Olanzapine Versus Risperidone in the Treatment of Manic or Mixed States in Bipolar I Disorder: A Randomized, Double-Blind Trial

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Objective: To compare olanzapine and risperidone in the treatment of nonpsychotic acute manic or mixed episodes.

Method: This 3-week, randomized, controlled, double-blind, parallel multicenter study compared olanzapine (5–20 mg/day; N = 165) and risperidone (1–6 mg/day; N = 164) among hospital inpatients who met DSM-IV criteria for bipolar I disorder, manic or mixed episode, without psychotic features. The study was conducted at 30 sites in the United States between July 2001 and June 2002. The primary outcome measure was the mean change in the Young Mania Rating Scale (YMRS) total score. Secondary measures included the 21-item Hamilton Rating Scale for Depression (HAM-D-21), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impressions-Bipolar Version (CGI-BP) severity of illness scale, and the Cognitive Test for Delirium (CTD). Quality of life (Short Form Health Survey [SF-12]), psychological well-being (Psychological General Well-Being [PGWB] inventory), and sexual functioning were also compared.

Results: Mean modal doses for olanzapine and risperidone were 14.7 mg/day and 3.9 mg/day, respectively. Between treatments, there was no difference in mean change in the YMRS, MADRS, CTD, PGWB, or SF-12 measures or in remission or response rates. Significantly more olanzapine-treated patients completed the study compared with risperidone patients (78.7% vs. 67.0%; p = .019). Olanzapine-treated patients had greater HAM-D-21 (p = .040) and CGI-BP (p = .026) score improvement across the study. Olanzapine-treated patients experienced greater elevations in liver function enzymes (p < .05) and increase in weight (2.5 kg vs. 1.6 kg; p = .004), while risperidone-treated patients were more likely to experience prolactin elevation (51.73 ng/mL vs. 8.23 ng/mL; p < .001) and sexual dysfunction (total score increase of 1.75 vs. 0.64; p = .049).

Conclusion: Both olanzapine and risperidone treatment yielded similar improvements in mania. The olanzapine group had significantly greater improvements in secondary measures of severity and depressive symptoms and better study completion rates but experienced more weight gain.

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Several randomized, placebo-controlled trials support the use of at least 8 medications in the treatment of acute mania, including lithium, divalproex, and 5 atypical antipsychotics (AAPs).[1–6] Contemporary treatment guidelines now include the use of an AAP, either as monotherapy or add-on therapy, as a first-line treatment option in manic patients.[7–11]

While the superiority of these drugs to placebo is well established, little data exist to guide clinical practice in selecting from among these treatment options. Two head-to-head studies of olanzapine and divalproex and a meta-analysis of the 2 studies suggested superior efficacy for olanzapine but noted better tolerability for divalproex.[12–14] Likewise, head-to-head studies of AAPs versus haloperidol found similar efficacy but differences in tolerability and treatment continuity.[15–20]

A recent meta-analysis suggests that overall efficacy, expressed in terms of placebo-subtracted improvement in Young Mania Rating Scale (YMRS) score, was similar between the AAPs,[21,22] but the comparability of the study populations across studies may be limited.

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We conducted a randomized, controlled, head-to-head study of monotherapy with olanzapine versus risperidone for the treatment of acute nonpsychotic manic or mixed states among hospitalized patients with bipolar disorder. To our knowledge, this is the first published head-to-head comparison of 2 AAPs in the treatment of bipolar mania.

METHOD

Patient Population

The study was conducted at 30 sites in the United States between July 2001 and June 2002 in 18- to 70-year-old subjects who were hospital inpatients at visit 1. The study protocol was approved by the sites' institutional review boards, and written informed consent was obtained from all participants prior to study entry. Subjects met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) diagnostic criteria for bipolar I disorder, manic or mixed episode, without psychotic features. Inclusion criteria also required a total score greater than or equal to 20 on the YMRS[23] at baseline (visits 1 and 2). Exclusion criteria included serious suicide risk, DSM-IV substance dependence within the previous 2 months (except for nicotine and caffeine), current hospitalization duration greater than 3 weeks prior to the initial visit, greater than or equal to 90-day duration of current manic or mixed episode, or documented history of failure to respond during an adequate period of treatment with olanzapine or risperidone for acute mania.

