Symptomatic Remission in Patients With Bipolar Mania: Results From a Double-Blind, Placebo-Controlled Trial of Risperidone Monotherapy

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Background: The purpose of this analysis was to assess rates of symptomatic remission in patients with bipolar mania receiving risperidone in a double-blind, parallel-group, multicenter, placebo-controlled trial conducted in India.

Method: Two hundred ninety-one adult patients who met DSM-IV criteria for bipolar I disorder manic or mixed episode were randomly assigned to flexible doses of risperidone (1–6 mg/day, N = 146) or placebo (N = 145) for up to 3 weeks. An entry Young Mania Rating Scale (YMRS) score of ≥ 20 was required at trial screening and baseline. Remission was defined as achieving and maintaining a YMRS score ≤ 8 for the remainder of the trial or until censor. Time to first onset of remission was assessed using Cox proportional hazards model. Presence or absence of remission was analyzed using logistic regression. Data were collected from March 2001 to December 2001.

Results: Of the 291 patients randomly assigned to treatment, 290 received at least 1 postbaseline assessment and were included in the analysis. The patients' mean YMRS score at baseline was 37.2 ± 7.9. Remission was achieved by 42% of patients in the risperidone group and 13% of patients in the placebo group. After adjusting for psychosis, baseline YMRS score, sex, number of mood cycles in the previous year, and treatment, the odds of remission for patients receiving risperidone was 5.6 (95% CI = 3.0 to 10.4; $\chi^2 = 29.9$, $p < .0001$). Similarly, the adjusted hazard of remission for the risperidone patients was 4.0 (95% CI = 2.3 to 6.8; $\chi^2 = 25.9$, $p < .0001$).

Conclusion: A significant proportion of acutely manic patients receiving risperidone monotherapy achieved symptomatic remission within 3 weeks.

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Antipsychotics have been used to treat acute mania since the introduction of chlorpromazine in the 1950s.[1] For patients with bipolar disorder, antipsychotics were initially used to treat agitation, but are now also used to control psychotic symptoms and stabilize mood.[2,3] Over the past 5 years, clinical trial data have emerged demonstrating that atypical antipsychotics also have efficacy in the treatment of acute mania.[4–8]

Many current bipolar mania trials distinguish between symptomatic responders and nonresponders.[4–8] In these studies, a responder is typically defined as having a ≥ 50% decrease in Young Mania Rating Scale (YMRS) scores from baseline to endpoint. While this approach can assess efficacy, it may not be useful for practicing clinicians. The goal of treatment in bipolar patients is not to reduce symptoms by 50%, but to attain total symptom remission (or as close to this as possible). A 50% reduction in YMRS scores can still leave patients with residual symptoms that significantly affect functioning and are in need of treatment.

A reduction in residual symptoms as a standard to measure clinical effectiveness has been examined extensively

in unipolar depression studies,[9–11] but not nearly as carefully in the bipolar mania literature. Further, the concepts of remission and full recovery have not been well defined in bipolar disorder. Yatham et al.[12] defined clinical remission in bipolar disorder as a maintained YMRS score of ≤ 8. Chengappa et al.[13] proposed a unique definition of remission from acute mania: at endpoint a YMRS total score of ≤ 7, a Hamilton Rating Scale for Depression (21-item) score of ≤ 7, and a Clinical Global Impressions (CGI) scale-bipolar version overall severity score of ≤ 2. In a recent analysis of data from 2 trials of risperidone in bipolar patients, Canuso et al.[14] used a criteria of YMRS total score ≤ 12 and ≤ 7 to define remission both at study endpoint and sustained during treatment.

Data for the present analysis were derived from a multisite study of 290 patients with bipolar disorder treated with risperidone or placebo. The major findings from the study are published elsewhere.[15] We chose to focus our analysis on remission rates in this clinical trial. Our primary hypothesis was that symptomatic remission (as defined below) would be achieved by more patients receiving risperidone than placebo.

METHOD

Study Design

This was a double-blind, parallel-group, multicenter, placebo-controlled trial conducted at 8 sites in India.[15] Of the 324 patients who were screened, 291 (90%) were randomly assigned to treatment (145 patients to placebo, 146 patients to risperidone) and entered a washout period of up to 3 days. The double-blind portion of the trial lasted 3 weeks. Patients were randomly assigned to 1 of 2 treatment groups according to a randomization code. The randomization was stratified according to the presence or absence of psychotic features associated with the manic episode and by center. Data were collected from March 2001 to December 2001.

