Risperidone in Combination With Mood Stabilizers: A 10-Week Continuation Phase Study in Bipolar I Disorder

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Received March 4, 2003; accepted Jan. 14, 2004. From the University of Texas Health Science Center, San Antonio (Dr. Bowden); and Johnson & Johnson Pharmaceutical Research and Development, Titusville, N.J. (Drs. Myers, Grossman, and Xie).

Financial support for this study was provided by Janssen Pharmaceutica Products, L.P., Titusville, N.J.

Dr. Bowden has received grant/research support from Abbott, Bristol-Myers Squibb, Glaxo Wellcome, Janssen, Lilly, National Institute of Mental Health, Parke Davis, R. W. Johnson Pharmaceutical Institute, SmithKline Beecham, and Stanley Foundation; has been on the speakers bureau for Abbott, AstraZeneca, Glaxo Wellcome, Janssen, Lilly, and Pfizer; and has been a consultant for Abbott, Glaxo Wellcome, Janssen, Lilly, Sanofi Synthelabo, and UCB Pharma. Dr. Myers has been a consultant for Janssen, Organon, and Ortho-McNeil and is a major stock shareholder in Johnson & Johnson. Dr. Grossman is an employee of Johnson & Johnson.

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Background: Combination therapy (risperidone and a mood stabilizer) for patients with a history of bipolar disorder (DSM-IV) and hospitalized for treatment of a manic episode was assessed in a 13-week study.

Method: Subjects received flexible doses of a mood stabilizer (lithium or divalproex) plus placebo, risperidone, or haloperidol in a 3-week double-blind study. They could then enter a 10-week open-label study during which they received risperidone combined with a mood stabilizer.

Results: Of the 156 patients enrolled in the 3-week study, 85 entered the 10-week open-label extension, of whom 48 completed 10 weeks of treatment. The mean ± SE doses of risperidone were 3.8 ± 0.3 mg/day during the 3-week study and 3.1 ± 0.2 mg/day during the 10-week study. At double-blind endpoint, mean reductions in Young Mania Rating Scale (YMRS) scores were significantly greater in patients receiving risperidone plus mood stabilizer than in those receiving placebo plus mood stabilizer (–14.3 vs. –8.2, $p < .001$). Further significant ($p < .001$) reductions were seen during the 10 weeks of treatment with risperidone plus mood stabilizer. Symptom remission (YMRS score ≤ 12) was seen in 38 patients (79%) at the end of the 10-week study. Scores on the Brief Psychiatric Rating Scale, Hamilton Rating Scale for Depression, and Clinical Global Impressions scale improved significantly ($p < .05$) during both the 3-week and 10-week studies. Treatment was well tolerated, and modest weight gain was observed during the 13-week study period.

Conclusion: The combination of risperidone and a mood stabilizer was efficacious and well tolerated in the continuation treatment of patients initially hospitalized for the management of an acute manic episode.

(J Clin Psychiatry 2004;65:707–714)

The efficacy of mood stabilizers combined with atypical antipsychotic agents in the treatment of acute mania has been demonstrated in several studies.[1–7] There is, however, less information from controlled studies assessing the longer-term efficacy of these combinations during the maintenance phase of treatment. The need for more effective pharmacotherapy during this phase is critically important because outcomes after an acute manic episode have been generally reported as poor. Several longitudinal studies after hospitalization have shown that many of these patients fail to experience full recovery in occupational and psychosocial functioning.[8–11] For those who do recover, over half can expect to experience a relapse within 1 year of treatment.[12]

Evidence from several studies in more refractory patients suggests that the atypical agents may be beneficial during continuation and maintenance treatment in these bipolar patients when used alone[13,14] or in combination with a mood stabilizer.[15–20] We report the results of a 13-week study in which the efficacy and safety of risperidone combined with a mood stabilizer were evaluated in patients initially hospitalized for an episode of acute mania. In the first 3-week, double-blind (DB), placebo-controlled phase of the study, the results of which have been published,[3] risperidone plus a mood stabilizer was significantly more efficacious than placebo plus a mood stabilizer and was well tolerated. The 3-week DB study was followed by a 10-week open-label (OL) phase to assess the longer-term efficacy and safety of risperidone as adjunctive treatment after initial treatment for acute mania.

