Do Atypical Antipsychotics Effectively Treat Co-Occurring Bipolar Disorder and Stimulant Dependence? A Randomized, Double-Blind Trial

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Objectives: The primary objective was to compare the efficacy and tolerability of quetiapine and risperidone in the treatment of mood symptoms, drug cravings, and drug use in outpatients with concurrent DSM-IV–defined bipolar I or II disorder and cocaine or methamphetamine dependence.

Method: Men and women of all ethnic origins, 20 to 50 years of age, were eligible to participate. Persons were excluded if they were inpatients, met DSM-IV criteria for substance-induced mood disorder, had any other substance dependence, were euthymic or suicidal, had any life-threatening illnesses, or were currently receiving antipsychotic medications. Duration of the trial was 20 weeks. Study participants attended weekly visits and were evaluated for mood symptoms, drug cravings, drug use, and medication side effects. Treatment outcomes were analyzed using linear mixed models. Fixed-effects terms for medication group, study week, and group-by-study-week were included in the models. The study was conducted between October 2002 and November 2006.

Results: Of 124 consenting outpatients, an evaluable sample of 80 patients who attended baseline and at least 1 follow-up study visit was formed. The mean ± SD exit dose for quetiapine was 303.6 ± 151.9 mg/day and 3.1 ± 1.2 mg/day for risperidone. Both quetiapine (N = 42) and risperidone (N = 38) significantly improved manic and depressive symptoms and reduced drug cravings ($p < .0005$) compared to baseline. Decreased drug cravings were related to less frequent drug use ($p = .03$). The 2 medications did not significantly differ in their effects on mood symptoms, drug craving, or drug use.

Conclusions: Relative to baseline mood and drug-craving status, both quetiapine and risperidone were associated with manic, mixed, and depressive symptom improvement and reduced drug cravings. Both medications were well tolerated. The interpretation of these results is limited by the absence of a placebo control.

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Dr. Nejtek served on the AstraZeneca speakers bureau from 2001–2005. Dr. Rush has provided scientific consultation to or served on advisory boards for Advanced Neuromodulation Systems, AstraZeneca (beginning March 2007), Best Practice Project Management, Bristol-Myers Squibb, Cyberonics, Forest, Gerson Lehman Group; GlaxoSmithKline; Jazz, Eli Lilly, Magellan Health Services, Merck, Neuronetics, Ono, Organon, PamLab, Personality Disorder Research, Pfizer, The Urban Institute, and Wyeth-Ayerst; has been on speakers bureaus for Cyberonics, Forest, GlaxoSmithKline, and Eli Lilly; owns stock in Pfizer; and has received royalties from Guilford Publications and Healthcare Technology Systems. Drs. Avila, Zielinski, Djokovic, Podawiltz, and Bae and Mss. Chen and Kaiser report no additional financial or other relationship relevant to the subject of this article.

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Bipolar disorder is associated with lifetime prevalence rates of substance abuse as high as 60%.[1,2] Compared to persons with bipolar disorder alone, those with comorbid substance use disorders have higher hospitalizations and poorer psychiatric recovery.[1–4] Risperidone and quetiapine are serotonin-2/dopamine-2 ($5\text{-}HT_2/DA_2$) receptor antagonists with U.S. Food and Drug Administration approval to treat bipolar symptoms—risperidone for acute manic and mixed symptoms; quetiapine for acute mania and bipolar depression. Yet, little is known about the efficacy these agents may have in treating drug use in persons with concurrent bipolar and stimulant use disorders.

A few studies have examined risperidone in cocaine users without psychiatric comorbidity. A 12-week random-

ized, double-blind, placebo-controlled trial of cocaine-dependent subjects (N = 193) reported that risperidone did not significantly reduce cocaine use and that it was not well-tolerated.[5] Similarly, risperidone was not associated with reductions in cocaine use in another 26-week, randomized, double-blind trial.[6] A small 2-week, double-blind, placebo-controlled trial found risperidone to be no more effective than placebo in reducing cocaine cravings in cocaine dependent persons (N = 35).[7] The effectiveness of quetiapine treatment for stimulant use in persons without mood disorders is unknown.

Some data are available from case reports and retrospective chart reviews of patients with schizophrenia and concurrent alcohol and/or stimulant use disorders.[8–11] In these studies, both quetiapine and risperidone appeared to improve mood and reduce cocaine use and/or craving.[8–11] One open-label quetiapine study[12] and 1 open-label risperidone study[13] reported improved psychiatric symptoms and reduced drug cravings and use in persons with schizophrenia and alcohol and/or stimulant use disorders. One conference abstract reporting a double-blind comparison of risperidone or quetiapine to placebo showed greater symptom reduction with risperidone in schizophrenia with and without substance use disorders, but no drug use data were provided.[14]

We have conducted 2 previous studies of quetiapine treatment in persons with bipolar disorder and stimulant use disorders.[15,16] The open-label trial found reduced depressive and manic symptoms and cocaine cravings ($p < .05$).[15] The randomized trial comparing quetiapine to haloperidol found that quetiapine significantly reduced mood symptoms ($p < .05$) and drug cravings ($p < .01$), while haloperidol increased both depressive symptoms and stimulant cravings ($p < .01$).[16] No prospective data comparing quetiapine to risperidone in this target population currently exist.

