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Research report

Randomized, placebo-controlled trial of risperidone for acute treatment of bipolar anxiety☆

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Abstract

Background: The treatment of bipolar disorder is often complicated by the presence of a co-occuring anxiety disorder. Although second generation antipsychotics are being used with increasing frequency in bipolar patients, their anxiolytic effects have not been well studied in this population.
Methods: The anxiolytic effect of risperidone 0.5–4 mg/day was tested in an 8-week, double-blind, placebo-controlled, randomized clinical trial in 111 patients with bipolar disorder and a co-occuring panic disorder or generalized anxiety disorder (GAD). The primary outcome measure was the Clinician Global Improvement-21 Anxiety scale (CGI-21 Anxiety). Secondary measures included the Hamilton Anxiety Scale (HAM-A) and the Sheehan Panic Disorder Scale.
Results: On the last-observation-carried forward analysis of repeated measures analysis of variance (ANOVA), risperidone was not more effective than placebo for the CGI-21 Anxiety score or the other anxiety outcome measures. Risperidone was well tolerated, with only two patients withdrawing because of adverse events.
Limitations: The risperidone treated group had more patients with mixed states and lifetime panic disorder at randomization than the placebo group. The study was limited to 8 weeks and to individuals with bipolar and comorbid panic disorder or GAD. The results may not be applicable to risperidone as an add-on treatment to mood stabilizers, or to bipolar disorder comorbid with anxiety disorders other than panic disorder or GAD.
Conclusions: Risperidone monotherapy was not an effective anxiolytic for bipolar patients with comorbid panic disorder or GAD in doses of 0.5–4 mg/day over 8 weeks of treatment. The efficacy of other second generation antipsychotics and mood stabilizers on anxiety in patients with bipolar disorder and a co-occuring anxiety disorder should be investigated in double-blind, placebo-controlled studies.

Keywords: Bipolar disorder; Anxiety; Panic disorder; Placebo; Atypical antipsychotic; Second generation antipsychotic

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1. Introduction

From 24–79% of patients with bipolar disorder present with at least one lifetime anxiety disorder (Pini et al., 1997; Feske et al., 2000; McElroy et al., 2001; Freeman et al., 2002, Henry et al., 2003; Kessler et al., 2005; Otto et al., 2006; Simon et al., 2007). Compared to patients without a comorbid anxiety disorder, those with comorbid anxiety have been shown to have an earlier age of illness onset (Schurhoff et al., 2000; Carter et al., 2003; Henry et al., 2003; Perlis et al., 2004) and higher rates of mixed states, depressive symptoms, alcohol abuse, and suicidal ideation (Young et al., 1993; Frank et al., 2002; Carter et al., 2003; Simon et al., 2004; Perlis et al., 2004). Bipolar patients with co-occurring anxiety have also been shown to have a poorer response to lithium or anticonvulsants and to experience more severe medication side effects (Young et al., 1993; Frank et al., 2002; Feske et al., 2000; Henry et al., 2003). These considerations have led to a growing recognition of the need to specifically target anxiety in the treatment of bipolar disorder.

The second generation antipsychotics aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone, when administered alone or in combination with mood stabilizers, have been shown to be effective and well tolerated in the treatment of manic and mixed episodes of bipolar I disorder (Derry and Moore, 2007; Perlis, 2007). Olanzapine, with and without fluoxetine, and quetiapine alone have been shown to be effective in episodes of bipolar depression (Calabrese et al., 2005; Thase et al., 2006; Tohen et al., 2007). In addition, olanzapine and aripiprazole have indications for maintenance treatment in bipolar I disorder (Derry and Moore, 2007; Perlis, 2007). Since second generation antipsychotics are being used with growing frequency in patients with bipolar disorder (Kessler et al., 2005; Ghaemi et al., 2006a), their anxiolytic effects are a matter of growing interest.

Preliminary research has shown that adding risperidone, olanzapine, or quetiapine to a selective serotonin reuptake inhibitor (SSRI) produces results superior to placebo in the treatment of refractory obsessive–compulsive disorder (OCD), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD) in patients without bipolar disorder (Gao et al., 2006). In addition, the anxiolytic effects of olanzapine and quetiapine have been evaluated in three large double-blind, placebo-controlled studies of bipolar depression using the HAM-A as a secondary measure. In one study, Tohen et al. (2007) found that olanzapine alone and olanzapine combined with fluoxetine were both superior to placebo in reducing HAM-A scores after 8 weeks of treatment. In a pooled analysis of data from 2 studies, Hirschfeld et al. (2006) found that quetiapine at doses of 300 and of 600 mg/d significantly reduced total HAM-A scores compared to placebo after 8 weeks. For individual HAM-A items, these results were more robust among patients with bipolar I disorder than among those with bipolar II disorder.

