throughout the treatment period. The mean changes from baseline in Montgomery-Asberg Depression Rating Scale (MADRS)[9] scores were 11.9 for placebo, 15.0 for olanzapine alone, and 18.5 for the olanzapine-fluoxetine combination. Although this study is limited by the fact that it did not include an antidepressant-alone group, it suggests that both olanzapine and the combination of olanzapine and fluoxetine may be effective in reducing the symptoms of bipolar depression.

By contrast, recent studies of the effects of antidepressants have produced disappointing results. Nemeroff et al.[10] compared paroxetine against placebo in bipolar depressed patients treated with lithium. There were no overall differences in outcome between groups, although a placebo plus lithium group with relatively low lithium levels (≤ 0.8 mEq/L) did worse than other patients. Young et al.[11] compared the addition of paroxetine to a mood stabilizer (lithium or divalproex) with the addition of a second mood-stabilizing medication (divalproex to lithium or vice versa) in bipolar depressed patients. There were no differences in outcome between these groups either.

Risperidone is a novel antipsychotic that is a moderately potent dopamine $D_2$ receptor and highly potent serotonin 5-$HT_{2A}$ receptor antagonist.[12,13] The effectiveness of risperidone for mania is supported by recent clinical trials.[14] However, the drug is largely untested in bipolar depression. A case report of a single patient suggested that risperidone monotherapy was effective in reducing symptoms in episodes of both mania and depression.[15] However, there are no controlled studies to date. The present trial was intended to test the comparative effectiveness of risperidone, risperidone plus the selective serotonin reuptake inhibitor (SSRI) paroxetine, and paroxetine in bipolar patients treated with mood stabilizers.

## METHOD

Approval for the study was given by the Institutional Review Board of Vanderbilt University, and written informed consent was obtained from all participants prior to engaging in any research procedures. Patients were eligible for participation in the study if they (1) had definite and principal diagnosis of bipolar type I or II disorder, currently in a depressed phase; (2) were free of current psychosis, lifetime history of non-affective psychotic disorder, and history of substance abuse in the past 6 months or substance dependence in the past 12 months; (3) were receiving a clinically acceptable type, dose, and plasma level of a mood-stabilizing agent (i.e., valproate, lithium, or carbamazepine) but were otherwise free of psychotropics or potentially psychoactive herbs; (4) had a score of 18 or above on the 17-item version of the Hamilton Rating Scale for Depression (HAM-D)[16] and 8 or below on the Young Mania Rating Scale (YMRS)[17] at both the screening and baseline visits; and (5) were medically healthy. Diagnosis was performed using the Structured Clinical Interview for DSM-IV.[18] At the screening visit, symptoms were rated using the HAM-D and the Beck Depression Inventory (BDI).[19] In addition, a physical examination and laboratory analyses (including blood chemistries, complete blood count, and thyroid-stimulating hormone) were completed.

Persons who met all inclusion and exclusion criteria were randomly assigned to one of the 3 treatment groups: risperidone alone (RIS + placebo), paroxetine alone (PAR + placebo), or risperidone plus paroxetine (RIS + PAR); drug and placebo were administered in blinded capsules. All patients continued their previous mood-stabilizer treatment. The double-blind period was 12 weeks. The dosages of medications or placebo were titrated upward as required and tolerated throughout the study. Paroxetine (or matched placebo) was initiated at 20 mg/day and titrated in 10-mg increments every week to a maximum of 40 mg/day (a minimum dose of 20 mg/day was maintained after week 3 of double-blind treatment). Risperidone (or matched placebo) was initiated at 1 mg/day and titrated in 1-mg increments every week to a maximum of 4 mg/day. Lorazepam, up to 3 mg/day, was allowed in the first month of treatment.

Subjects were evaluated using the HAM-D, MADRS, BDI, CGI-Severity of Illness (CGI-S) and CGI-I, YMRS, Simpson-Angus Scale (SAS),[20] and Barnes Akathisia Scale (BAS)[21] at baseline and then on a weekly or biweekly basis throughout the double-blind treatment phase. Data were gathered from August 1999 to September 2001.

### Data Analysis

Demographics were compared between groups using 1-way analysis of variance (ANOVA) or the Fisher exact test as appropriate. The primary (HAM-D) and secondary (MADRS, BDI, YMRS, and CGI) outcome variables were compared using ANOVA with post hoc t tests. The main analyses were conducted using a last-observation-carried-forward (LOCF) method. In addition, response and remission status was analyzed. Response was defined as a ≥ 50% improvement on the HAM-D (17-item) and a score of 1 or 2 on the CGI-S (LOCF). Remission was defined as a final HAM-D score of ≤ 7 and no longer meeting DSM-IV criteria for major depressive disorder (LOCF). Proportions were compared using the Fisher exact test.