METHOD

Subjects were patients aged 18 to 65 years with a history of bipolar disorder and at least 1 prior manic episode who were hospitalized for the treatment of a manic episode. Inclusion criteria included a minimum score of 20 on the Young Mania Rating Scale (YMRS)[21] and a DSM-IV diagnosis of bipolar disorder, with most recent episode manic or mixed (296.4x, 296.6x). Exclusion criteria included another DSM-IV Axis I diagnosis, alcohol or substance abuse/dependence in the last month, serious medical or laboratory abnormalities, central nervous system disorders, serious suicidal risk, or pregnancy. Institutional review board approval was obtained for the study, and written informed consent to participate in the study was obtained from each patient.

Procedures

At the start of the 3-week DB study, subjects were randomly assigned to receive flexible doses of a mood stabilizer (lithium or divalproex) plus placebo (placebo/MS group), risperidone (risperidone/MS group), or haloperidol (haloperidol/MS group). Patients who completed the 3-week study or at least 7 days of DB treatment but had discontinued because of lack of efficacy or an adverse event not attributable to the DB treatment were eligible to enter the 10-week OL extension study. During the 10-week OL study, patients received risperidone combined with lithium, divalproex, or carbamazepine. Patients judged to be noncompliant by the investigator during the DB phase were not eligible for the 10-week study. Patients were required to enter the OL study within 5 days of discontinuing or completing the DB phase. All patients who received placebo or haloperidol during the DB study were reassigned to receive risperidone during the 10-week OL study.

Assessments

All patients received an initial psychiatric evaluation to establish the diagnosis of bipolar disorder. Efficacy measures including the YMRS,[21] the Brief Psychiatric Rating Scale (BPRS),[22] the Clinical Global Impressions scale (CGI),[23] and the 21-item Hamilton Rating Scale for Depression (HAM-D)[24] were completed before the start of the DB treatment and at days 1, 8, 15, and 22 (or DB endpoint). Laboratory tests and physical examinations (including body weight) were performed at baseline and day 22 (or DB endpoint). Adverse events were assessed weekly.

During the 10-week study, assessments with the YMRS, BPRS, CGI, and HAM-D were completed at baseline of open-label treatment and weeks 1, 2, 6, and 10 (or endpoint). Adverse events were assessed weekly. Vital signs were measured at weeks 1, 2, 6, and 10 (or endpoint). At week 10 (or endpoint), patients received a physical examination and were weighed, an electrocardiogram and laboratory tests were performed, and serum levels of mood stabilizers were measured.

Dosing Schedule

Patients who initially received risperidone during the DB phase continued to receive risperidone at the same dose during the 10-week study. Haloperidol doses were reduced over a 4-day period before the start of the 10-week study while risperidone was introduced at 2 mg on days 1 and 2, 4 mg on days 3 and 4, and up to 6 mg/day at the start of the 10-week study. The risperidone dose was then adjusted based on clinical response. During the 10-week study, the patient's mood stabilizer could be changed or a second mood stabilizer, antidepressant, or anxiolytic agent added if clinically indicated in the investigator's judgment. Serum trough levels of divalproex and lithium continued to be maintained at 50 to 120 μg/mL and 0.6 to 1.4 mEq/L, respectively. Carbamazepine (serum trough level, 4–12 μg/mL) could also be used during this phase. Serum concentrations of mood stabilizers were measured whenever felt to be clinically indicated and at week 10 or endpoint.

Concomitant Medications

No antipsychotic medications other than risperidone and no mood stabilizers other than lithium, divalproex, or carbamazepine were permitted. Patients could receive benzodiazepines (lorazepam, temazepam, oxazepam, or flurazepam) if the medication had been initiated during the DB phase of the study. Rescue medications were not allowed for agitation.