In none of the latter studies, however, was it specified whether or not subjects had co-occurring syndromal anxiety disorders. Moreover, although second generation antipsychotics may be beneficial for anxiety symptoms in patients with bipolar depression, these agents have been reported to exacerbate the symptoms of panic disorder and OCD, possibly because of their serotonergic antagonistic properties (Baker et al., 1992; de Haan et al., 2002). There is therefore a need for systematic examination of the effects of second generation antipsychotics on the anxiety cluster of symptoms in patients with bipolar disorder and a co-occuring anxiety disorder.

2. Methods

2.1. Study design

This randomized, double-blind, parallel group, 8-week study compared risperidone monotherapy and placebo in adult outpatients with a lifetime bipolar I, II, or NOS disorder, a lifetime panic or generalized anxiety disorder, and current at least moderately severe anxiety symptoms. The institutional review board for each site approved the protocol and written informed consent was received from each participant after the study was fully explained. Following a 1–2 week screening, patients were randomized in a 1:1 ratio to receive risperidone or matching placebo in a flexible dose regimen of 0.5–4 mgs/day for 8 weeks.

2.2. Patients

Patients were recruited from three sites (University of South Florida, University of Cincinnati Medical Center, University of Texas Southwestern Medical Center) with advertisements requesting patients with a combination of mood swings and anxiety or anxiety attacks. Patients enrolled in the study had to be 18–65 years of age. All patients had to meet DSM-IV criteria for a lifetime bipolar I, II, or NOS disorder and a lifetime panic disorder or GAD. However, for the purpose of the study, the GAD Criterion F clause, "does not occur exclusively during a mood disorder," was suspended. DSM-IV diagnostic criteria were documented with the Mini

International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Each patient's bipolar symptoms had to be no more than moderately severe (defined as a score of ≤4 on the Clinical Global Impressions Scale for use in Bipolar Illness (CGI-BP; Spearing et al., 1997) and his or her anxiety symptoms had to be at least moderately severe (defined as a score of ≥4 on the Clinician Global Impression Severity Scale (CGI-S; Guy, 1976). Patients were excluded if they had an acute, serious, or unstable medical illness or clinical abnormality, were currently receiving an antimanic or mood stabilizing medication, met DSM-IV substance dependence criteria within the past 6 months, had psychotic symptoms, or were judged clinically to be at a serious risk for suicide. All patients had to discontinue psychotropic drugs 7 days before baseline or 4 weeks in the case of fluoxetine and depot antipsychotics.

2.3. Assessments

Patients were evaluated at baseline and at weekly visits with the Clinician Global Improvement Scale for Anxiety (CGI-21 Anxiety) (primary efficacy measure), the Sheehan Panic Disorder Scale (SPS; Sheehan, 1983), the Hamilton Anxiety Scale (HAM-A; Hamilton, 1959), the Patient Global Improvement for Anxiety (PGI-21 Anxiety), the Young Mania Rating Scale (YMRS; Young et al., 1978), the Inventory of Depressive Symptoms (IDS; Rush et al., 1996), the Clinical Global Impression Scale for Bipolar Disorder (CGI BP), and the Sheehan Disability Scale (SDS; Sheehan, 1983) (secondary efficacy measures).

A physical, electrocardiogram (EKG), and routine laboratory tests were performed at screen and the EKG and laboratory tests were repeated at study termination. Vital signs, including blood pressure, pulse, height and weight, and adverse events were recorded weekly. In addition, all patients were rated weekly for extrapyramidal symptoms (EPS) on the Abnormal Voluntary Movement Scale (AIMS) (Guy, 1976), the Simpson Angus Scale (SAS; Simpson and Angus, 1970), and the Barnes Akathisia Rating Scale (BARS; Barnes, 1989).

To improve data acquisition and completion accuracy, all data were collected at the time of treatment using a computerized direct entry source data system onto a Tablet PC touch screen.