## RESULTS

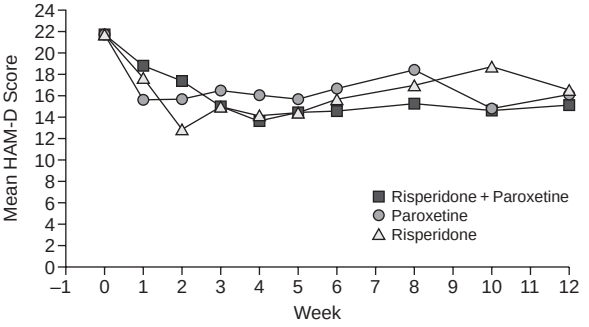
Thirty patients were randomly assigned to the double-blind treatment phase. The sample was evenly divided between women and men; the mean age was 35.6 years (SD = 10.7). The mean baseline scores were HAM-D

21.5 (SD = 3.8), BDI 27.8 (SD = 12.2), and MADRS 17.7 (SD = 7.1). Distribution of diagnoses were as follows: RIS + PAR, bipolar I = 6, bipolar II = 4; PAR + placebo, bipolar I = 9, bipolar II = 1; RIS + placebo, bipolar I = 6, bipolar II = 4 ($\chi^2 = 2.86$, df = 2, p = NS). There were no significant differences between groups by age, sex, or baseline ratings. The distribution of mood-stabilizer treatment by group was as follows: RIS + PAR, divalproex = 4, lithium = 3, carbamazepine = 0, combined lithium plus anticonvulsant = 2, topiramate = 1; PAR + placebo, divalproex = 4, lithium = 1, carbamazepine = 2, lithium plus anticonvulsant = 0, topiramate = 3; RIS + placebo, divalproex = 5, lithium = 2, carbamazepine = 3, lithium plus anticonvulsant = 0, topiramate = 0 ($\chi^2 = 11.54$, df = 8, p = NS).

The mean maximum dose of risperidone was 1.16 (SD = 0.67) mg/day for the RIS + PAR group and 2.15 (SD = 1.2) mg/day for the RIS + placebo group (t = –1.2, df = 18, p = NS). The mean maximum dose of paroxetine was 22.0 (SD = 12.3) mg/day for the RIS + PAR group and 35.0 (SD = 21.2) mg/day for the PAR + placebo group (t = –2.2, df = 18, p < .05).

The 3 groups experienced equivalent change in depression rating scores from baseline to endpoint (Figure 1) (1-way ANOVA: MADRS, F = 0.370, df = 2,27; p = NS; HAM-D, F = 0.058, df = 2,27; p = NS). The mean changes from baseline to endpoint (LOCF) for HAM-D and MADRS scores, respectively, were as follows: RIS + PAR = 6.3 (SD = 6.5; Cohen's d = 1.044, effect size = 0.463) and 5.8 (SD = 6.1; Cohen's d = 0.680, effect size = 0.322); PAR + placebo = 5.6 (SD = 6.5; Cohen's d = 1.069, effect size = 0.472) and 7.9 (SD = 7.3; Cohen's d = 1.008, effect size = 0.450); RIS + placebo = 5.2 (SD = 8.7; Cohen's d = 0.838, effect size = 0.386) and 4.2 (SD = 13.7; Cohen's d = 0.428, effect size = 0.209) (HAM-D: F = 0.058, df = 2,27; p = NS; MADRS: F = 0.370, df = 2,27; p = NS). There were no significant differences between groups at any rating point (LOCF) for any of the assessments (including HAM-D, MADRS, BDI, CGI, YMRS, SAS, BAS) except for the following: The YMRS showed a small but significant difference between groups at week 4; mean scores: RIS + PAR = 2.2 (SD = 2.4), PAR + placebo = 0, RIS + placebo = 1.3 (SD = 1.04) (F = 4.19, df = 2,23; p < .03); Tukey honestly significant difference (HSD), combined versus paroxetine, p < .03; all other comparisons were nonsignificant. The mean CGI-I scores at week 4 were RIS + PAR = 1.5 (SD = 0.8), PAR + placebo = 2.2 (SD = 1.3), RIS + placebo = 2.9 (SD = 1.1) (F = 3.59, df = 2,25; p < .05); Tukey HSD, combined versus risperidone, p < .04; all other comparisons were nonsignificant. The mean scores for the Simpson-Angus Scale were as follows: RIS + PAR = 1.2 (SD = 1.3), PAR + placebo = 0, RIS + placebo = 0.4 (SD = 0.5) (F = 4.3, df = 1,22; p < .03); Tukey HSD, combined versus paroxetine, p < .03; others nonsignificant. For patients who completed 12 weeks of treatment, all comparisons between groups on all ratings were nonsignificant. Figure 1 summarizes HAM-D scores by group. There were no cases of mania in any group. There was 1 case of very mild hypomania (YMRS score = 13) in the PAR + placebo group.