Superior efficacy for quetiapine compared to haloperidol in treating both mood symptoms and drug cravings was previously found.[16] Risperidone, like haloperidol, is associated with high DA_2 receptor binding compared to quetiapine.[17–19] High DA_2 receptor binding found in haloperidol enhances cocaine self-administration in animals[20,21] and increases drug use in humans.[22] Therefore, risperidone may be less effective in treating stimulant dependence, which would be consistent with negative findings among cocaine users treated with risperidone.[5–7] We hypothesized that quetiapine would be superior to risperidone in treating mood and drug use in persons with bipolar disorder and cocaine or methamphetamine dependence.

METHOD

Study Design

This 20-week, randomized, double-blind trial was designed to compare the efficacy of quetiapine to risperidone in treating mood symptoms, drug cravings, and drug use in patients with co-occurring bipolar disorder and stimulant use disorders and to examine (1) the length of time until and duration of expected efficacy; (2) the difference in tolerability, if any, between quetiapine and risperidone; and (3) whether mood improvement would be associated with reduced drug use or less treatment attrition in outpatients with bipolar disorder and cocaine or methamphetamine dependence. The study was conducted between October 2002 and November 2006 at the University of Texas Southwestern (UTSW) Medical Center at Dallas and University of North Texas Health Science Center in Fort Worth. Institutional review boards at both sites approved the protocol.

Participants

Participants were recruited from psychiatrist referrals and through flyers placed in local community mental health outpatient clinics and drug treatment facilities. Written, informed consent was obtained prior to study enrollment. Participants were protected with a Confidentiality Certificate issued by the National Institute of Mental Health. Study patients received compensation (i.e., a $40 gift card) after successful completion of 4 study weeks. The protocol required that patients attend weekly study visits and be evaluated for mood symptoms, drug cravings, drug use, and adverse events.

Inclusion Criteria

Those eligible to participate (1) were English-speaking men and women (20–50 years old) of all ethnic origins; (2) were outpatients with a current DSM-IV diagnosis of bipolar I disorder with or without psychotic features or bipolar II disorder; (3) had current DSM-IV cocaine or methamphetamine dependence; (4) were currently experiencing hypomanic, manic, or mixed state episodes with a Young Mania Rating Scale[23] (YMRS) score of ≥ 9; (5) were currently craving stimulants with a craving score of ≥ 20 on the 10-item, self-reported Stimulant Craving Questionnaire[24] (SCQ-10); and (6) had a high school diploma, GED, or Shipley IQ test score of ≥ 85.

Exclusion Criteria

Those ineligible to participate (1) were inpatients or anyone with a high risk of suicide (i.e., active suicidal ideation with a proposed plan, history of any suicide attempt within the last 6 months); (2) had a DSM-IV diagnosis of substance-induced mood disorder; (3) were pregnant or breast-feeding; (4) had a history of special education, mental retardation, or dementia; (5) had HIV/AIDS, reactive hepatitis, hepatic cirrhosis or any active liver disease, a personal or familial history of diabetes, or a personal history of heart disease (i.e., congenital heart abnormalities, congestive heart failure, chronic atrial fibrillation, rheumatic heart disease, or heart attack); (6) had central

nervous system diseases (e.g., multiple sclerosis, severe head trauma, or seizures); (7) had contraindications or allergic reactions to study medications; (8) were currently participating in any other research program; (9) had a positive urine screen for glucose or ketones; (10) were currently receiving any antipsychotic medications or more than 2 psychotropic medications; (11) were currently receiving benzodiazepines, sedatives, or stimulants; (12) had any other current substance dependence; (13) had cataracts or glaucoma; and/or (14) had electrocardiogram (ECG) evidence of QT prolongation.

Intervention

Study medications were purchased (risperidone) or provided by the manufacturer (quetiapine), randomly assigned to participants under blinded conditions, and dispensed by Investigation Drug Service pharmacists at UTSW. All study medications looked identical. Study participants, research personnel, study doctors, and the principal investigator (PI) were blind to study medication. Study patients were randomly assigned in blocks of 10 to receive either quetiapine or risperidone. Weekly dosing of quetiapine was 50 mg/day for the first week, 100 mg/day for the second week, and up to 600 mg/day by the 12th week. Weekly dosing of risperidone was 0.5 mg/day for the first week, 1 mg/day for the second week, and up to 6 mg/day by the 12th week. Study doctors could adjust each subsequent weekly dose by titrating up or down in increments of 50 mg/day for quetiapine and 0.5 mg/day for risperidone, as clinically needed. Patients received study medication dispensed in a 7-day "med-minder," and they were instructed to bring it with them at each subsequent visit so that medication adherence could be monitored and refills provided for the next week.

Concomitant Medications/Treatment

Patients who entered the study with no more than 2 allowable psychotropics (i.e., antidepressant or mood stabilizer) were permitted to continue those medications concomitantly with the study drug. Dose adjustments of concomitant psychotropics were proscribed. No other psychotropic medications could be added after study entry. Other allowable medications for general medical conditions included those to treat hypertension, acute care antibiotics, and over-the-counter cold or allergy (nonnarcotic) medications. Behavioral drug treatments (e.g., residential treatment, intensive outpatient classes, drug aftercare classes, and Narcotics or Alcoholics Anonymous meetings) were allowed.