2.4. Medication

Risperidone and matching placebo were provided in 0.5 mg capsules. Patients were initially instructed to take 0.5–1 mg of study medication in the morning. The dose was then titrated upwards based on tolerability and adverse events but not to exceed 2.0 mg/day by the end of week 2. Subsequently, risperidone could be increased, based on clinical response and tolerability, to a maximum of 4.0 mg/day. A study-prescribed benzodiazeine (lorazepam) was allowed as needed in the first 2 weeks of the study up to 2 mg day in the first week and up to 1 mg/day in the second week. During the final 6 weeks, zolpidem (10–20 mg/day) or zaleplon (10–20 mg/day) were allowed for the management of insomnia. No other psychopharmacologic agents or structured psychotherapy was permitted during the trial. Treatment compliance was monitored by tablet counts.

2.5. Statistical analysis

Demographic and baseline clinical characteristics of the risperidone and placebo groups were compared using analysis of variance (ANOVA) for continuous measures and chi-square, or Fisher's Exact Test, for categorical variables.

The main hypothesis, that risperidone would be superior to placebo in reducing anxiety on the CGI-Anxiety scale, was tested with a last-observation-carried forward (LOCF) repeated-measures analysis of variance (ANOVA). Secondary hypotheses were tested using repeated-measures analysis of covariance (ANCOVA) with the baseline score for each scale as a covariate. ANOVA models, with treatment as the between effect and time were used to analyze the LOCF baseline-to-endpoint changes for continuous safety measures (vital signs and weight). In addition, categorical outcomes including response (defined as a 50% endpoint improvement on the efficacy measures) and adverse events were analyzed using Fisher's Exact test.

The modified LOCF intent-to-treat (ITT) population consisted of all patients who were randomized, took at least one dose of study medication, and had at least one post-baseline visit. The safety population consisted of those who were randomized and took at least one dose of study medication. Data for the 3 sites was pooled. All statistical tests were two-sided with the alpha set at 0.05.

3. Results

3.1. Patient characteristics

Patient characteristics at baseline are shown in Table 1. The risperidone group had a significantly higher proportion of patients presenting with a mixed mood state (defined as meeting criteria for current mania or hypomania *and* current depression on the MINI [59%

Table 1
Baseline characteristics of patients.

	Risperidone ($n=54$)		Placebo ($n=57$)	
	N	%	*N*	%
Bipolar I Disorder	48	88.9	49	86.0
Bipolar II or NOS Disorder	6	11.1	8	14.0
Mood Episode at Study Entry [a]				
Current euthymia	2	3.7	2	3.5
Current hypomania/mania	6	11.1	10	17.5
Current mixed state	32	59.3	23	40.4
Current depressive episode	14	25.9	22	38.6
Panic Disorder, Life	45	83.3	35	61.4
Generalized Anxiety Disorder	45	83.3	53	92.9
Female	36	66.7	35	61.4
Race, White	43	79.6	49	85.9
Employed full time	22	40.7	23	40.3
Past outpatient treatment	33	61.2	39	71.7
Past psych. hospitalization	14	25.9	15	26.3
Prior benzodiazepine use [b]	2	3.7	6	10.5
Prior mood stabilizer or antidepressant [b]	3	5.5	4	7.0
Past suicide attempt(s)	16	29.6	17	29.8
	Mean±SD		Mean±SD	
Age, yrs	35.1±12.4		38.4±12.8	
Age of onset of symptoms	16.4±10.4		19.3±11.8	
Duration of illness (yrs/median)	17.9±12.5		19.3±12.6	
CGI-Severity	4.5±0.5		4.4±0.6	
Hamilton Anxiety Scale	24.5±9.5		22.2±9.1	
Sheehan Panic Scale	50.6±24.2		43.1±24.0	
Inventory of Depressive Symptoms	31.9±11.3		31.2±11.5	
Young Mania Rating Scale	12.5±6.1		10.9±6.5	
Sheehan Disability Scale (work)	5.7±2.8		5.3±3.3	
Sheehan Disability Scale (social)	6.2±2.6		5.5±3.0	
Sheehan Disability Scale (family)	6.2±2.7		5.5±2.9	
Days missed work –past week [c]	0.9±1.6		1.4±2.1	
Days underproductive–past week [c]	2.3±2.3		2.8±2.2	
Abnormal Voluntary Movement Scale	0.48±1.6		0.47±1.6	
Simpson Angus Scale	0.04±0.2		0.12±0.4	
Barnes Akathisia Scale	1.2±1.8		1.0±1.7	

[a] Defined using current episode on MINI (Euthymic=meeting criteria for past mania or hypomania but not for current mania, hypomania, or current depression; Hypomanic/Manic=meeting criteria for current mania or hypomania but not for current depression; Mixed State=meeting criteria for current depression and current mania or hypomania; Depressed=meeting criteria for current depression but not for current mania or hypomania.
[b] Past 30 days only. All subjects were free of medication in the 7 days before randomization.
[c] For patients employed full or part time.

vs. 40%, chi square=3.9, $p<0.05$], and a higher proportion of patients with a lifetime history of panic disorder compared to the placebo group [83% vs. 61%, chi-square=6.6, $p<0.01$]). The two groups were otherwise well matched on demographic and clinical characteristics at the start of treatment.