Efficacy Measures

The primary outcome measure was change in YMRS score (possible scores range from 0–60). Secondary measures included the BPRS (scores range from 18–126), the CGI-Severity of Illness scale (from 0, not ill, to 7, extremely ill), the CGI-Change scale (CGI-C) (from 1 = very much better to 7 = very much worse), and the HAM-D. Efficacy was assessed from DB baseline to week 3 of DB treatment, from week 1 to week 10 of OL treatment, and from DB baseline to week 10 of OL treatment. This permitted comparative assessment of treatment efficacy for 3-week, 10-week, and 13-week intervals, respectively.

Symptomatic remission was measured according to 3 criteria: YMRS total score ≤ 12, YMRS total score ≤ 8, and YMRS total score ≤ 8 plus HAM-D total score ≤ 7.

Statistical Analysis

All patients who had at least 1 assessment during OL treatment were included in the observed-case analysis. The paired t test was used to evaluate the within-group differences between DB baseline, change at 3 weeks of

Table 1. Background Characteristics of Patients at Baseline of the Double-Blind Study and of the 10-Week Open-Label Risperidone/Mood Stabilizer (MS) Study (patients grouped according to DB treatment)

Characteristic	Placebo/MS	Risperidone/MS	Haloperidol/MS
Double-blind baseline			
N	51	52	53
Sex, N, male/female	24/27	26/26	30/23
Age, mean ± SE, y	42.1 ± 1.6	41.4 ± 1.5	42.7 ± 1.7
Bipolar episode type, N (%)			
Manic	40 (78)	42 (81)	41 (77)
Mixed	11 (22)	10 (19)	12 (23)
Current bipolar episode severity, N (%)			
Mild	0 (0)	1 (2)	3 (6)
Moderate	22 (43)	22 (42)	23 (43)
Severe with psychosis	22 (43)	21 (40)	18 (34)
Severe without psychosis	7 (14)	8 (15)	9 (17)
Open-label baseline			
N	26	34	25
Sex, N, male/female	10/16	15/19	14/11
Age, mean ± SE, y	41.3 ± 2.2	40.4 ± 1.8	42.6 ± 2.5
Bipolar episode type, N (%)			
Manic	20 (77)	29 (85)	18 (72)
Mixed	6 (23)	5 (15)	7 (28)
Current bipolar episode severity, N (%)			
Mild	0 (0)	0 (0)	2 (8)
Moderate	11 (42)	15 (44)	9 (36)
Severe with psychosis	10 (38)	13 (38)	8 (32)
Severe without psychosis	5 (19)	6 (18)	6 (24)

DB treatment, and total change score from DB baseline to 10 weeks of OL treatment for the primary and secondary efficacy variables. Safety data were collected on all patients who received at least 1 dose of study medication during the DB and OL phases of treatment.

RESULTS

Patients are grouped according to their initial treatment during the 3-week DB study to account for differences in exposure to risperidone over the total course of the 13 weeks of treatment. Characteristics of the total patient sample (N = 156) and of the 85 patients who entered the 10-week study are listed in Table 1. All had received a DSM-IV diagnosis of bipolar disorder, manic or mixed, the severity of which was moderate to severe in most. During DB treatment, 35% of risperidone/MS patients, 53% of haloperidol/MS patients, and 49% of placebo/MS patients discontinued the trial. Patient disposition during the 10-week study (during which all patients received risperidone) and reasons for early discontinuation are listed in Table 2.

Table 2. Disposition of Patients During the 10-Week Open-Label Risperidone/Mood Stabilizer (MS) Study (patients grouped according to double-blind treatment)

Variable	Placebo/MS (N = 26)	Risperidone/MS (N = 34)	Haloperidol/MS (N = 25)
Discontinued treatment, N (%)	9 (35)	15 (44)	13 (52)
Reasons for discontinuation, N			
Adverse event	0	3	4
Withdrew consent	1	3	2
Noncompliance	3	0	2
Lost to follow-up	0	3	1
Insufficient response	2	2	0
Ineligible	0	1	0
Other	3	3	4