Diagnostic and Efficacy Measures

The Structured Clinical Interview for DSM-IV Clinical Version (SCID-CV)[25] was used to determine current and lifetime Axis I diagnoses and history of illness. The SCID-CV life chart was utilized to document a chronological timeline for age of mood symptom onset preceding the onset of substance abuse or dependence. A final consensus diagnosis was determined by the PI, study psychiatrist, and project coordinator. At baseline and weekly thereafter, the 11-item YMRS,[23] the 30-item Inventory of Depressive Symptomatology–Clinician-rated (IDS-C-30),[26–29] and the 10-item SCQ-10[24] measured mood symptoms and drug craving. The YMRS and the IDS-C-30 were used to assess current manic and depressive symptom severity.[29] The SCQ-10 is a simple modification of the Cocaine Craving Questionnaire[24] used to assess methamphetamine cravings in the same manner as cocaine and yields a craving score ranging from 10 to 70. Somatic complaints and adverse events were evaluated weekly using the Psychobiology of Recovery in Depression-III Somatic Symptom Scale (PRD-III).[30] The PRD-III has a raw score range from 0 to 46, and it assesses neurologic, gastrointestinal, libidinal, urologic, dermatologic, and cardiovascular domains. Higher scores on the YMRS, IDS-C-30, SCQ-10, and PRD-III indicate greater severity of mood symptoms, drug cravings, and somatic complaints, respectively.

Safety Protocol

The PRD-III was used to evaluate adverse events. Weight and blood pressure were measured weekly. Eyes were checked for cataract opacity every 2–4 weeks. Heart rhythm was recorded with an ECG machine. Study patients who had any baseline abnormal variant received ECGs every 2 to 4 weeks, while those who had normal baseline results received ECGs every 8 to 11 weeks and again at exit.

Urinalyses

Weekly urine samples were tested for drug use, pregnancy, glucose, and ketones. A 6-panel urine drug screen was used to identify cocaine (benzoylecgonine, 300 ng/mL), methamphetamine (d-methamphetamine, 1000 ng/mL), phencyclidine (PCP, 25 ng/mL), cannabis (11-norΔ^9 THC-9 COOH, 50 ng/mL), opiate (morphine, 300 ng/mL), and benzodiazepine (oxazepam, 300 ng/mL) use.

Data Analyses

We defined the baseline sample as all randomly assigned patients (N = 94) who completed baseline assessments and received a 7-day supply of study medication. Analysis of variance (ANOVA) and χ^2 tests were used to compare the study groups on baseline and sociodemographic variables. Kaplan-Meier survival curves were used to compare time to discontinuation of treatment in the medication groups. Reasons for study withdrawal and/or exclusion during the 20-week trial were determined and compared using χ^2 tests.

Treatment outcomes were analyzed using an evaluable sample that included all participants who completed

baseline assessments and attended at least 1 follow-up visit (N = 80). Primary outcome variables were mood scores (YMRS and IDS-C-30), drug craving scores (SCQ-10), overall drug use, and somatic side effect scores (PRD-III). Linear mixed models were run using SPSS version 14.0 (SPSS Inc., Chicago, Ill.) and used to compare the treatment groups using the YMRS, IDS-C-30, SCQ-10, and PRD-III total scores and body mass index (BMI). Fixed-effects terms for medication group (quetiapine or risperidone), study week (1–20), and group-by-study-week were included in the models. Study patients were treated as a random effect. Restricted maximum likelihood estimation was used, and autoregressive covariance structures were specified.

For each study participant, the percentage of actual drug screens that were positive for cocaine or methamphetamine was used to examine the overall drug use for each subject during the trial (i.e., number of positive screen divided by the number of weeks in the study). ANOVA compared the overall drug use in the 2 medication groups. Analyses were also performed on study patients who discontinued the study in which the percentages of drug use were calculated assuming a positive drug screen for all remaining, noncompleted study weeks (i.e., number of positive drug screens plus number of remaining weeks after dropout divided by 20). Follow-up contact with these noncompleting study patients or their families, friends, or drug treatment providers confirmed a return to drug use.

To examine the length of time required to achieve clinically significant improvement in the 2 groups, we employed Kaplan-Meier survival analyses using a YMRS cutoff of ≤ 9 and an IDS-C-30 cutoff of ≤ 14. The YMRS, IDS-C-30, and SCQ-10 change scores from baseline to study exit were used to examine the relationship between changes in symptoms and overall drug use. For these secondary analyses, linear regression models were used to estimate the unique contribution of clinical change, controlling for the number of study weeks, to the overall percentage of positive drug screens.

RESULTS

Sample Characteristics

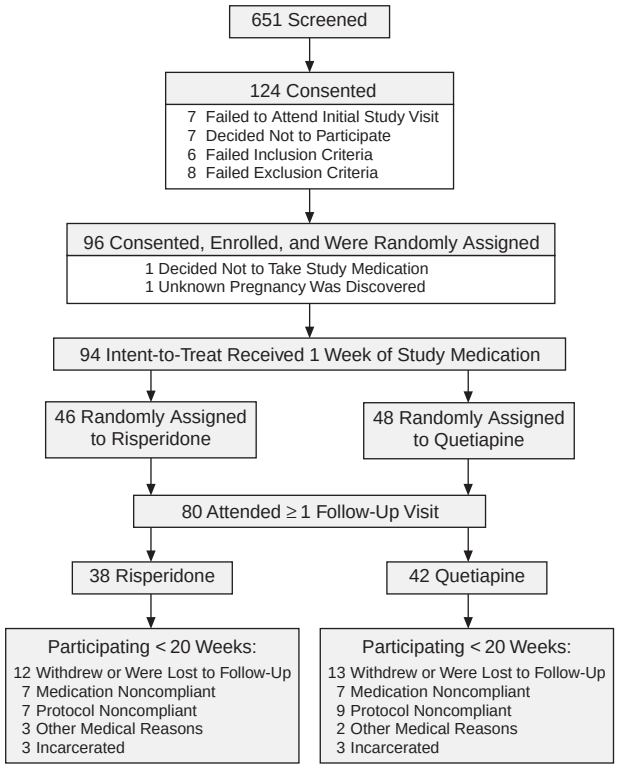
Of 651 volunteers screened for study participation, 124 were enrolled, 96 were randomly assigned, and 94 received study medication (Figure 1). There were no significant between-group differences in baseline sociodemographic characteristics, diagnoses, mood states, or drug use (Table 1).