3.2. Study completion

One hundred and eleven patients were enrolled and randomized to receive risperidone ($n=54$) or placebo ($n=57$). Twenty-seven risperidone-treated patients (50%) and 36 placebo-treated patients (63%) completed 8 weeks of treatment. Nine randomized patients (5 on risperidone and 4 on placebo) did not return for a post baseline visit and were not included in the LOCF efficacy analysis. The mean±sd time to discontinuation for those who withdrew early was 2.3±1.6 weeks for risperidone and 2.1±1.5 for placebo. The most common reasons for early discontinuation were lack of efficacy and failure to return (Fig. 1).

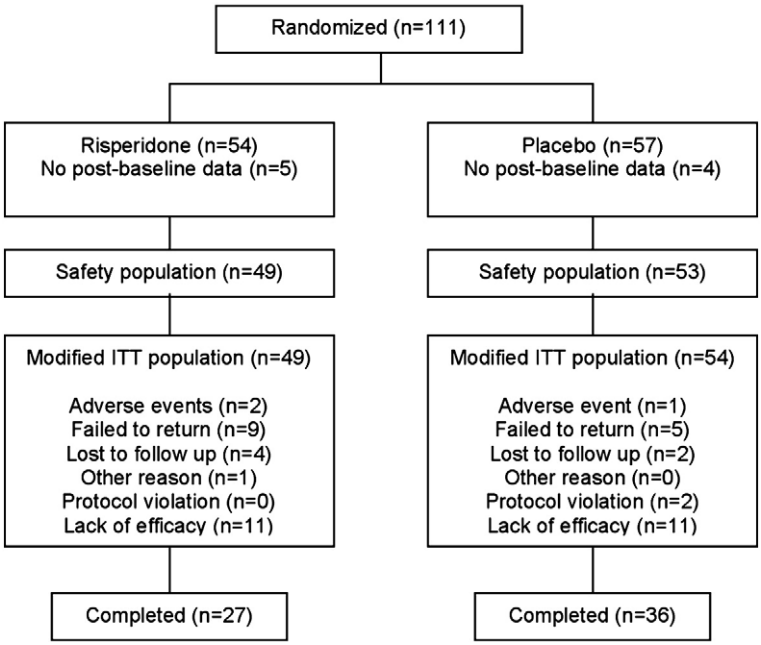

Fig. 1. Study flow chart.

3.3. Study medication and dosage

The mean±sd dose of risperidone was 1.6±0.5 mg/day at the end of the second week, 2.7±1.1 mg/day at the end of week 5, and 2.5±1.1 mg/day at the end of week 8. At week 8 or study termination, 18 patients (37%) were taking <2 mg/day, 22 (45%) were taking 2–3 mg/day, and 9 (18%) were taking 4 mg/day. Ten patients (5 on risperidone and 5 on placebo) had study prescribed lorazepam (0.25–2 mg prn in week 1 and/or 0.25–1 mg prn in week 2).

3.4. Primary outcome measure

3.4.1. Clinician-rated global improvement in anxiety (CGI-21 Anxiety)

Almost half of the patients who had at least one post baseline visit (48/102) showed a 50% improvement on the CGI-21 Anxiety. However, repeated measures ANOVA failed to show any significant difference between risperidone and placebo in improvement on this scale (Fig. 2).

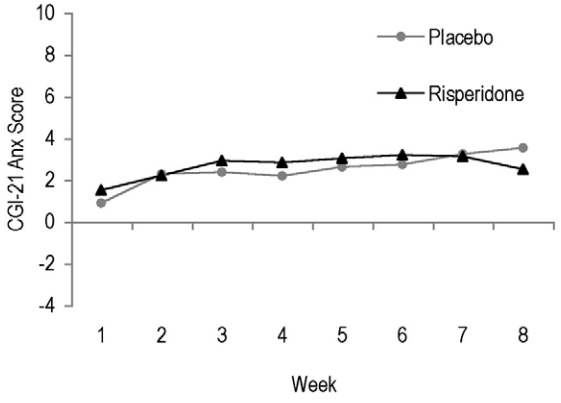

Fig. 2. Mean Clinician Global Improvement Scale for Anxiety (CGI-21 Anxiety) scores for risperidone and placebo.