Medications

During DB treatment, the mean ± SE modal doses were 3.8 ± 0.3 mg/day of risperidone and 6.2 ± 2.9 mg/day of haloperidol. During the 10-week OL phase, the mean ± SE modal dose of risperidone was 3.1 ± 0.2 mg/day. The mean duration of exposure for patients during the 10-week study in the placebo/MS, risperidone/MS, and haloperidol/MS groups was 52.9 ± 4.1 days, 47.2 ± 4.6 days, and 45.7 ± 5.4 days, respectively. Lithium was received by 25% (21/85) of patients, divalproex by 74% (63/85), and carbamazepine by 1 patient during the OL treatment. Mean serum concentrations of lithium and divalproex at week 3 of the DB phase and at endpoint of the 10-week OL study are shown in Table 3. The serum carbamazepine level in the 1 patient in the haloperidol/MS group was 2.0 mg/μL at week 10.

During the DB phase, antiparkinsonian medications were administered to 8% (4/51) of placebo/MS patients, 17% (9/52) of risperidone/MS patients, and 38% (20/53) of haloperidol/MS patients; during OL treatment, the respective numbers were 12% (3/26), 26% (9/34), and 40% (10/25). Lorazepam was administered to 2 patients who

Table 3. Serum Concentrations of Lithium and Divalproex at Week 3 of the Double-Blind (DB) Study and Week 10 of the Open-Label (OL) Risperidone/Mood Stabilizer (MS) Study (patients grouped according to double-blind treatment)

	Placebo/MS		Risperidone/MS		Haloperidol/MS	
Drug	N	Mean ± SE	N	Mean ± SE	N	Mean ± SE
Lithium concentration, mEq/L						
DB week 3	6	0.8 ± 0.1	11	0.7 ± 0.1	8	0.7 ± 0.1
OL week 10	3	0.7 ± 0.2	6	0.6 ± 0.1	1	0.2
Divalproex concentration, µg/mL						
DB week 3	18	77.3 ± 6.4	26	65.4 ± 5.3	24	76.2 ± 5.2
OL week 10	11	66.6 ± 8.9	10	52.8 ± 9.2	11	70.3 ± 11.5

Table 4. YMRS Scores During the Double-Blind (DB) and Open-Label (OL) Studies and Change From DB Baseline[a]

	Placebo/MS		Risperidone/MS		Haloperidol/MS	
Timepoint	N	Mean ± SE	N	Mean ± SE	N	Mean ± SE
DB baseline	50	28.0 ± 0.9	52	28.0 ± 0.8	53	27.3 ± 0.8
DB week 3	25	14.1 ± 1.9	38	10.8 ± 1.5	33	10.9 ± 1.4
Change		–13.4 ± 1.7[b]		–16.6 ± 1.3[b]		–15.4 ± 1.6[b]
OL week 1	26	12.5 ± 1.9	33	9.0 ± 1.4	24	8.4 ± 1.7
Change		–15.2 ± 1.5[b]		–17.7 ± 1.4[b]		17.7 ± 1.8[b]
OL week 10	17	6.3 ± 1.7	19	7.3 ± 2.1	12	6.7 ± 2.4
Change		–20.0 ± 1.6[b]		–18.4 ± 2.1[b]		–19.5 ± 2.4[b]

[a]Patients grouped according to DB treatment. During the OL study, all patients received a risperidone/MS combination.
[b]$p < .001$ vs. DB baseline (within-group analysis by paired t test).
Abbreviations: MS = mood stabilizer, YMRS = Young Mania Rating Scale.

had received placebo/MS and 4 patients who had received risperidone/MS during the DB phase of the study.