Design

After study entry, subjects were screened for 2 to 5 days, and all psychotropic agents were tapered off gradually and discontinued by 24 hours prior to randomization (lithium was tapered off over 5 days). Subjects were randomly assigned in a 1:1 fashion to receive either olanzapine or risperidone for 3 weeks. Olanzapine and risperidone doses were administered per product label. The olanzapine group received 15 mg on the day of randomization and on the following day; subsequently, flexible dosing was allowed up to a maximum of 20 mg/day. The risperidone group received 2 mg on day 1 and 3 mg on day 2; subsequently, flexible dosing was permitted up to a maximum of 6 mg/day. Subjects were evaluated 2 days after randomization, then 5 days later, and finally, weekly. Anticholinergic medication (benztropine mesylate, 2 mg/day maximum, but not for prophylaxis) was permitted for extrapyramidal symptoms (EPS), and lorazepam was permitted for severe manic agitation (2 mg/day during screening/tapering period; 2 mg/day maximum from visit 2 up to visit 3, followed by up to 1 mg/day for the next 5 days; duration not exceeding the initial 7 consecutive days of study drug receipt).

Outcome Measures

The primary outcome measure was the mean change from baseline to 3 weeks in the YMRS score. In order to assess the overall illness severity of the patient, the Clinical Global Impressions-Bipolar Version (CGI-BP) severity of illness scale[24] was collected. In addition, improvement in depressive symptoms was measured by the 21-item Hamilton Rating Scale for Depression (HAM-D-21)[25] and the Montgomery-Asberg Depression Rating Scale (MADRS).[26] The CGI-BP, YMRS, HAM-D-21, and MADRS were collected at every visit. Quality of life was assessed with the Medical Outcomes Study Short-Form 12-Item Health Survey (SF-12)[27] and the Psychological General Well-Being (PGWB) inventory.[28] Additional scales collected included the Drug Attitude Inventory-10 (DAI-10)[29] and the Cognitive Test for Delirium (CTD).[30] A clinician-rated assessment of sexual functioning was collected at baseline and endpoint. This scale included 4 questions measuring current level of sexual interest, ability to become aroused, ability to achieve an orgasm, and overall satisfaction and enjoyment, each with a score ranging from 0 to 4 (a high score indicating greater dysfunction).

Safety was assessed by the evaluation of treatment-emergent adverse events, discontinuations due to adverse events, vital sign measurements, and clinical laboratory tests. Adverse events were elicited by nonprobing inquiry and were recorded regardless of perceived causality. An event was considered "treatment-emergent" if it occurred for the first time or worsened during the double-blind treatment period. Extrapyramidal side effects were assessed by the modified Simpson-Angus Scale (Simpson-Angus)[31] and the Barnes Akathisia Scale (BAS)[32] at each visit.

Statistical Methods

All analyses performed were specified in the protocol. Analyses of change from baseline in the CGI-BP, YMRS, HAM-D-21, MADRS, Simpson-Angus, and BAS scales were conducted using a mixed-models repeated-measures (MMRM) analysis with visit, treatment, investigator, visit-by-treatment interaction, baseline score, and baseline score-by-treatment interaction as effects in the model. An unstructured covariance matrix was fit to the within-patient repeated measures. To assess the differential treatment effects across the entire double-blind period, the overall treatment test (with least-squares means) was reported from the MMRM model. In addition, change from baseline to each visit was tested between treatment groups within the repeated-measures model. To investigate whether subtypes (manic/mixed) or rapid cycling had an effect on treatment differences, a planned analysis examined an additional model, which also included effects for diagnosis and rapid cycling, and the 2-way interaction between treatment and either diagnosis or rapid cycling.

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The change from baseline to endpoint (last observation carried forward) in the sexual functioning scale (each individual item as well as the total score) was evaluated with an analysis of covariance with treatment, investigator, and baseline score in the model.

Response and remission rates were also used to compare efficacy between olanzapine and risperidone. Response was defined as 50% or greater reduction in the YMRS score at endpoint. Remission was defined as an endpoint YMRS score of 12 or less and HAM-D-21 score of 8 or less. Rates of response were compared between groups with Fisher exact test, and time to event (response or remission) was compared between groups using a log-rank test.