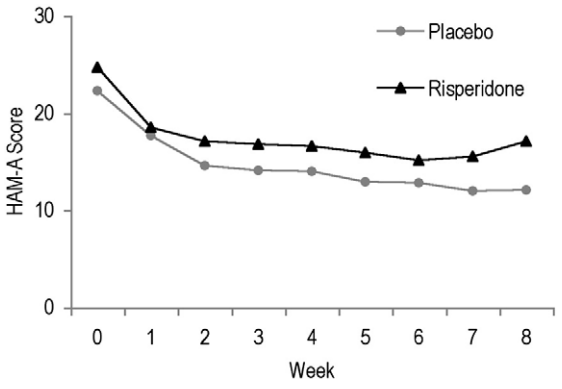

Fig. 3. Mean Hamilton Anxiety Scale scores for risperidone and placebo.

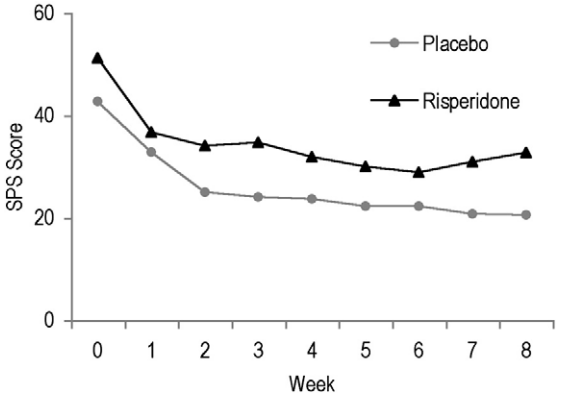

Fig. 4. Mean Sheehan Panic Scale scores for risperidone and placebo.

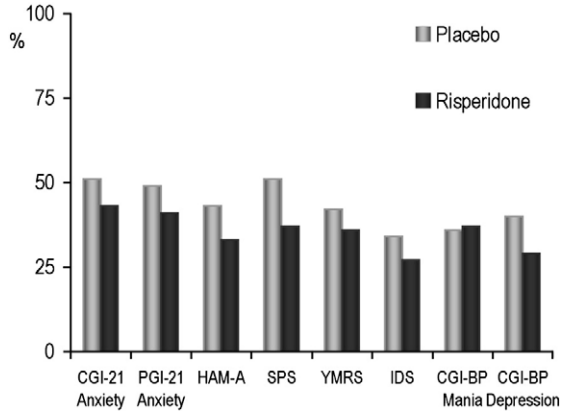

Fig. 5. Responder analysis (% with ≥ 50% improvement).

3.5. Secondary outcome measures

3.5.1. Other anxiety ratings

As shown in Figs. 3 and 4, patients on risperidone showed improvement on the HAM-A and SPS scales. However, the improvement on risperidone was not significantly different from placebo on repeated measures ANCOVA.

3.6. Depression and mania symptom ratings

There were no significant differences between treatments in improvement on any of the depression or mania symptom measures. On the repeated measures ANCOVA of LOCF, the IDS score showed a decrease from a mean±sd of 32.1±11.4 to 26.5±15.7 on risperidone and from a mean±sd of 31.2±11.8 to 19.5±12.7 on placebo. Although the time effect was significant ($p<0.0001$), the group and group by time effects were not. In addition, significant group differences were not found on the repeated measures ANCOVA of CGI-BP scores for mania or depression.

3.7. Disability

The risperidone group did not improve more than placebo on any of the disability measures. Mean±sd decreases from baseline to LOCF endpoint on the work, social, and family disability subscales of the SDS and the total SDS scores were 1.7±3.7, 2.0±3.8, 1.9±3.7 and 5.4±10.0 for risperidone and 1.8±4.0, 2.4±3.9, 2.4±.9 3 and 7.4±11.3 for placebo. Corresponding decreases for days missed from work and days underproductive at work were 0.40±2.1 and 1.5±2.1 for risperidone and 0.46±2.1 and 1.3±2.7 for placebo. These differences were not statistically significant on the repeated measures ANCOVA.

3.8. Responder analysis

As shown in Fig. 5, the percentages of patients with a 50% improvement were similar for both treatment groups for the primary and all secondary efficacy measures. There was no indication of a dose response relationship. Among completers at week 8, the mean±sd risperidone dose for the 11 patients with at least a 50% improvement on the HAM-A was similar to that for the 16 patients without such an improvement (2.6±1.0 mg/day vs. 2.4±1.2 mg/day). Corresponding risperidone doses for responders and nonresponders on the LOCF analysis were 2.3±1.0 mg/day and 2.2±1.2 mg/day.