After randomization and the initiation of double-blind medication (placebo or 1–6 mg/day of risperidone), subjects were hospitalized for ≥ 7 days. As early as day 8, patients were discharged and followed as outpatients if they were rated by the investigator to be at no significant risk for suicidal or violent behavior and if their CGI-Severity of Illness (CGI-S) scale[16] score was 3 (mildly ill) or less. The antimanic efficacy of 3 weeks of treatment was determined primarily by the treatment group change in YMRS scores from baseline.

Subjects

Adult patients aged 18 to 65 years who fulfilled DSM-IV criteria for bipolar I disorder manic or mixed episode were eligible to enter the trial. Subjects who entered the trial gave their informed consent after possible risks, benefits, and side effects were fully explained.

Inclusion criteria included age 18 to 65 years, a DSM-IV diagnosis of bipolar I disorder manic or mixed episode, screening and baseline YMRS scores ≥ 20, and a history of at least 1 prior manic episode that required treatment. Female patients had to be either postmenopausal or using an acceptable form of contraception. Exclusion criteria included schizoaffective disorder, rapid-cycling bipolar disorder, or borderline or antisocial personality disorder; a history of neuroleptic malignant syndrome or substance dependence; serious or unstable illnesses; significant risk of suicidal or violent behavior; alcohol or illegal drug use within 3 days prior to screening; and use of an antidepressant, clozapine, or depot antipsychotic within 30 days prior to screening. Pregnant or nursing women were also excluded.

Remission Criteria

For the primary analysis of this study, remission was defined as achieving and maintaining for the trial duration a YMRS score ≤ 8. Two additional remission criteria were also analyzed: a YMRS score ≤ 12 and ≤ 7 at treatment endpoint. Sustained remission was defined as a YMRS score ≤ 12 or ≤ 7 during treatment and at endpoint.

Data Analyses

Two main statistical models were used in this analysis: (1) survival analysis using Cox proportional hazards model and (2) multiple logistic regression analysis. The outcome variable of interest for the Cox model is the time to first onset of remission (YMRS score ≤ 8). The presence or absence of remission was examined in our multiple logistic regression model.

The primary outcome variable tested was the dichotomous presence or absence of remission (YMRS score ≤ 8) during the entire trial period or until time of censorship. Because survival analysis methods allow for varying lengths of follow-up time, we did not use any special imputation methods for missing values. All patients were censored at 21 days or at trial withdrawal if earlier. All statistical analyses were performed using SAS Analyst Application 8.02 (SAS Institute Inc, Cary, N.C.).

A 10% significance level was used to test for interactions. Univariate plots for all continuous predictor variables were used to assess linearity. Collinearity diagnostics of tolerance, variance/inflation, and standard error were used to determine interrelationships between variables. Log-minus-log survival plots were examined to assess assumptions of proportional hazards.

RESULTS

Of the 291 patients who were randomly assigned to treatment, 290 received at least 1 postbaseline assessment and are included in the analysis. Baseline demographic and clinical characteristics of the patients in the risperi-

Table 1. Characteristics at Baseline of Patients With Bipolar I Disorder Who Received Risperidone or Placebo

Characteristic	Risperidone (N = 146)	Placebo[a] (N = 145)
Sex, N (%)		
Men	100 (68)	81 (56)
Women	46 (32)	64 (44)
Age, mean ± SD, y	34.7 ± 12.0	35.5 ± 12.3
Diagnosis, N (%)		
Manic with psychotic features	84 (58)	79 (54)
Manic without psychotic features	58 (40)	57 (39)
Mixed with psychotic features	3 (2)	4 (3)
Mixed without psychotic features	1 (< 1)	4 (3)
No. of prior manic episodes, mean ± SD	4.7 ± 4.5	4.8 ± 3.7
Age at onset, mean ± SD, y	24.6 ± 8.8	25.2 ± 10.4
GAS score, mean ± SD	35.2 ± 10.3	34.6 ± 10.3
MADRS score, mean ± SD	5.1 ± 3.4	5.9 ± 4.5
YMRS score, mean ± SD	36.9 ± 8.0	37.4 ± 7.9

[a]One patient did not take double-blind medication and was excluded from all statistical analyses.
Abbreviations: GAS = Global Assessment Scale, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

Table 2. Disposition of Patients With Bipolar I Disorder Receiving Risperidone or Placebo

	Risperidone		Placebo	
Variable	N	%	N	%
Completed study	130	89	103	71
Discontinued	16	11	42	29
Insufficient response	7	5	21	15
Lost to follow-up	1	< 1	10	7
Adverse event	5	3	3	2
Withdrew consent	1	< 1	6	4
Other	2	1	2	1

done and placebo groups were similar (Table 1). The study was completed by 89% of the risperidone group and 71% of the placebo group (Table 2), and the mean ± SD duration of treatment was 19.9 ± 0.3 and 17.9 ± 0.5 days in the 2 groups, respectively. The mean ± SD modal dose of risperidone was 5.6 ± 0.1 mg/day.