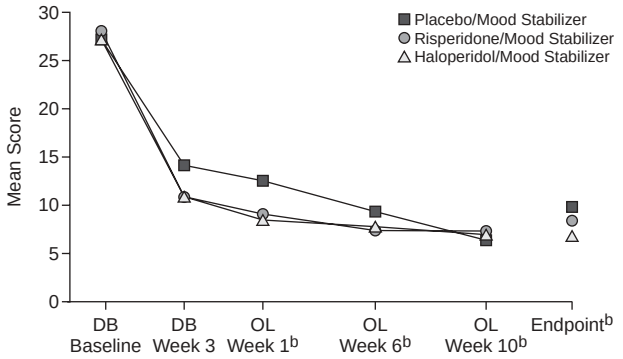
Efficacy

Mean YMRS total scores at baseline were similar in the 3 groups and ranged from 27.3 to 28.0 (Table 4). Significant improvements in YMRS scores were seen during the 3-week DB period and were maintained during the subsequent 10 weeks of OL treatment with risperidone/MS (Figure 1). At the DB endpoint, mean ± SE reductions in YMRS scores were significantly greater in patients receiving risperidone/MS (–14.3 ± 1.4; $p < .001$ vs. placebo/MS) or haloperidol/MS (–13.3 ± 1.4; $p < .05$ vs. placebo/MS) than an MS alone (placebo/MS, –8.2 ± 1.5). Similar reductions in YMRS scores were observed in the subsets of patients who initially presented with a mixed episode and psychotic symptoms, but patient numbers were too small to permit statistical analysis (N = 8 and N = 15, respectively).

Symptomatic remission (YMRS score ≤ 12) was seen in 38 patients (79%) at week 10. According to more stringent criteria of remission, 32 patients (67%) met a criterion of a YMRS score ≤ 8 and 17 (35%) met a criterion of a YMRS score ≤ 8 plus a HAM-D score ≤ 7 at week 10 (Figure 2). Mean ± SE time to first remission was 32 days at criteria of YMRS scores ≤ 12 and ≤ 8 and 34 days at a criterion of a YMRS score ≤ 8 plus a HAM-D score ≤ 7.

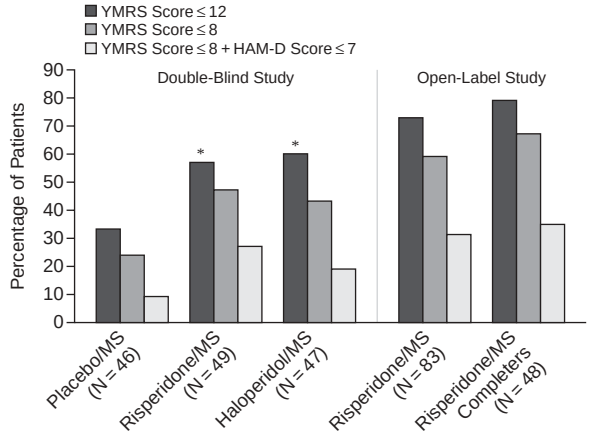
Reductions in YMRS scores were reflected by a parallel improvement in CGI-C scores: the percentage of patients who were rated as much or very much improved increased from 59% (49/83) at week 1 of OL treatment to 71% (34/48) at week 10 (Figure 3). The most substantial improvements in CGI-C scores at week 10 were observed in the placebo/MS patients, among whom 82% (14/17) were much or very much improved, compared with 63% (12/19) of risperidone/MS patients and 67% (8/12) of haloperidol/MS patients.

Figure 1. YMRS Scores During the Double-Blind (DB) Study and Weeks 1 Through 10 and Endpoint of Open-Label (OL) Treatment With Risperidone and Mood Stabilizer[a]



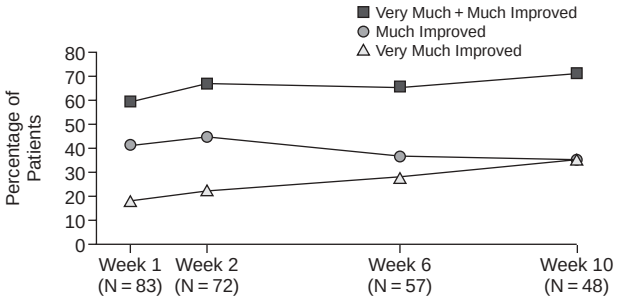
[a]$p < .001$ vs. DB baseline at all timepoints and at endpoint.
[b]All patients received risperidone/mood stabilizer combination during OL treatment.
Abbreviation: YMRS = Young Mania Rating Scale.

Figure 2. Patients in Remission According to 3 Remission Criteria



*p < .05 vs. placebo/MS.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MS = mood stabilizer, YMRS = Young Mania Rating Scale.