Treatment-emergent adverse events and rates of discontinuation were compared between treatment groups with Fisher exact test. Change from baseline to endpoint in laboratory values and vital signs were compared between treatment groups with analysis of covariance with treatment, investigator, and baseline value in the model. Treatment-emergent abnormal laboratory values were compared between treatment groups using Fisher exact test.

All analyses were based upon the intent-to-treat principle and were performed using Statistical Application Software version 8.2 (SAS Institute Inc., Cary, N.C.). All tests of treatment effects were conducted at a 2-sided α level of .05. Investigators with fewer than 2 randomized patients per treatment group were pooled for statistical analysis purposes.

On the basis of differences identified in a previous study,[12] the present study was designed to detect a total score mean change difference of 3.57 from baseline between treatment groups in YMRS scores, assuming a standard deviation (SD) of 11.0 with 80% power.

RESULTS

Participant Characteristics

In all, 329 patients met entry criteria and were randomly assigned to receive either olanzapine (N = 165) or risperidone (N = 164). Patients were predominantly white (73.6%), and 54.7% were women. Demographic data and baseline clinical characteristics were similar for both groups (Table 1). The mean modal dose was 14.7 mg/day for olanzapine and 3.9 mg/day for risperidone.

Participant Discontinuation

Overall, significantly more olanzapine-treated patients (78.7%) completed the study compared with risperidone-treated patients (67.0%, p = .019). More discontinuations because of "patient decision" occurred in the risperidone group (10.9%) compared with the olanzapine group (4.2%, p = .023); typical reasons, when provided, included withdrawal of consent or no longer wishing to participate. Proportion of patients discontinuing the study because of an adverse event was similar between treatment groups (5.4% for olanzapine, 8.5% for risperidone, p = .289). Other reasons for discontinuation were also similar between treatment groups: noncompliance (olanzapine 2.4%, risperidone 1.8%, p = 1.00), lack of efficacy (4.2% for both groups, p = 1.00), lost to follow-up (olanzapine 4.8%, risperidone 5.4%, p = .809), and physician decision (olanzapine 0%, risperidone 0.6%, p = .498).

Table 1. Baseline Clinical Characteristics and Illness Severity of Patients With Bipolar I Disorder

Characteristic	Olanzapine (N = 165)	Risperidone (N = 164)
Female, N (%)	94 (57.0)	86 (52.4)
Age, mean (SD), y	38.1 (11.1)	37.7 (10.9)
White, N (%)	124 (75.2)	118 (72.0)
Weight, mean (SD), kg	84.4 (23.6)	84.8 (20.5)
Bipolar, mixed, N (%)	93 (56.4)	100 (61.0)
Bipolar, rapid cycling, N (%)[a]	78 (47.3)	71 (43.3)
CGI-BP score, mean (SD)	4.5 (0.7)	4.4 (0.6)
YMRS score, mean (SD)	26.6 (5.0)	26.7 (5.0)
HAM-D-21 score, mean (SD)	16.0 (6.9)	15.7 (6.8)
MADRS score, mean (SD)	16.6 (7.8)	16.1 (7.5)

[a]Rapid cycling is defined as having 4 or more episodes of major depression, mania, or hypomania during a 1-year period.[33,34]
Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Version severity of illness scale, HAM-D-21 = 21-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

Efficacy

Change from baseline to week 3 (MMRM analysis) was not significantly different between treatment groups for YMRS (olanzapine –15.03, risperidone –16.62), HAM-D-21 (olanzapine –6.06, risperidone –5.20), MADRS (olanzapine –6.22, risperidone –5.40), or CGI-BP (olanzapine –1.64, risperidone –1.46) scores (all p values > .05). Secondary analyses included evaluation of the difference between treatment groups across the entire 3-week study period, i.e., averaged across each study visit, as obtained from the MMRM overall treatment effect. The olanzapine-treated patients experienced a significantly greater mean improvement compared with the risperidone-treated patients in the CGI-BP score (olanzapine –1.33, risperidone –1.16, p = .026) and the HAM-D-21 score (olanzapine –6.35, risperidone –5.36, p = .040) but not the YMRS (olanzapine –14.04, risperidone –13.97, p = .913) or the MADRS (olanzapine –6.39, risperidone –5.55, p = .106) scores. Time course of improvement in YMRS and HAM-D-21 scores is illustrated in Figures 1 and 2, respectively.