Study Discontinuation

Frequency data for the evaluable sample (N = 94) showed that 15% (14/94) completed all 20 weeks. Reasons for attrition are outlined in Figure 1. One patient in the risperidone group who was discontinued for medical reasons needed additional antidepressant therapy. Chi-square analysis showed that the reasons for discontinuation occurred with similar frequency in the 2 medication groups ($\chi^2 = 0.90$, df = 4, p = .92).

A Kaplan-Meier survival analysis found no significant differences in study attrition between the medication groups; log rank (Mantel-Cox $\chi^2 = 0.36$, df = 1, p = .55). Residential behavioral drug treatment, length of drug abstinence, drug of choice, or living arrangements were not associated with study attrition. Patients who reported part- or full-time employment during the study had a slightly lower attrition rate than the unemployed (62% vs. 87%; Mantel-Cox $\chi^2 = 5.44$, df = 1, p = .02). A Cox regression model showed no significant interaction between employment status and study medication in predicting rate of attrition (p = .44).

Figure 1. Enrollment and Screening Outcomes



Intervention

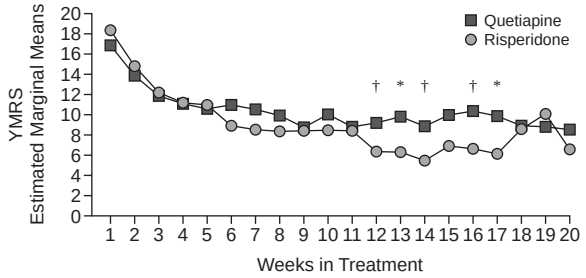
For risperidone, the mean ± SD daily dose at study exit was 3.1 ± 1.2 mg/day, and the mean ± SD maximum dose was 3.2 ± 1.2 mg/day. The median ± SD risperidone dose for each individual study patient across study weeks was 2.3 ± 1.0 mg/day. For quetiapine, the mean ± SD daily dose at study exit was 303.6 ± 151.9 mg/day and the mean ± SD maximum dose was 309.5 ± 150.7 mg/day.

Table 1. Sociodemographic and Clinical Characteristics of 80 Patients With Bipolar Disorder and Stimulant Dependence Randomly Assigned to Quetiapine or Risperidone[a]

Characteristic	Quetiapine (N = 48)	Risperidone (N = 46)
Sociodemographic characteristics[b]		
Age, mean ± SD, y	36.8 ± 6.7	34.7 ± 6.7
Sex, female, % (N)	52 (25)	54 (25)
Race/ethnicity, % (N)		
White	71 (34)	70 (32)
Black	29 (14)	24 (11)
Hispanic	0 (0)	6 (3)
Education, mean ± SD, y	13.3 ± 1.4	13.0 ± 1.1
Employment, % (N)		
Full-time employment	4 (2)	7 (3)[c]
Part-time employment	8 (4)	9 (4)[c]
Unemployed	88 (42)	84 (37)[c]
Living arrangements, % (N)		
Independent living	17 (8)	11 (5)[c]
Family/significant other	35 (17)	34 (15)[c]
Residential treatment	42 (20)	55 (24)[c]
Shelter	6 (3)	0 (0)[c]
Psychiatric history[d]		
Bipolar diagnosis, % (N)		
Bipolar I disorder[e]	79 (38)	89 (41)
Bipolar II disorder	21 (10)	11 (5)
Duration of bipolar illness, mean ± SD, y	24.7 ± 8.3	23.3 ± 7.6
Baseline mood state, % (N)		
Mania	8 (4)	4 (2)
Hypomania	19 (9)	22 (10)
Depressed	50 (24)	41 (19)
Mixed	23 (11)	33 (15)
Secondary (current) Axis I diagnosis, % (N)		
Obsessive-compulsive disorder	25 (12)	15 (7)
Posttraumatic stress disorder	33 (16)	39 (18)
Allowable concomitant psychiatric medications, % (N)		
None	48 (23)	61 (28)
Mood stabilizer	8 (4)	4 (2)
Mood stabilizer + antidepressant	13 (6)	15 (7)
Antidepressant	29 (14)	20 (9)
Other mood	2 (1)	0 (0)
Baseline clinical measures, mean ± SD		
Young Mania Rating Scale score	16.8 ± 4.9	18.2 ± 4.3
Inventory of Depressive Symptomatology score	24.8 ± 9.6	26.8 ± 8.4
PRD-III score	7.7 ± 4.1	8.5 ± 3.8
BMI	26.5 ± 4.6	27.5 ± 6.5
Drug history[f]		
Duration of chronic drug use, mean ± SD, y	10.7 ± 6.4	10.8 ± 5.6
Current primary drug of abuse, % (N)		
Methamphetamine	38 (18)	37 (17)
Cocaine	62 (30)	63 (29)
Alcohol abuse or dependence, % (N)		
None	38 (18)	37 (17)
Past abuse/dependence	39 (19)	43 (20)
Current abuse	23 (11)	20 (9)
Baseline positive drug screen, % (N)		
Primary drug of choice (cocaine/methamphetamine)	27 (13)	26 (12)
Other drugs (THC, opiates, PCP)	17 (8)	15 (7)
Baseline Stimulant Craving Questionnaire score, mean ± SD	50.5 ± 14.3	48.2 ± 13.8
Receiving behavioral treatment at baseline, % (N)[g]	81 (39)	89 (41)