Figure 3. Patients Who Were Much and Very Much Improved (CGI-C) During 10 Weeks of Treatment With a Risperidone/ Mood Stabilizer Combination



Abbreviation: CGI-C = Clinical Global Impressions-Change scale.

At DB baseline, mean HAM-D scores in the 3 treatment groups ranged from 14.6 to 16.0 (Table 5). At DB endpoint, reductions in HAM-D scores of the risperidone/MS (–4.0) and haloperidol/MS (–2.5) groups were not significantly different from that of the placebo group (–3.0). At week 10 of OL treatment, a significant reduction in total HAM-D scores was observed in patients initially treated with placebo/MS and risperidone/MS, but not in those initially treated with haloperidol/MS (Table 5). Among all treatment groups, 60% (29/48) of patients had a HAM-D score of 8 or less after 10 weeks of OL treatment. Of the 6 HAM-D factors, sleep disturbance and anxiety/somatization were the most improved from baseline in all groups during the 10-week OL phase ($p < .05$).

Baseline total BPRS scores ranged from 41.2 in the haloperidol/MS group to 44.1 in the placebo/MS group (Table 5). Significant reductions in BPRS scores from baseline were seen in all groups at DB week 3, DB endpoint, and OL week 10, with no significant between-group differences. Significant score reductions from DB baseline to endpoint of OL treatment were observed on 3 of 5 BPRS subscales (Figure 4), including activity (mean = –2.0, $p < .01$), hostility (mean = –2.8, $p < .001$), and thought disturbance (mean = –3.9, $p < .01$).

Adverse Events

The most common adverse events reported in the patients were extrapyramidal disorder (in 29%), somnolence (in 27%), tremor (in 15%), and rhinitis (in 15%) (Table 6). As noted in Table 2, only 7 patients withdrew from the trial because of an adverse event. Adverse events leading to treatment discontinuation that the investigators judged as possibly related to the study drug included confusion, depression, somnolence, tremor, and fatigue (each in 1 patient in the haloperidol/MS group) and dyskinesia (in 1 patient in the risperidone/MS group). No clinically significant changes in vital signs or standard laboratory test results were noted at endpoint.

The mean increases in body weight from DB baseline to DB endpoint were 1.1 lb (0.5 kg), 5.3 lb (2.4 kg), and 0.3 lb (0.1 kg) in the placebo/MS, risperidone/MS, and haloperidol/MS groups, respectively. Weight gains during the 10-week OL treatment were 3.1 lb (1.4 kg) in the placebo/MS group, 2.6 lb (1.2 kg) in the risperidone/MS group, and 2.9 lb (1.3 kg) in the haloperidol/MS group.

DISCUSSION AND CONCLUSIONS

The combination of risperidone and a mood stabilizer was efficacious and well tolerated in the continuation treatment of patients who had been initially hospitalized for the management of an acute manic episode. The improvements seen in these patients were in addition to the significant symptom reductions seen in the patients during the preceding 3-week double-blind study[3] (Figure 1). These results are consistent with those from several studies that indicated antimanic properties of atypical antipsychotics such as risperidone.[1–7,13–20,25]

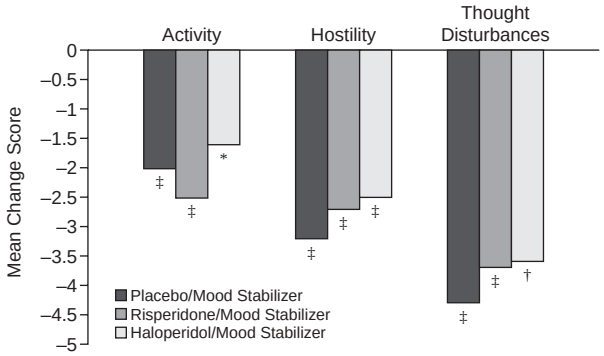
On the primary measure of efficacy, YMRS scores, patients' symptoms of mania were reduced from moderate to severe at baseline to remitted or very mild at the end of 13 weeks of treatment. According to a standard criterion of remission (YMRS score ≤ 12), 73% of all patients and 79% of those who completed the open-label trial were in remission at week 10. Symptoms of depression were also almost completely remitted in many cases, indicating that the combination of risperidone and valproate or lithium may also be an efficacious treatment for depressive symptoms associated with bipolar disorder. It is interesting to note in Figure 3 that the proportion of patients rated as much and very much improved continued to increase over the 10 weeks of treatment. These improvements occurred with serum levels of lithium and divalproex that were