In all, 62.1% of the olanzapine-treated patients met the response definition compared with 59.5% of the risperidone-treated patients (Fisher exact test and survival analysis log-rank test, p > .600). Using protocol-specified remission criteria of YMRS score less than or equal

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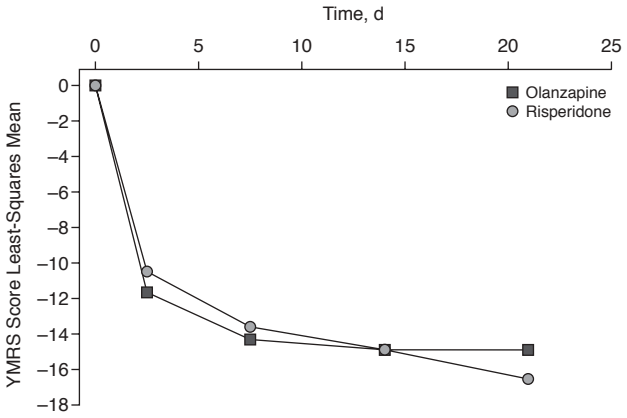
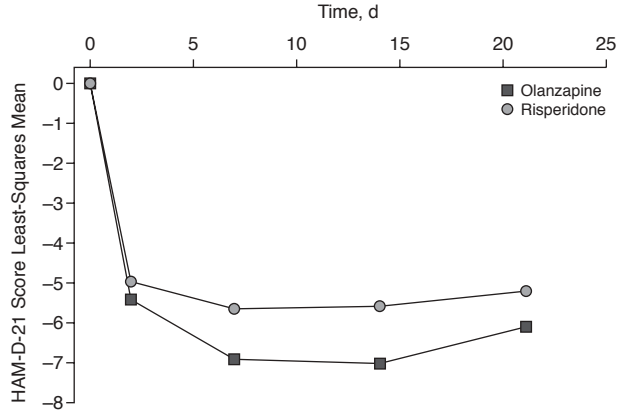
Figure 1. YMRS Score Least-Squares Mean Change From Baseline Among Patients With Bipolar I Disorder



Abbreviation: YMRS = Young Mania Rating Scale.

Figure 2. HAM-D-21 Score Least-Squares Mean Change From Baseline Among Patients With Bipolar I Disorder



Abbreviation: HAM-D-21 = 21-item Hamilton Rating Scale for Depression.

to 12 and HAM-D-21 score less than or equal to 8 at endpoint, 38.5% of the olanzapine-treated patients remitted compared with 28.5% of the risperidone-treated patients (Fisher exact test, p = .075; log-rank test from survival analysis, p = .141).

There were also no statistically significant differences detected between treatment groups in the SF-12 (change in mental component: 12.7 ± 13.9 vs. 11.0 ± 13.9, p = .119; change in physical component: –2.8 ± 11.9 vs. –2.1 ± 9.6, p = .260), PGWB (change: 18.6 ± 19.0 vs. 18.0 ± 20.2, p = .512), DAI-10 (change: 4.85 ± 4.4 vs. 4.7 ± 4.5, p = .872), or CTD (change: 0.5 ± 2.7 vs. 0.3 ± 3.1, p = .878). (All values are mean ± SD for olanzapine vs. risperidone, respectively.)

Table 2. Outcome Analysis by Rapid-Cycling Status of Patients With Bipolar I Disorder

Variable	Interaction, p Value[a]	Least-Squares Mean[b] Olanzapine	Risperidone	p Value
YMRS score	.209			
Rapid cyclers		–14.83	–17.14	.082
Non–rapid cyclers		–15.14	–16.25	.367
HAM-D-21 score	.082			
Rapid cyclers		–5.64	–6.27	.566
Non–rapid cyclers		–6.48	–4.30	.032
CGI-BP score	.028			
Rapid cyclers		–1.60	–1.73	.445
Non–rapid cyclers		–1.68	–1.25	.010
MADRS score	.114			
Rapid cyclers		–5.36	–6.56	.307
Non–rapid cyclers		–7.03	–4.45	.019