3.9. Panic disorder subgroup analysis

Overall, improvement on the CGI-21 and HAM-A was similar for patients with and without panic disorder. However, *within* the panic disorder subgroup, placebo-treated patients with lifetime panic disorder had significantly lower mean±sd endpoint HAM-A scores compared to those on risperidone (11.9±9.1 vs. 18.4±10.7, $p<0.007$) and also showed a trend towards greater improvement on the CGI-21 (4.3±5.2 vs. 2.1±5.0, $p<0.07$).

3.10. Benzodiazepine use

All 8 patients who reported receiving benzodiazepines in the month before baseline withdrew early, 2 between baseline and week 1 and the remainder by week 4. Of the 10 patients administered protocol approved benzodiazepines in the first two weeks of the study, 7 (all 5 on risperidone and 2 of 5 on placebo) dropped out by week 4. Overall, mean±sd HAM-A improvement for risperidone patients with and without benzodiazepine

Table 2
Adverse events.

	Risperidone ($n=54$)	Placebo ($n=57$)
	%	%
Headache	30	33
Drowsiness	19	9
Sedation	6	5
Fatigue	4	4
Insomnia	4	5
Nausea	9	12
Diarrhea	4	11
Dry Mouth	9	11
Muscle stiffness, tension, aches	7	9
Dizziness	6	4

use in the month prior to study entry and/or in the first two study weeks was similar (8.5±8.2 vs. 7.5±9.0).

3.11. Adverse events

Two patients on risperidone discontinued treatment due to an adverse event: 1 because of pregnancy and 1 because of an episode of heightened anxiety and anger. In addition, one placebo-treated patient withdrew early after complaining of multiple symptoms, including "word slurring," hair loss, and fluid retention. The most common adverse events, reported by 5% or more patients in each group, are shown in Table 2. Drowsiness was the only adverse event that was two or more times as frequent in the risperidone group.

3.12. Extrapyramidal symptom measures

Changes from baseline to endpoint in extrapyramidal symptoms, as measured on the AIMS, SAS, and BARS (LOCF analysis), were minimal and did not differ significantly between risperidone and placebo. Mean decreases were 0.47 for risperidone and 0.20 for placebo on the AIMS and 0.02 for risperidone and 0.04 for placebo on the SAS. Both groups had similar mean increases on the BARS (0.79 for risperidone and 0.55 for placebo).

3.13. Vital signs, EKG, laboratory measures and weight

There were no statistically significant differences between treatment groups in the frequencies of categorical changes on vital signs, laboratory values, or ECG. Mean±sd LOCF change in weight was numerically higher on risperidone (4.7±6.7 lbs.) than placebo (1.7±6.7 lbs) ($F=3.4$, $df=1$, $p=0.07$). Mean weight gain for completers was also higher on risperidone (5.5±7.0 lbs.) than placebo (2.6±7.4), but was not statistically significantly different ($F=1.85$, $df=1$, $p=0.17$). Two patients (10%) on risperidone and none on placebo had a ≥7% increase in weight ($p=0.15$ Fisher's Exact Test).

4. Discussion

Co-occurring anxiety and anxiety disorders have been identified as significant impediments to recovery in patients with bipolar disorder types I and II (Feske et al., 2000; McElroy et al., 2001; Cassano et al., 1999; Young et al., 1993). Nonetheless, the treatment of comorbid anxiety disorders in bipolar disorder is largely based on anecdotal reports and open clinical experience (Perugi and Toni, 2004; Singh and Zarate, 2006).

To our knowledge, this is the first parallel-group, double-blind, placebo-controlled trial of a second generation antipsychotic with anxiety as the primary target of treatment in patients with bipolar disorder and a co-occuring panic disorder or GAD. The study failed to show that risperidone was superior to placebo in reducing anxiety on any of the efficacy measures over 8 weeks of treatment at the dose used, 0.5–4 mg/day. However, risperidone was well tolerated with only two patients withdrawing from the study because of medication related adverse events.