Table 5. HAM-D and BPRS Scores During the Double-Blind (DB) and Open-Label (OL) Studies and Change From DB Baseline[a]

	Placebo/MS		Risperidone/MS		Haloperidol/MS	
Scale	N	Mean ± SE	N	Mean ± SE	N	Mean ± SE
HAM-D						
DB baseline	50	16.0 ± 1.2	52	14.7 ± 1.2	53	14.6 ± 1.1
DB week 3	25	11.7 ± 2.0	38	10.0 ± 1.4	33	9.3 ± 1.3
Change		–5.9 ± 1.4[b]		–4.4 ± 1.2[b]		–3.7 ± 1.3[c]
OL week 1	26	9.8 ± 1.5	33	7.9 ± 1.2	24	9.0 ± 1.4
Change		–7.2 ± 1.5[b]		–6.8 ± 1.4[b]		–5.2 ± 1.3[b]
OL week 10	17	7.6 ± 1.7	19	7.9 ± 1.5	12	10.9 ± 2.4
Change		–7.1 ± 2.2[c]		–4.3 ± 1.9[d]		–3.4 ± 2.2
BPRS						
DB baseline	50	44.1 ± 1.5	52	42.5 ± 1.5	53	41.2 ± 1.5
DB week 3	25	33.3 ± 2.4	38	32.0 ± 2.1	33	29.5 ± 1.5
Change		–10.3 ± 2.7[b]		–9.1 ± 1.5[b]		–9.3 ± 1.4[b]
OL week 1	26	32.7 ± 2.9	33	30.0 ± 1.7	24	30.6 ± 2.3
Change		–11.4 ± 2.7[b]		–11.1 ± 1.7[b]		–9.1 ± 2.2[b]
OL week 10	17	28.1 ± 2.1	19	30.2 ± 2.4	12	30.3 ± 2.8
Change		–13.0 ± 2.0[b]		–8.6 ± 2.4[c]		–11.4 ± 2.2[b]

[a]Patients grouped according to DB treatment. During the OL study, all patients received a risperidone/MS combination.
[b]$p < .001$ vs. DB baseline (within-group analysis by paired t test).
[c]$p < .01$ vs. DB baseline (within-group analysis by paired t test).
[d]$p < .05$ vs. DB baseline (within-group analysis by paired t test).
Abbreviations: BPRS = Brief Psychiatric Rating Scale, HAM-D = Hamilton Rating Scale for Depression, MS = mood stabilizer.

Figure 4. Improvement in BPRS Subscale Scores From Double-Blind Baseline to Open-Label Endpoint (patients grouped according to double-blind treatment)



*$p < .05$ vs. baseline.
†$p < .01$ vs. baseline.
‡$p < .001$ vs. baseline.
Abbreviation: BPRS = Brief Psychiatric Rating Scale.

Table 6. Number of Patients With Adverse Events and Events Reported in ≥ 3 Patients in Any Treatment Group During Open-Label Treatment With Risperidone/Mood Stabilizer (MS)

Variable	Placebo/MS (N = 26)	Risperidone/MS (N = 34)	Haloperidol/MS (N = 25)
Patients with adverse events, N	25	32	22
Adverse events in ≥ 3 patients, N			
Extrapyramidal disorder	6	10	9
Somnolence	9	9	5
Tremor	7	3	3
Rhinitis	5	5	3
Increased saliva	3	6	3
Headache	7	3	1
Hypertonia	4	3	4
Insomnia	3	3	4
Back pain	5	2	3
Hyperkinesia	3	3	3
Fatigue	5	2	2
Dyspepsia	4	2	2
Constipation	2	1	4
Dizziness	3	3	0
Depression	1	4	1
Nausea	1	3	2
Vomiting	0	3	1
Pain	1	3	0