[a]Interaction between rapid-cycling status and treatment group.
[b]Least-squares means are change from baseline to week 3.
Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Version severity of illness scale, HAM-D-21 = 21-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

Table 3. Treatment-Emergent Adverse Events Occurring in ≥ 10% of Patients With Bipolar I Disorder

Adverse Event	Olanzapine (N = 165), %	Risperidone (N = 164), %	p Value
Sedation	31.5	27.4	.469
Headache	12.7	15.2	.529
Dry mouth	28.5	14.0	.002
Appetite increase	13.9	12.8	.872
Dizziness	13.9	11.0	.505
Akathisia	7.9	10.4	.451
Weight increase	16.4	3.7	< .001

Differences Across Subtypes

Results in change from baseline for the YMRS and MADRS were similar for rapid cycling patients and non–rapid cycling patients (Table 2; p > .10 for interaction between rapid cycling status and treatment). There was, however, a marginally significant interaction between rapid cycling status and treatment for both the CGI-BP and HAM-D-21, indicating that the differences between treatment groups depended on whether the patient had a history of rapid cycling or not. For those patients who were non–rapid cyclers, there was a significant benefit from olanzapine over risperidone; for rapid cycling patients, there was no difference detected between treatment groups. Among mixed versus pure manic patients, no interactive effect was observed on any efficacy measure.

Safety

Treatment-emergent adverse events occurring in greater than or equal to 10% of the patients are displayed in Table 3. Significantly more dry mouth and weight gain (by patient report) occurred in the olanzapine group compared with the risperidone group. Nine patients in the olanzapine arm discontinued because of adverse events (bipolar symptom worsening, N = 2; dizziness, N = 1;

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Table 4. Sexual Function in Patients With Bipolar I Disorder Treated With Olanzapine or Risperidone[a,b]

	Olanzapine (N = 129)		Risperidone (N = 121)		
Assessment of Sexual Function	Baseline	Change	Baseline	Change	p Value
Total score	6.96 (4.61)	0.64 (4.22)	6.74 (4.91)	1.75 (4.38)	.049
Q1: interest level score	2.04 (1.31)	0.24 (1.32)	1.76 (1.43)	0.57 (1.36)	.400
Q2: arousal ability score	1.64 (1.28)	0.10 (1.28)	1.60 (1.36)	0.46 (1.43)	.028
Q3: orgasm ability score	1.78 (1.30)	0.07 (1.13)	1.72 (1.39)	0.52 (1.28)	.004
Q4: overall satisfaction score	1.55 (1.29)	0.22 (1.31)	1.62 (1.42)	0.32 (1.39)	.461

[a]All data are reported as mean (SD).
[b]Individual question scores ranged from 0 to 4, with higher scores indicating sexual dysfunction.

lethargy, N = 1; substance abuse, N = 1; rash, N = 1; sedation, N = 2; somnolence, N = 1). In the risperidone arm, 14 discontinued due to adverse events (alcohol poisoning, N = 1; bipolar symptom worsening, N = 1; depression, N = 2; EPS, N = 3; loss of libido, N = 1; pregnancy, N = 1; suicidality, N = 3; tremor, N = 1; vomiting, N = 1).

Analysis of change from baseline to endpoint in laboratory analyses detected significantly greater changes for olanzapine compared with risperidone for alkaline phosphatase (olanzapine 3.84 U/L, risperidone –0.03 U/L, p = .013), alanine aminotransferase (olanzapine 15.72 U/L, risperidone 4.79 U/L, p = .007), aspartate aminotransferase (olanzapine 7.53 U/L, risperidone –0.02 U/L, p = .001), and γ-glutamyltransferase (olanzapine 6.56 U/L, risperidone 0.95 U/L, p = .013). Significantly greater changes were detected for risperidone compared with olanzapine for prolactin (olanzapine 8.23 ng/mL, risperidone 51.73 ng/mL, p < .001) and inorganic phosphorus (olanzapine –0.07 mg/dL, risperidone 0.17 mg/dL, p = .045). No significant differences were detected between treatment groups in change in any other laboratory values, including nonfasting cholesterol (olanzapine 10.61 mg/dL, risperidone 4.40 mg/dL, p = .087) and glucose (olanzapine 0.14 mg/dL, risperidone 1.44 mg/dL, p = .465). Differences between treatment groups for treatment-emergent abnormally high laboratory values were detected only for prolactin; 23.4% of olanzapine-treated patients had abnormally high values compared with 79.8% of risperidone-treated patients (p < .001). There were no significant differences between the 2 treatment groups in change from baseline to endpoint for any vital sign measurement except weight gain (olanzapine 2.46 kg, risperidone 1.60 kg, p = .004).