Remission (maintenance of a YMRS score ≤ 8 for the remainder of the trial) was achieved by 61 (42%) of 146 patients in the risperidone group and 18 (13%) of 144 patients in the placebo group. Risperidone treatment was significantly correlated with shorter time to remission (hazard ratio = 3.7, 95% CI = 2.2 to 6.2) (Table 3 and Figure 1). The unadjusted odds ratio for remission in the risperidone group was 5.0 (95% CI = 2.8 to 9.1) (Table 3). The Cochran-Mantel-Haenszel test controlling for site was used to test the homogeneity of odds ratios across the different investigational sites. The odds ratios for remission and a Breslow-Day χ^2 test revealed no evidence of significant differences between the sites ($\chi^2 = 4.6$, df = 5, p = .5).

Five predictors of remission were chosen for their clinical relevance before the analyses were performed. The 5 predictors were risperidone treatment, sex (female), baseline YMRS score, absence of psychotic features, and number of mood cycles in the year before enrollment. The multivariable Cox model showed that for both remission criteria, 2 of the variables, risperidone treatment and absence of psychosis, were significant independent predictors of remission (Table 3).

Multiple logistic regression analysis confirmed that patients treated with risperidone had significantly higher odds of remission. The adjusted odds ratio for remission in the risperidone group was 5.6 (95% CI = 3.0 to 10.4). No significant interactions were found, and hence, only main effects were included in our multivariate models.

Since absence of psychosis appears to be a predictor of remission, we determined whether disease severity was related to the presence or absence of psychotic features at trial entry. Disease severity was assessed by YMRS, Global Assessment Scale (GAS),[17] and CGI-S scores. Baseline scores on the YMRS (95% CI difference between means = 4.4 to 7.9, t = 7.0, p < .0001) and GAS (95% CI difference between means = –5.0 to –9.5, t = 6.3, p < .0001) were significantly higher for subjects with than without psychotic features. Baseline CGI-S scores were converted to an ordinal scale and then correlated to the presence or absence of psychotic features at baseline. As expected, baseline CGI-S scores were also significantly correlated with presence of psychotic features (odds ratio = 3.1, 95% CI = 2.2 to 4.4, p < .0001).

Additional Remission Criteria

According to the YMRS score ≤ 12 criterion, remission was achieved by 77 (54%) of 144 patients in the risperidone group and by 33 (23%) of 142 patients in the placebo group, and sustained remission was achieved by 42 (29%) of 144 patients and by 18 (13%) of 142 patients, respectively. According to the YMRS score ≤ 7 criterion, remission was achieved by 54 (38%) of 144 patients in the risperidone group and by 14 (10%) of 142 patients in the placebo group, and sustained remission was achieved by 25 (17%) of 144 patients and by 5 (4%) of 142 patients, respectively. Between-group differences for both criteria were significant (p < .001, Cochran-Mantel-Haenszel test controlling for presence of psychotic features at baseline). The odds ratios for remission and a Breslow-Day χ^2 test revealed no evidence of significant differences between treatment sites ($\chi^2 = 5.1$, df = 5, p = .4 for the ≤ 12 criterion and $\chi^2 = 4.0$, df = 5, p = .5 for the ≤ 7 criterion).