**Figure 1. Hamilton Rating Scale for Depression (HAM-D) Scores by Group (LOCF)**




Abbreviation: LOCF = last observation carried forward.

Remission (HAM-D score ≤ 7 at endpoint) was achieved in 3 patients in the RIS + PAR group, 2 in the PAR + placebo group, and 1 in the RIS + placebo group. Response (≥ 50% improvement in HAM-D score at endpoint) occurred in 3 patients in RIS + PAR, 2 in PAR + placebo, and 3 in RIS + placebo (Fisher exact test = NS, both contrasts).

A total of 11 patients dropped out before completing the study, 4 in RIS + PAR, 2 in PAR + placebo, and 5 in RIS + placebo group ($\chi^2 = 2.01$, df = 2, p = NS). Five participants dropped out for side effects, 3 in the RIS + PAR group and 1 each in the PAR + placebo and RIS + placebo groups. One patient dropped out of the RIS + PAR group and 3 dropped out of the RIS + placebo group for lack of improvement in depression. One patient each in the PAR + placebo and RIS + placebo groups was lost to follow-up. The commonest adverse events included appetite increase (2 in each group), weight gain (4 in RIS + PAR, 1 each in the other groups), diarrhea (RIS + PAR = 1, PAR + placebo = 3, RIS + placebo = 2), gastrointestinal distress (2 in each group), somnolence (RIS + PAR = 2, PAR + placebo = 2, RIS + placebo = 5), and sexual dysfunction (RIS + PAR = 3, PAR + placebo = 2, RIS + placebo = 0) (Table 1).

## DISCUSSION

The addition of risperidone, paroxetine, or the combination to a mood-stabilizing medication resulted in a statistically equivalent improvement from baseline on the main outcome comparisons, the HAM-D and MADRS, over the 12-week study period (Figure 1). The differences between groups on other measures generally were small and not clinically significant. The YMRS showed a statis-

Table 1. Frequency of Adverse Events by Group (N)

| Adverse Event | Risperidone + Paroxetine | Paroxetine + Placebo | Risperidone + Placebo |
|---|---|---|---|
| Agitation | 1 | 0 | 0 |
| Anxiety | 0 | 0 | 1 |
| Appetite decrease | 0 | 1 | 0 |
| Appetite increase | 2 | 2 | 2 |
| Blurred vision | 1 | 0 | 0 |
| Constipation | 0 | 0 | 1 |
| Depression increased | 1 | 0 | 0 |
| Dermatitis | 0 | 0 | 1 |
| Diaphoresis | 0 | 1 | 1 |
| Diarrhea | 1 | 3 | 2 |
| Dizziness | 1 | 1 | 0 |
| Dreaming increased | 0 | 0 | 1 |
| Dry mouth | 1 | 3 | 1 |
| Edema | 0 | 0 | 1 |
| Fatigue | 1 | 2 | 2 |
| Gastrointenstinal distress | 2 | 2 | 2 |
| Hair loss | 0 | 1 | 0 |
| Headache | 0 | 1 | 1 |
| Insomnia | 1 | 2 | 0 |
| Joint pain | 0 | 0 | 1 |
| Memory problems | 1 | 0 | 0 |
| Myoclonus | 0 | 0 | 1 |
| Nausea | 0 | 2 | 0 |
| Paresthesias | 1 | 0 | 0 |
| Salivation increased | 1 | 0 | 0 |
| Sexual dysfunction | 3 | 2 | 0 |
| Somnolence | 2 | 2 | 5 |
| “Spaciness” | 0 | 1 | 0 |
| Tremor | 1 | 1 | 1 |
| Urinary tract infection | 0 | 1 | 0 |
| Weight gain | 4 | 1 | 1 |

tically significant but probably not clinically meaningful difference in score between groups at week 4 (mean scores: combined = 2.2, paroxetine alone = 0, risperidone alone = 1.25). Similarly, the SAS scores were different at week 12, but scores were low.