There were also no significant differences between treatment groups in the analysis of the EPS scales (Simpson-Angus or BAS). In total, 22.7% of the risperidone-treated patients required anticholinergic drugs at some time during the study compared with 14.1% of the olanzapine-treated patients (p = .063). The mean proportion of time that patients were taking an anticholinergic drug was 7.2% for olanzapine patients and 11.7% for risperidone patients (p = .047).

Risperidone-treated patients experienced significantly greater worsening in sexual function than olanzapine-treated patients; total score increased 0.64 points for olanzapine-treated patients compared with 1.75 for risperidone-treated patients (p = .049). Significant differences between treatment groups were also detected for the individual items of ability to achieve orgasm and ability to become aroused (Table 4).

DISCUSSION

To our knowledge, this study represents the first randomized, double-blind clinical trial that compares 2 AAPs in the treatment of mania. In this comparison of risperidone and olanzapine as monotherapy for the treatment of acute manic or mixed episodes in bipolar disorder, we found no significant difference in the primary efficacy outcome measure (change in YMRS score) over 3 weeks of treatment. The rates of response and remission for the present study were also similar between the 2 groups. Magnitude of improvement and response were within the ranges of other reported acute mania studies[22,35] (remission rarely reported[1,6]). Remission rates are not consistently reported across acute mania studies,[22] but the results from the present study are generally similar to those previously observed. For example, a 3-week monotherapy remission rate of 20% was reported in a risperidone study arm[3] (vs. 9% in the placebo arm, compared with 28.5% in the present study risperidone arm). Of note, short-term trials may be inadequate to fully establish remission for most patients, as continued improvement beyond 3 weeks is often observed,[22] but such data have not been published for olanzapine study arms.[12] Modest but statistically significant differences were observed on 1 of 2 measures of depression (HAM-D-21) and on a measure of improvement in overall symptom severity; these differences appear to be the result of differential improvement among non–rapid cycling patients in the olanzapine-treated group.

Taken together, these results suggest similar efficacy for the 2 agents in the treatment of manic symptoms. The suggestion of a differential effect for olanzapine on depressive symptoms in mania must be interpreted cautiously given that the study was not designed to assess these effects and that the difference was only evident on 1 of 2 scales.

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The suggestion of differential response on the secondary outcome measures only among a subgroup of non–rapid cycling patients is also of interest. A secondary analysis of a large trial of olanzapine or placebo plus valproate or lithium produced a parallel finding: the efficacy difference was most apparent in the non–rapid cycling patients who improved significantly in ratings of depressive symptoms, mania, and suicidality.[36] Also, in another secondary analysis, olanzapine compared with placebo was effective in reducing symptoms of mania and well tolerated in patients with bipolar I disorder with a rapid cycling course.[37] A possible explanation is that subjects with rapid cycling experience briefer mood episodes in which mood change may be less impacted by extrinsic, drug-specific factors.

Rates of study completion were significantly greater among the olanzapine group. Treatment discontinuations may be affected by various domains of efficacy and tolerability. This study did find distinct tolerability differences; greater weight gain was observed among olanzapine-treated patients, and more sexual dysfunction and elevated prolactin levels were observed among the risperidone-treated patients. These differences are consistent with observations in schizophrenia trials.[38] For risperidone, these results are consistent with the increases in serum prolactin levels in other acute trials.[3] Likewise, for olanzapine, an increase in alanine aminotransferase has also been reported previously; however, this increase did not result in study discontinuation or exceed the threshold generally considered to be clinically significant.[1]

Bipolar patients may experience syndromal remission without functional recovery,[39] highlighting the inadequacy of a purely efficacy-based approach to treatment selection. However, the balance of efficacy and tolerability is difficult to operationalize. In particular, quality of life and functional status are complex concepts, which may be impacted by residual mood symptoms and adverse events, as well as by consequences of prior illness.[40] In this sample, 2 measures of functioning and well-being, the SF-12 and PGWB, do not distinguish significantly between risperidone and olanzapine treatment. The short-term duration of the study limits the interpretation of functional scales. More broadly, our findings fit into a shifting approach to selecting treatment options that incorporates considerations in addition to efficacy on a single outcome measure. The ultimate goal of this approach would be to match patients to the treatment that is most likely to be safe, well tolerated, and effective for them, which requires an understanding of the priorities of the individual patient.