[a]ANOVA was used to compare medication groups for continuous variables, and χ^2 tests were used to analyze categorical variables.
[b]There were no significant differences in sociodemographic characteristics between the medication groups.
[c]Percentages based on N = 44, as this information was missing for 2 cases.
[d]There were no significant differences in psychiatric characteristics between the medication groups.
[e]Eight patients (6 receiving quetiapine and 2 risperidone) met criteria for bipolar I disorder with psychotic features.
[f]There were no significant differences in drug history between the medication groups.
[g]Behavioral treatment included classes attended as part of 90-day residential treatment and follow-up, intensive outpatient therapy, or 12-step programs offered in the community. Participants were encouraged but not required to maintain behavioral treatment during the trial.
Abbreviations: ANOVA = analysis of variance, BMI = body mass index, PCP = phencyclidine, PRD-III = Psychobiology of Recovery in Depression-III Somatic Symptom Scale, THC = tetrahydrocannabinol.

Figure 2. Young Mania Rating Scale (YMRS) Total Scores for Quetiapine and Risperidone Groups[a]

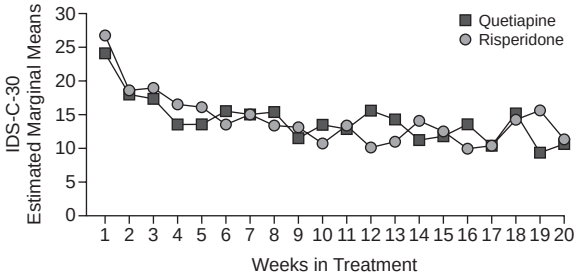


Retained N

Quetiapine, N =	42	42	39	31	30	28	24	22	21	20	19	17	17	15	14	13	11	10	8	8
Risperidone, N =	38	38	33	32	29	27	25	23	23	18	14	11	10	9	8	8	8	7	7	6

[a]Type III tests of fixed effects. Treatment (study) weeks: F = 13.21, df = 19,530.2; p < .0005; treatment (study)-weeks-by-medication-group: F = 1.12, df = 19,530.0; p = .32.
†p < .10.
*p < .05.

Figure 3. Clinician-Rated Inventory of Depressive Symptomatology (IDS-C-30) Total Scores for Quetiapine and Risperidone Groups[a]



Retained N

Quetiapine, N =	42	42	39	31	30	28	24	22	21	20	19	17	17	15	14	13	11	10	8	8
Risperidone, N =	38	38	33	32	29	27	25	23	23	18	14	11	10	9	8	8	8	7	7	6

[a]Type III tests of fixed effects. Treatment (study) weeks: F = 8.35, df = 19,519.8; p < .0005; treatment (study)-weeks-by-medication-group: F = 1.19, df = 19,519.8; p = .26.

The median ± SD quetiapine dose for individuals across study weeks was 215.5 ± 125.9 mg/day.

Overall, 23 (48%) of 48 quetiapine patients and 61% (28/46) of risperidone patients received only the study medication during the trial as monotherapy. Fifty-two percent of patients on quetiapine therapy and 39% on risperidone therapy received the study medication as adjunctive therapy ($\chi^2 = 1.59$, df = 1, p = .21). In each medication group, patients receiving study medication as adjunctive therapy or monotherapy did not significantly differ (Table 1).

Efficacy

Figure 2 shows estimated marginal means for the YMRS. The mixed model yielded a significant test of study week (p values < .0005). Modest differences were found between medication groups for weeks 12 to 14 and 16 to 17 (p values ranging from .04 to .09), but there was no significant study-week-by-medication-group interaction (p = .32). Both medication groups experienced similar decreases in YMRS scores over the 20-week trial. Figure 3 shows IDS-C-30 total scores over the 20-week trial. A mixed model yielded a significant test of study week (p < .0005); the study-week-by-medication-group interaction was not significant (p = .26).

Results for the YMRS and IDS-C-30 were the same when patients receiving only study medication as monotherapy (quetiapine or risperidone) were compared to those receiving study medication as adjunctive therapy (for tests of the fixed effects of study week in YMRS and IDS-C-30 models, p < .0005; for interaction terms, p = .50 and p = .22, respectively). Similar reductions in manic and depression symptoms were observed in both medication groups regardless of whether study medications were received as adjunctive therapy or monotherapy.