generally lower than those reported in monotherapy trials for mania with these agents.[26] These findings are similar to those reported by Suppes et al.[15] and Muller-Oerlinghausen et al.,[27] who also observed that the combination of mood stabilizers and atypical antipsychotics permitted lower dosing of both agents to control symptoms. This clinical strategy also possibly obviated some of the untoward side effects associated with higher doses used with either agent as monotherapy. The combination treatment of risperidone and mood stabilizer used in this study was well tolerated with a low incidence of reported adverse events and a modest increase in weight.

Both lithium and divalproex and some atypical antipsychotics have been associated with significant weight gain in bipolar patients.[28,29] Sachs and Guille[28] report that among patients they treat with divalproex, weight gain is the most common reason patients cite for discontinuing treatment. These authors also report that about 25% of patients treated with lithium gain enough weight to be

considered obese. Weight increase with lithium appears to be dose-dependent, with increases in weight less likely at plasma lithium levels below 0.8 mmol/L.[28] Since the combination with risperidone may have permitted the use of lower doses of lithium (with resulting decreased serum lithium levels—mean plasma lithium levels ranged from 0.6 to 0.7 mmol/L at week 10 of the present study), it is possible that weight gain seen with lithium may be reduced by combining it with risperidone for longer-term maintenance. Since treatment discontinuation is considered the most important predictor of relapse and poor outcome in bipolar patients,[30–33] optimizing long-term treatment in these patients by reducing the potential for weight gain and other adverse events should be one of the primary goals of treatment.

The combination of mood stabilizer and risperidone was effective for the treatment of depressive symptoms over the 13 weeks of treatment. The contribution of risperidone alone cannot be assessed in this study; however, significant reductions in symptoms of depression (Montgomery-Asberg Depression Rating Scale scores) were reported in a recent study of risperidone given alone in the treatment of bipolar patients with mania.[25] The potential antidepressant effects of risperidone are consistent with its receptor profile, i.e., 5-HT_2 and α_2-adrenoceptor antagonism increases serotonin and norepinephrine levels.[34,35] One or both of these receptor activities is considered the primary mode of action of newer antidepressants such as nefazodone[36] and mirtazapine.[37] Risperidone has also demonstrated antidepressant efficacy in several small case studies when used adjunctively in patients with treatment-resistant depression and in other psychiatric disorders with comorbid depressive symptoms.[9,38] It is also noteworthy that, of the 6 HAM-D factors, those most improved included sleep disturbance and anxiety/somatization. No induction of mania was observed in the patients.[39] The improvement in sleep and decrease in anxiety/somatization observed over time tend to support the benefit of risperidone in the treatment of both manic and depressive symptoms, resulting in effective mood stabilization over longer-term follow-up.

The study has several limitations. First, approximately 45% of patients who participated in the acute 3-week study discontinued treatment before completing the study; this limits the ability to draw stronger conclusions about long-term efficacy in patients who were initially treated for mania. Second, the treatment was not consistent throughout both the double-blind and open-label phases of the study. Patients started with one treatment—placebo, risperidone, or haloperidol in combination with a mood stabilizer—and then all received risperidone with a mood stabilizer for the open-label phase. These changes in treatment regimen over the course of the study make assessment of patient outcomes with a mood stabilizer and risperidone over time difficult to interpret. Despite these limitations, this 13-week study was able to demonstrate that risperidone plus a mood stabilizer was more efficacious than mood stabilizer alone for the treatment of mania. Additionally, the continuation of treatment over the next 10 weeks showed significant overall stabilization of both depressive and manic symptoms with a favorable side effect profile. This finding suggests that this combination may be an effective treatment for longer-term maintenance treatment of bipolar disorder. Further longer-term study is suggested to confirm these findings.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), divalproex (Depakote), flurazepam (Dalmane and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), mirtazapine (Remeron), nefazodone (Serzone and others), oxazepam (Serax and others), risperidone (Risperdal), temazepam (Restoril and others).

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