The findings may have been influenced by several factors. First, the risperidone dose was in the low range and it was titrated relatively quickly. It is possible that a higher dose or a slower titration could have produced a more optimal response in the risperidone group. Second, patients were seen weekly which may have contributed to a nonspecific positive response in the placebo group. Third, the risperidone group had a higher percentage of patients with panic disorder. Such patients may have a poorer prognosis than those with GAD only. Indeed, there is increasing evidence from genetic and epidemiological research to suggest that bipolar disorder with panic disorder may represent a distinct and more severe phenotype or subtype within the bipolar spectrum (MacKinnon et al., 1997, 1998, 2002, 2003; Rotondo et al., 2002; Dilsaver et al., 2006; Nardi et al., 2007). If this is the case, patients with a combination of panic disorder and bipolar disorder may require a different treatment than bipolar patients with anxiety or GAD but without panic disorder. Fourth, risperidone treated patients also had a higher rate of mixed states at study entry. Patients with mixed states may have a poorer prognosis than patients without such states (González-

Pinto et al., 2007). Risperidone may therefore not have separated from placebo on some outcome variables because the risperidone group was more severely ill than the placebo group at baseline.

Our results with risperidone are inconsistent with earlier analyses showing olanzapine, alone and combined with fluoxetine, and quetiapine alone have anxiolytic properties in bipolar depression (Hirschfeld et al., 2006; Thase et al., 2006; Tohen et al., 2007). Important differences in patient populations and study design may account for these apparently discrepant findings. However, it might also be possible that risperidone has a different anxiolytic profile in bipolar disorder compared with olanzapine and/or quetiapine or that it does not have anxiolytic properties in bipolar disorder complicated by GAD and/or panic disorder, though the latter possibility should not be extended to bipolar disorder with other anxiety disorders without further research. One hypothesis to account for these observations is that among second generation antipsychotics in bipolar disorder, anxiolytic properties might be positively related to antidepressant properties but negatively related to ability to cause extrapyramidal effects. The former would be supported by our findings that risperidone did not significantly reduce depressive symptoms compared with placebo along with the study by Nierenberg et al. (2006) showing that this antipsychotic may not be effective in acute bipolar depression. The latter possibility could be supported by reports of higher rates of akathisia in bipolar patients receiving high versus low potency antipsychotic agents (Ghaemi et al., 2006b), since akathisia can be associated with anxiety. It was not supported, however, by our findings of low rates of EPS in general and of akathisia in particular in patients receiving risperidone.

5. Conclusions

Over an 8-week trial, risperidone monotherapy at doses of 0.5–4 mg/day was not effective in the treatment of bipolar disorder with GAD and/or panic disorder and was possibly even less effective than placebo in those with bipolar disorder and panic disorder. These findings add to growing evidence that bipolar disorder with panic disorder represents a distinct subgroup that may require unique therapeutic strategies. Given the increased risk of suicide in this population (Young et al., 1993; Valtonen et al., 2005), additional research investigating other second generation antipsychotics and mood stabilizers in patients with bipolar disorder and a co-occurring anxiety disorder should be a priority.

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Conflict of interest

DVS is a consultant to and/or has received speaker fees from Abbott Laboratories, Alexa, Alza Pharmaceuticals, American Psychiatric Association, Anxiety Disorders Resource Center, US Food and Drug Administration, Applied Health Outcomes/ XCENDA, AstraZeneca, Avera Pharmaceuticals, Boehringer Ingelheim, Boots Pharmaceuticals, Bristol-Myers Squibb, Burroughs Wellcome, Cephalon,, Charter Hospitals, Ciba Geigy, Cortex Pharmaceutical, Council on Anxiety Disorders, CPC Coliseum Medical Center, Cypress Bioscience, Dista Products Company, Division of Drugs & Technology, American Medical Association, EISAI America, Inc., Eli Lilly, Excerpta Medica Asia, Faxmed, Inc, Forest Laboratories, Glaxo Pharmaceuticals, GlaxoSmithKline, Hospital Corporation of America, Humana, ICI, Janssen Pharmaceutica, Jazz Pharmaceuticals, Kali-Duphar, Layton Bioscience, Lilly Research Laboratories, Lundbeck, Denmark, Marion Merrill Dow, McNeil Pharmaceuticals, Mead Johnson, MediciNova, Merck Sharp & Dohme, National Anxiety Awareness Program, National Anxiety Foundation, National Depressive & Manic Depressive Association, National Institute of Mental Health, Novo Nordisk, Organon, Orion Pharma, Parexel International Corporation, Parke-Davis, Pfizer, Pharmacia, Pharmacia & Upjohn, Pierre Fabre, France, Rhone Laboratories, Rhone-Poulenc Rorer Pharmaceuticals, Roche, Roerig, Sandoz Pharmaceuticals, Sanofi-Aventis, Sanofi-Synthelabo Recherche, Schering Corporation, Shire Laboratories, Inc, SmithKlineBeecham, Solvay Pharmaceuticals, Takeda Pharmaceutical Co., TAP Pharmaceuticals, Targacept, Tikvah Therapeutics, Titan Pharmaceuticals, Upjohn Company, U.S. Congress-House of Representatives Committee, USF Friends of Research in Psychiatry, Board of Trustees, Warner Chilcott, World Health Organization, Wyeth-Ayerst, ZARS.