The one surprising finding of the study was that risperidone alone produced as much effect as the other 2 treatment conditions at all time points. This suggests that risperidone may produce some direct antidepressant effects that are not merely dependent on the antipsychotic action of the drug, which is consistent with data from prior studies in other diagnostic groups.[22] For example, when used in patients with schizophrenia or schizoaffective disorder, risperidone has been shown to produce a greater effect on ratings of depression than haloperidol or placebo.[23,24] In addition, Ostroff and Nelson[25] showed that risperidone was effective in augmenting the actions of SSRIs in a series of 8 nonpsychotic, treatment-resistant depressed patients. By contrast, however, in the current trial, the combined treatment condition did not produce an effect that was greater than the medications given singly. Therefore, there was no evidence of an augmenting effect of risperidone with paroxetine in patients with bipolar disorder without treatment resistance. Furthermore, although all groups showed reduction in depression ratings from baseline to endpoint, the overall effect was modest, averaging only about 6 points with effect sizes ranging from 0.386 to 0.472 on the HAM-D.

Overall, the switch rate into mania or hypomania was very low in this trial. Only 1 patient in the PAR + placebo group experienced very mild hypomania, with a YMRS score of only 13. While this rate seems comparatively low, recent trials of adding an antidepressant to a mood stabilizer in bipolar depression suggest that switch rates in short-term treatment studies of bipolar disorder may be low.[10,11,26] For example, Nemeroff et al.[10] randomly assigned 117 bipolar depressed patients receiving lithium to paroxetine, imipramine, or placebo. While the outcomes did not differ between groups, there were no reported switches into mania or hypomania in the paroxetine-treated group, as opposed to 7.7% of the imipramine group and 2% of those given placebo. These rates also are similar to those derived from a meta-analysis of clinical trials that found rates of 3.7% with SSRIs, 11.2% with tricyclics, and 4.2% with placebo.[27] Together, these data indicate that persons included in trials of bipolar depression show relatively low switch rates into mania or hypomania. Whether this is true of other bipolar depressed patients is unknown.

The relative lack of effect with paroxetine, either alone or in combination with risperidone, is somewhat surprising as well. Paroxetine is an effective antidepressant in non-bipolar depressed patients, and a similar effect would be expected in this population. However, the results of this study are consistent with 2 trials of paroxetine in bipolar depression cited earlier, which showed limited effect.[10,11]

A higher proportion of patients dropped out of the RIS + placebo (N = 5) and RIS + PAR groups (N = 4) than the PAR + placebo group (N = 2), although this difference did not reach statistical significance. Dropouts for side effects were about equally distributed between the groups. Most of the side effects were consistent with previous studies; for example, patients reported sexual dysfunction in both paroxetine groups and none in the RIS + placebo group. Gastrointestinal distress was equally distributed between groups (2 each); however, more patients reported diarrhea in the PAR + placebo and RIS + placebo groups. The difference between the PAR + placebo and RIS + PAR groups may have resulted from the lower dose given to the patients in the combined condition. There was a higher frequency of weight gain in the RIS + PAR group (N = 4) in contrast to the other groups (N = 1 each), although this was not statistically significant ($\chi^2$ = NS).

The mean maximal dose of paroxetine was lower in the RIS + PAR group than in the PAR + placebo group. The reason for this is uncertain. It could have been a result of a pharmacokinetic interaction between paroxetine and risperidone, such that the plasma levels of one or both might have been higher than expected. Therefore, although there

was a lower mean maximal dose of paroxetine in the combined group, the average plasma levels might or might not have been different. The burden of most side effects did not differ between groups. However, extrapyramidal symptoms as measured by the Simpson-Angus Scale were greater in the RIS + PAR group, suggesting that the plasma risperidone level may have been higher in this group.

The results of this study must be considered preliminary and interpreted with caution. The sample size was very small (N = 10 per group) and, therefore, may not have been statistically powerful enough to detect small but meaningful differences. The group was exclusively moderately depressed outpatients, which limits generalizability of the findings. In addition, the dose of paroxetine in the PAR + placebo condition was significantly higher than in the combined treatment group; therefore, this cannot be considered a definitive test of the effects of risperidone added to an SSRI in bipolar depression. In addition, the participants had to be on treatment with a mood stabilizer at a stable dose for at least 3 weeks; however, a recent change in dose of the mood stabilizer could account for the improvement in depression in some patients. Finally, although all 3 conditions produced significant change from baseline to endpoint in depression ratings, it is not known whether this change was greater than would be produced by placebo alone (i.e., placebo + placebo). Clearly, more research is needed in this area.

*Drug names:* carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril, Fazaclo, and others), divalproex (Depakote), fluoxetine (Prozac and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), paroxetine (Paxil and others), risperidone (Risperdal), topiramate (Topamax), valproic acid (Depakene and others).

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