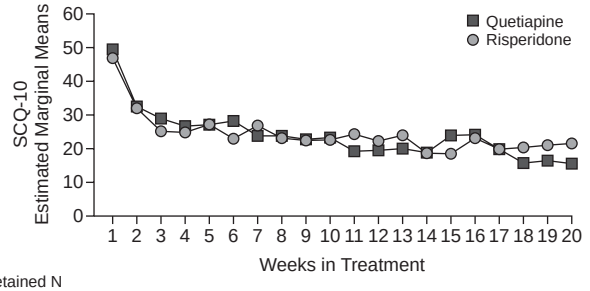
Kaplan-Meier survival analyses examined the time to meaningful clinical improvement of manic symptoms (YMRS score of ≤ 9) and remission of depression symptoms (IDS-C-30 score of ≤ 14). No differences in rates of clinical improvement were observed between the medication groups (YMRS log rank [Mantel-Cox] $\chi^2 = 0.16$, df = 1, p = .69; IDS-C-30 log rank [Mantel-Cox] $\chi^2 = 0.46$, df = 1, p = .50). By week 3, 40% (17/42) of quetiapine patients and 24% (9/38) of risperidone patients had YMRS scores of 9 or less. By week 6, 62% (26/42) of quetiapine patients and 61% (23/38) of risperidone patients showed clinical improvement of manic symptoms. For IDS-C-30, 10 (24%) of 42 quetiapine and 9 (24%) of 38 risperidone patients achieved remission. By week 6, 19 (40%) of 48 quetiapine and 19 (50%) of 38 risperidone patients remitted.

Drug Craving and Use

Mixed-model tests of the fixed effects of study medication, study week, and study-medication-by-study-week for SCQ-10 showed a significant effect of study week (p < .0005); the study-week-by-medication-group interaction was not significant (p = .69). Figure 4 shows the estimated marginal means for SCQ-10 scores for patients receiving quetiapine and risperidone over the 20-week trial. Decreases in cocaine and methamphetamine cravings for both medication groups were not different, and results were not different when study medications were used as monotherapy versus adjunctive therapy (for the interaction term, p = .99).

There were no missing urine drug screens during active participation; thus, we collected a urine sample at every study visit from every participant. Overall, 41 (51%) of the 80 evaluable patients abstained from cocaine or methamphetamine while enrolled in the study, but the

Figure 4. Stimulant Craving Questionnaire (SCQ-10) Total Scores for Quetiapine and Risperidone Groups[a]

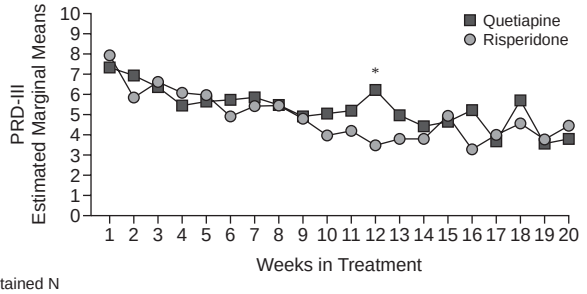


Retained N

Quetiapine, N = 42	42	39	31	30	28	24	22	21	20	19	17	17	15	14	13	11	10	8	8
Risperidone, N = 38	37	33	32	29	27	25	23	23	18	14	11	10	9	8	8	8	7	7	6

[a]Type III tests of fixed effects. Treatment (study) weeks: F = 11.73, df = 19,546.2; p < .0005; treatment (study)-weeks-by-medication-group: F = 0.82, df = 19,546.2; p = .69.

Figure 5. Psychobiology of Recovery in Depression-III Somatic Symptom Scale (PRD-III) Total Scores in Quetiapine and Risperidone Groups[a]



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Quetiapine, N = 42	42	39	31	30	28	24	22	21	20	19	17	17	15	14	13	11	10	8	8
Risperidone, N = 38	37	34	32	29	27	25	23	23	18	14	11	10	9	8	8	8	7	7	6

[a]Type III tests of fixed effects. Treatment (study) weeks: F = 3.53, df = 19,509.2; p < .0005; treatment (study)-weeks-by-medication-group: F = 1.44, df = 19,509.2; p = .10.
*p < .05.

remaining 39 study patients (49%) had at least one positive drug screen. Twenty-three (29%) of 80 study patients tested positive at least once for drugs other than cocaine or methamphetamine (16 for cannabis, 5 for opiates, and 2 for phencyclidine). The mean ± SD overall drug use, defined as the number of positive screens for the drug of choice divided by the number of weeks in the study, was 27% ± 38%.

The mean ± SD overall drug use in the quetiapine and risperidone groups was not statistically different (F = 1.67, df = 1,78; p = .20): overall, the mean ± SD percentage of positive urine screens was 32% ± 40% for quetiapine and 22% ± 33% for risperidone. Projecting positive screens for drug of choice drug status for remaining weeks after study discontinuation resulted in mean ± SD frequencies of drug of choice use in the quetiapine and risperidone groups of 63% ± 35% and 60% ± 32%, respectively (F = 0.17, df = 1,78; p = .68). In those who continued to use drugs, there were no observable adverse events related to concomitant study medication and illicit drug use.

Mood and Drug Use

As might be expected, modest positive correlations were observed between weeks enrolled in the study and reductions in YMRS (r = 0.44, p < .0005), IDS-C-30 (r = 0.26, p = .02), and SCQ-10 (r = 0.29, p = .009). Thus, in these analyses study week was entered first into a regression model to obtain the unique relationship between clinical changes and overall drug use, controlling for weeks in the study. Study patients exhibited a mean ± SD baseline-to-exit positive change (i.e., lower scores) of 7.3 ± 5.8 points on the YMRS, 7.3 ± 14.1 points on the IDS-C-30, and 22.0 ± 19.2 points on the SCQ-10.

Regression analysis showed that changes in YMRS and IDS-C-30 scores were not significantly associated with drug use—explaining less than 2.7% and 0.4% of the variance in overall drug use among study participants (t tests of the b-weights, t = –1.5, p = .14 and t = 0.6, p = .57, respectively). In contrast, decreases in drug craving were significantly but modestly associated with less frequent drug use—explaining 5.7% of the variance in overall drug use (t test of the b-weight, t = –2.2, p = .03).