An important limitation of the present study is that the results can only be generalized to patients without psychotic features. In addition, as with other randomized trials in mood disorders, patients with substance dependence and severe medical comorbidities were excluded. Further, as this is a short-term study, we are unable to examine differences in tolerability or safety, which may only emerge with longer-term use.

Lastly, this study was powered to detect differences in the primary efficacy measure between treatment groups. As such, it was not designed specifically to identify differences in tolerability per se; the failure to detect significant differences does not necessarily imply that no differences exist. Conversely, as these were secondary comparisons, correction for multiple testing was not performed, so some differences may represent inflated type I errors.

CONCLUSION

Olanzapine and risperidone treatment were associated with similar improvement in acute mania symptoms after 3 weeks and similar response and remission rates, but differed in rates and times to discontinuation and adverse event profiles. Further comparative studies will be important in clarifying differences in tolerability and symptomatic improvement between these and other modern treatments.

Drug names: benztropine (Cogentin and others), divalproex sodium (Depakote), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal).

This study involved the participation of the following investigators and sites: Dan Anderson, M.D., PsyCare Alliance, Torrance, Calif.; Louise M. Beckett, M.D., I.P.S. Research, Oklahoma City, Okla.; Jeffrey Borenstein, M.D., Holliswood Hospital, Holliswood, N.Y.; Mathew Brams, M.D., Bayou City Research Corporation, Houston, Tex.; Andrew Cutler, M.D., Coordinated Research of Florida, Inc., Winter Park, Fla., and Life Stream Behavioral Center, Leesburg, Fla.; Michael Dempsey, M.D., Albuquerque Neuroscience, Inc., Albuquerque, N.M.; Natalie Gershman, M.D., Geny Research, Newton Center, Mass.; John Gilliam, M.D., Westbrook Behavioral Associates, Richmond, Va.; Ramanath Gopalan, M.D., Comprehensive Neuroscience of Northern Virginia, Falls Church, Va.; Robert Grillo, M.D., Middlesex Hospital, Middletown, Conn.; Sanjay Gupta, M.D., Global Research and Consulting, Olean, N.Y.; Mahlon Hale, M.D., New Britain General Hospital, New Britain, Conn.; Scott P. Hoopes, M.D., Mountain West Clinical Trials, Boise, Idaho; Saleem Ishaque, M.D., Synergy Clinical Research Center, Chula Vista, Calif.; Zerrin E. Kayatekin, M.D., University of Massachusetts Medical School, Worcester, Mass.; Michael Levy, M.D., Staten Island Hospital, Behavioral Medical Research, Staten Island, N.Y.; Adam Lowy, M.D., CNS, Inc., Washington, D.C.; Gerald Maguire, M.D., UC Irvine Medical Center, Orange, Calif.; Arvin Mirow, M.D., Psychiatric Centers at San Diego, Craven Road, San Marcos, Calif.; Frederick Petty, M.D., Creighton University, Omaha, Neb.; Michael Plopper, M.D., Sharp Mesa Vista Hospital, San Diego, Calif.; Joel Posener, M.D., Washington University School of Medicine, St. Louis, Mo.; Robert A. Riesenberg, M.D., Atlanta Center for Medical Research, Atlanta, Ga.; Cliff Roberson, M.D., Tennessee Christian Medical Center, Madison, Tenn.; Bruce Rosen, M.D., North Shore Psychiatry Consultants, Smithtown, N.Y.; Leon Rubenfaer, M.D., Harbor Oaks Hospital, New Baltimore, Mich.; Marshall Thomas, M.D., University of Colorado Health Science Center, Denver, Colo.; Richard H. Weisler, M.D., Raleigh, N.C.

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