DVS is or has been an investigator or coinvestigator on research studies sponsored by Abbott Laboratories, American Medical Association, AstraZeneca, Avera Pharmaceuticals, Bristol-Myers Squibb, Burroughs Wellcome, Cephalon, EISAI, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Glaxo-Wellcome, International Clinical Research (ICR), Janssen Pharmaceutica, Jazz Pharmaceuticals, Kali-Duphar, Mead Johnson, MediciNova, Merck Sharp & Dohme Ltd., National Institute of Drug Abuse, National Institute of Health (NIH), Novartis Pharmaceuticals Corp., Parke-Davis, Pfizer, Quintiles, Sandoz Pharmaceuticals, Sanofi-Aventis, Sanofi-Synthelabo Recherche, SmithKlineBeecham, TAP Pharmaceuticals, The Upjohn Company, Warner Chilcott, Worldwide Clinical Trials, Wyeth-Ayerst, and Zeneca Pharmaceuticals. He holds stock in Medical Outcome Systems.

SLM is a consultant to, or member of the scientific advisory boards of Abbott Laboratories, Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceutica, Ortho-McNeil, and Wyeth-Ayerst; and a principal or co-investigator on research studies sponsored by Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Esai, Eli Lilly and Company, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, Jazz Pharmaceuticals, Inc., National Institute of Mental Health, OREXIGEN Therapeutics, Inc., Ortho-McNeil, Pfizer, Sanofi-Synthelabo, Somaxon Pharmaceuticals, Inc., Stanley Medical Research Institute, and Takeda Pharmaceutical Company Limited. She is also

inventor on United States Patent No. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and, along with the patent's assignee, University of Cincinnati, Cincinnati, OH, receives payments from Johnson & Johnson Pharmaceutical Research & Development, L.L.C., which has exclusive rights under the patent.

PEK is a principal or co-investigator on research studies sponsored by Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly and Company, Janssen Pharmaceutica, National Institute of Mental Health (NIMH), National Institute of Drug Abuse (NIDA), Pfizer, and UCB Pharma; and has been reimbursed for consulting to Bristol-Myers Squibb, Eli Lilly and Company, Forest Laboratories, Organon, and Pfizer. He is also inventor on United States Patent No. 6,387,956: Shapira NA, Goldsmith TD, Keck, PE Jr. (University of Cincinnati) Methods of treating obsessive–compulsive spectrum disorder comprises the step of administering an effective amount of tramadol to an individual. (Filed March 25, 1999; approved May 14, 2002.

JJ is a consultant to and/or has received speaker fees from Sanofi-Synthelabo, Merck, Pfizer, GlaxoSmithKline, Wyeth-Ayerst, TAP Pharmaceuticals, Allergan, Biovail/Ingenix, Roche, Cephalon, Boehringer-Ingelheim and Synosia Therapeutics. He has been an investigator or coinvestigator on studies sponsored by AstraZeneca, Avera Pharmaceuticals, Bristol-Myers Squibb, Burroughs Wellcome, Cephalon, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, Jazz Pharmaceuticals, Kali-Duphar, Mead Johnson, MediciNova, Merck Sharp & Dohme Ltd., Novartis Pharmaceuticals Corp., Parke-Davis, Pfizer, Quintiles, Sandoz Pharmaceuticals, Sanofi-Aventis, SmithKline-Beecham, and TAP Pharmaceuticals.

KHS has been an investigator or coinvestigator on studies sponsored by the American Medical Association, AstraZeneca, Avera Pharmaceuticals, Bristol-Myers Squibb, Burroughs Wellcome, Cephalon, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, Jazz Pharmaceuticals, Kali-Duphar, Layton Bioscience, Mead Johnson, MediciNova, Merck Sharp & Dohme Ltd., Novartis Pharmaceuticals Corp., Parke-Davis, Pfizer, Quintiles, Sandoz Pharmaceuticals, Sanofi-Aventis, SmithKlineBeecham, Solvay, the Stanley Foundation, TAP Pharmaceuticals, and the Upjohn Company.

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