Safety Measures

Participants reported minimal somatic complaints during the study, as the mean ± SD total score on the PRD-III for all study patients was 7.6 ± 3.7 (scores ranged from 0 to 46). Mixed model analysis showed a significant decrease in PRD-III scores over the 20-week trial in both medication groups (p < .0005). Figure 5 shows the estimated marginal means for the PRD-III. The test of the study-week-by-medication-group interaction was not significant (p = .10). When analyzed using monotherapy versus adjunctive therapy as a primary factor, effects of both medication (p < .0005) and study-medication-by-study-week (p = .005) were significant. This result suggests that somatic symptoms are more pronounced for participants receiving adjunctive study medication than for those receiving study medication as monotherapy.

Initial ECGs were available for 70 of the 80 patients who completed at least 2 weeks of the trial. We examined these data for participants who had both an initial ECG and at least 1 additional ECG performed at study exit (N = 37) and found nonsignificant changes—4 participants showed borderline or abnormal heart rhythms at baseline that improved to normal at exit, and 3 participants whose initial heart rhythms were normal showed minimal rhythm changes at exit. No one showed postmedication QT prolongation. Analyses of systolic and diastolic blood

Table 2. Adverse Events Reported in 80 Patients With Bipolar Disorder and Stimulant Dependence Receiving Quetiapine or Risperidone[a]

PRD-III Item	Quetiapine (N = 42), N	Risperidone (N = 38), N	Total (N = 80) N	Total (N = 80) %
Dizziness	2	1	3	4
Clumsiness	2	2	4	5
Blurred vision	1	3	4	5
Headache	3	3	6	8
Nervousness	7	3	10	13
Nausea or vomiting	2	1	3	4
Sexual difficulties	3	3	6	8
Diarrhea	1	1	2	3
Constipation	1	0	1	1
Dry mouth	3	1	4	5
Decreased appetite	3	3	6	8
Increased appetite	6	2	8	10
Difficulty urinating	0	0	0	0
Palpitations	0	0	0	0
Tiredness, fatigue	9	6	15	19
Skin rash	0	0	0	0
Tremor	0	0	0	0
Increased perspiration	1	1	2	3
Daytime sleepiness	6	5	11	14

[a]Adverse events were determined based on a PRD-III rating of 2 ("present and causing significant distress or incapacity").
Abbreviation: PRD-III = Psychobiology of Recovery in Depression-III Somatic Symptom Scale.

pressure using mixed model analyses showed no significant changes across study week ($p = .89$ and $p = .99$ for systolic and diastolic, respectively), and there were no significant study-medication-by-study-week interactions ($p = .17$ and $p = .83$, respectively). No patient developed cataracts, and no medication-induced hyperglycemia was found.

Body Mass Index

Changes in BMI weight status (e.g., a change from overweight to obese) occurred in 11 patients, 5 of whom began the study at normal weight and were overweight at exit, and 6 of whom began the study overweight and were obese at exit. When weight gain was defined in this way, the 2 medication groups did not differ—4 of the 11 were in the quetiapine group and 7 of the 11 were in the risperidone group. Overall, 20 (48%) of 42 quetiapine patients versus 11 (29%) of 38 risperidone patients exhibited an increase of 1.0 BMI point (approximately 6 lb) or greater from baseline to study exit ($\chi^2 = 2.93$, df = 1, $p = .087$). The mean ± SD change in BMI among these individuals in the 2 medication groups was 2.6 ± 1.5 for quetiapine and 2.2 ± 1.2 points for risperidone ($F = 0.66$, df = 1,29; $p = .42$). Comparison of monotherapy versus adjunctive therapy with respect to weight gain showed significant effects of study week ($p < .0005$) and medication-by-study-week ($p = .04$).

Adverse Events

Adverse events for each medication group are shown in Table 2. Prior to study medication initiation, baseline PRD-III scores were higher than at study exit (Figure 5). Adverse events were minimal and occurred with similar frequency in both medication groups. To our knowledge, no patients discontinued the study due to adverse events. Three serious adverse events occurred—each was considered unrelated to the study medication. Against protocol, 1 woman took 2 doses of an excluded conventional antipsychotic in addition to the study medication, resulting in mouth twitching; 1 man self-discontinued study medication and became severely psychotic after a 3-day cocaine binge; and 1 woman self-discontinued study medication, binged on methamphetamines, and took 23 hydrocodone tablets in a suicide attempt to avoid returning to jail following a probation violation. All 3 participants were immediately discontinued from the study and provided referrals for subsequent care.