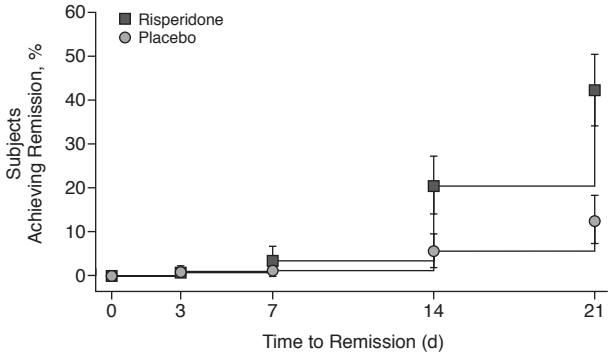
As in the analysis of the 5 predictors at the remission criterion of YMRS score ≤ 8, 2 of the 5 variables, risperidone treatment and absence of psychosis, were significant independent predictors of remission at the additional remission criteria. At the criterion of YMRS score ≤ 12, the adjusted hazard ratios were 2.4 (95% CI = 1.6 to 3.7, p < .0001) and 1.9 (CI = 1.3 to 2.9, p < .01), respectively. At the criterion of YMRS score ≤ 7, the adjusted hazard

Table 3. Adjusted and Unadjusted Analyses in Patients With Bipolar I Disorder Who Received Risperidone or Placebo

Analysis	Odds Ratio (95% CI)	p Value (χ^2)	Cox Hazard Ratio (95% CI)	p Value (χ^2)
Unadjusted				
Risperidone treatment	5.0 (2.8 to 9.1)	< .0001 (31.4)	3.7 (2.2 to 6.2)	< .0001 (23.5)
Adjusted				
Risperidone treatment	5.6 (3.0 to 10.4)	< .0001 (29.9)	4.0 (2.3 to 6.8)	< .0001 (25.9)
Sex (women)	1.3 (0.7 to 2.4)	.3 (0.9)	1.2 (0.7 to 1.9)	.39 (0.73)
Baseline YMRS score	0.99 (0.95 to 1.03)	.5 (0.4)	0.99 (0.96 to 1.02)	.4 (0.7)
No psychotic features	2.1 (1.1 to 3.8)	.01 (5.7)	1.8 (1.1 to 2.9)	.01 (6.2)
No. of mood cycles in the past year	0.96 (0.62 to 1.47)	.84 (0.04)	0.97 (0.68 to 1.37)	.84 (0.04)

Abbreviation: YMRS = Young Mania Rating Scale.

Figure 1. Kaplan-Meier Estimates of the Time to Remission in Patients With Bipolar I Disorder Who Achieved Remission With Risperidone or Placebo



ratios were 3.8 (95% CI = 2.1 to 6.8, $p < .01$) and 1.8 (95% CI = 1.1 to 2.9, $p < .05$), respectively.

CONCLUSION

The results of this study demonstrate that acutely manic patients treated with risperidone monotherapy have approximately 5 times higher odds of achieving remission than patients who receive placebo. The patients in this study can be classified as being severely ill (baseline YMRS score of 37.2 compared with a baseline score of 29.0 in a similar study completed in the United States[5]). Univariate and multivariate analysis confirmed that treatment with risperidone was associated with statistically greater odds and relative risk of achieving remission compared with placebo. Since acutely manic patients are at high risk for mortality and disability, the results suggest that treatment with risperidone can offer clinicians a rapid treatment option with an excellent chance that many patients will experience symptomatic remission.

Results of the analyses of the additional remission criteria (YMRS score ≤ 12 and YMRS score ≤ 7) support the findings of the primary remission criterion (YMRS score ≤ 8), suggesting that, however remission is defined, a substantial proportion of acutely manic patients treated with risperidone will achieve remission.

Results of the multivariate analyses indicated that treatment with risperidone and absence of psychotic features were significant predictors of remission. Disease severity and presence of psychotic features at study entry correlated with higher CGI-S and lower GAS scores. In general, subjects with psychotic features had more severe disease at entry. This finding could account for the difference in remission outcome in patients with and without psychotic features. Our findings confirm those of other studies,[18,19] which found that patients with psychotic features are less likely to achieve remission of manic symptoms. We expected that patients with a greater number of mood cycles would be less likely to achieve clinical remission. Our analysis, however, found no significant relationship between number of mood cycles and remission of manic symptoms, although there was clinical evidence (not statistically significant) that each additional mood cycle had a somewhat deleterious effect on the likelihood of remission.

In conclusion, this study provides evidence that many acutely manic patients who receive risperidone monotherapy will experience symptomatic remission; 42% of the patients treated with risperidone, compared with 13% of the placebo patients, achieved remission by the third week of treatment. Patients treated with risperidone had a 5.6 times greater odds of achieving remission than subjects who were given placebo. Significant separation of remission rates between placebo and risperidone was apparent by treatment day 14.

Drug names: chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril, FazaClo, and others), risperidone (Risperdal).

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