DISCUSSION

To our knowledge, this is the first double-blind, randomized trial to compare atypical antipsychotic efficacy and tolerability in patients with co-occurring bipolar disorder and cocaine or methamphetamine dependence. Both quetiapine and risperidone, used as monotherapy or as adjunctive medications, were associated with significant improvements in manic, mixed, and depressive symptoms in comparison to baseline mood status. Improvement of manic and depression symptoms was evident by week 3. Regardless of illicit drug use status, mood stabilization was evident, on average, for all study patients in both treatment groups by week 10. The length of time until and duration of expected treatment efficacy are consistent with others reporting remitted bipolar symptoms between 3 to 10 weeks using quetiapine or risperidone.[31–38]

Both quetiapine and risperidone were significantly associated with reduced cocaine or methamphetamine cravings; reductions in cravings predicted less frequent drug use. These results are similar to those in our prior studies showing reduced drug cravings and use in a comorbid population.[8–16] However, our findings contrast with the reports that risperidone is not effective in reducing cocaine cravings or use.[5–7]

Mean baseline PRD-III scores showed that persons in both medication groups had more somatic complaints at study entry than at exit. These results suggest that illicit drug use was the primary contributor to these premedication adverse events. Study participants, some of whom intermittently used illicit drugs during the trial, were in the stages of early recovery. Thus, we cannot wholly ascribe adverse events during the trial to the study medications, illicit drug use, or to some combination of the 2. Both medications were well tolerated, and to our knowledge no patients discontinued the study due to somatic symptoms.

Both risperidone and quetiapine were associated with gradual BMI increases. We found a slightly greater risk of

weight gain in some analyses with quetiapine. Receiving atypicals as adjunctive therapy was associated with higher weight gain. Early recovering drug abusers often show immediate weight gain as a result of becoming drug abstinent, which results in the resetting of physiologic and homeostatic thresholds. Weight gain during the study could be due to drug abstinence and/or study medication.

At entry, most participants were in mixed, hypomanic, or depressed mood states and craving drugs at a moderately high rate. Some study participants showed significant mood improvement but continued to use drugs, while others experienced minimal mood improvements and became drug abstinent. We found no direct evidence that improved mood was associated with less overall drug use. Our failure to find a direct association between mood and drug use is similar to findings of other researchers that report reductions in depression symptoms but not cocaine craving.[39] Our results offer no support for the self-medication hypothesis of Khantzian,[40] who suggests that stimulant drugs are used to alleviate depression or augment mania.

There were no obvious drug interactions related to concomitant study medication and illicit drug use, although a number of discontinued subjects may have encountered such problems. This finding may be clinically relevant for physicians who hesitate to treat mood symptoms in persons who are currently abusing illicit drugs. Reluctance to treat mood symptoms in the co-occurring mood and drug use population is evident in the high rate of untreated patients entering the study. Our results suggest that both quetiapine and risperidone, used as adjunctive therapy or monotherapy, are effective and well tolerated, regardless of drug use status.

Limitations and Strengths

The study results are limited by a relatively small sample size, high attrition rates, and lack of a placebo control. The sample size may reflect the strict inclusion/exclusion criteria as indicated in the volume of screening and enrollment numbers shown in Figure 1. However, our sample size is substantially larger than those in the currently available case reports and open-label studies.[8–16] Inclusion of persons with bipolar disorder I and II, in manic, mixed, and depressed mood states meeting criteria for stimulant dependence, yielded a sample likely to be representative of the typical urban community mental health population. These sample characteristics strengthen the ecological validity and generalizability of the findings.

Although high, the attrition rate in this study is similar to those found in other studies. Other atypical antipsychotic trials lasting 21 days to 12 weeks in patients with bipolar disorder *without* stimulant use disorders report attrition rates between 42% to 53%,[31–33,35,36] and up to an 82% discontinuation rate is reported in the large multisite CATIE trial.[41] Our study discontinuation rates are comparable, as 69% remained in the study for 6 weeks, and almost 50% of the entire sample completed 12 weeks.

Those who remained in the study for at least 6 weeks experienced clinically relevant improvements in mood symptoms, reductions in drug cravings, and fewer somatic symptoms than reported at baseline. This finding suggests that attrition was not due to a worsening of mood or somatic symptoms. The duration of the 20-week trial, even with high attrition, was sufficient to observe cycles of mood and drug use in relation to treatment outcomes, a relationship that has not been thoroughly studied.

With regard to the absence of a placebo control in this study, most study patients were not receiving *any* pharmacotherapy for their bipolar illness, were experiencing mixed mood states, and were craving drugs at a moderately high rate. As these patients were symptomatic, they may have declined to participate in a placebo-controlled study, thereby creating more recruitment and attrition problems. In addition, failure to give an active intervention to this population could have increased untoward serious adverse events, potentially jeopardizing study continuance. In addition, those few who were fortunate enough to have received pharmacotherapy prior to study entry may not have volunteered to have those medications removed in exchange for the possibility of receiving a placebo. Thus, our ability to recruit would have been further limited had this study been placebo controlled.

The study was designed to provide a direct comparison of quetiapine versus risperidone based on an a priori hypothesis that quetiapine would produce superior efficacy; thus a placebo was not needed to test that hypothesis. Although the results are compelling, we acknowledge that symptom improvement and decreases in drug cravings cannot be unequivocally attributed to the effects of the 2 study medications in the absence of a placebo. However, numerous placebo comparisons demonstrating the efficacy of these FDA-approved medications[32,33,35,36,38] support our conclusion that both quetiapine and risperidone effectively treated mood symptoms and reduced drug cravings relative to baseline.

CONCLUSIONS

Compared to baseline, both quetiapine and risperidone were associated with improved manic, mixed, and depressive symptoms and reduced cocaine or methamphetamine cravings. Our results suggest that quetiapine and risperidone, used as adjunctive therapy or monotherapy, are effective and well tolerated, regardless of drug use status in persons with co-occurring bipolar disorder and stimulant dependence. Although these results appear clinically relevant, a lack of placebo control limits the interpretation of these findings.

Drug names: methamphetamine (Desoxyn), morphine (Kadian, Avinza, and others), quetiapine (Seroquel), risperidone (Risperdal).

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