

# A 12-Week, Double-blind Comparison of Olanzapine vs Haloperidol in the Treatment of Acute Mania

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**Background:** This randomized controlled trial compares the efficacy and safety of olanzapine vs haloperidol, as well as the quality of life of patients taking these drugs, in patients with bipolar mania.

**Methods:** The design consisted of 2 successive, 6-week, double-blind periods and compared flexible dosing of olanzapine (5-20 mg/d, n=234) with haloperidol (3-15 mg/d, n=219).

**Results:** Rates of remission (Young-Mania Rating Scale score of  $\leq 12$  and 21-item Hamilton Rating Scale for Depression score of  $\leq 8$  at week 6) were similar for olanzapine- and haloperidol-treated patients (52.1% vs 46.1%, respectively;  $P = .15$ ). For the subgroup of patients whose index episode did not include psychotic features, rates of remission were significantly greater for the olanzapine group compared with the haloperidol group (56.7% vs 41.6%,  $P = .04$ ). Relapse into an affective episode (mania and/or depression) occurred in 13.1% and 14.8% of

olanzapine- and haloperidol-treated patients, respectively ( $P = .56$ ). Switch to depression occurred significantly more rapidly with haloperidol than with olanzapine when using survival analysis techniques ( $P = .04$ ), and significantly more haloperidol-treated patients experienced worsening of extrapyramidal symptoms, as indicated by several measures. Weight gain was significantly greater in the olanzapine group compared with the haloperidol group (2.82 vs 0.02 kg,  $P < .001$ ). The olanzapine group had significant improvement in quality of life on several dimensions compared with the haloperidol group.

**Conclusions:** These data suggest that olanzapine does not differ from haloperidol in achieving overall remission of bipolar mania. However, haloperidol carries a higher rate of extrapyramidal symptoms, whereas olanzapine is associated with weight gain.

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**A**LTHOUGH LITHIUM, valproate, and, more recently, atypical antipsychotics are widely used to treat bipolar disorder, typical antipsychotic agents continue to be an integral part of treatment regimens.<sup>1,2</sup> They are often used to achieve rapid control of acute manic symptoms, particularly for agitated patients. However, a number of authors have suggested that their use may in fact worsen the course of the bipolar disorder by increasing the risk of depressive episodes, switching patients into depression, and possibly increasing the likelihood of rapid cycling.<sup>3-8</sup> Typical antipsychotics have the additional risks of causing acute extrapyramidal symptoms (EPSs), tardive dyskinesia, and neuroleptic malignant syndrome,<sup>9</sup> a risk reportedly higher among patients with bipolar disorder.<sup>9,10</sup> The literature available to date inadequately addresses how atypical antipsychotic drugs compare with older agents in efficacy and whether they will pose less risk

of switch into depression.<sup>11,12</sup> This 12-week, double-blind study compared the safety and efficacy of olanzapine vs haloperidol, as well as the quality of life of patients taking these drugs, in patients diagnosed as having acute mania.

## METHODS

### PATIENT POPULATION

Patients enrolled in this study were 18 years and older; met the DSM-IV<sup>13</sup> criteria for bipolar I disorder manic or mixed type (with or without psychotic features), based on the *Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Patient Version (SCID-P)*<sup>14</sup>; and had a baseline Young-Mania Rating Scale (YMRS) score of 20 or higher. Patients were excluded if they had a serious, unstable medical illness, had DSM-IV substance dependence (except nicotine or caffeine) within the past 30 days, or were considered a serious risk of suicide. Before participation, all patients signed an informed consent form approved by the study site's institutional review board.

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## STUDY DESIGN

This 12-week, randomized, double-blind, parallel group study compared olanzapine and haloperidol in the short-term treatment of bipolar I disorder. Patients were recruited from inpatient and outpatient settings at 58 centers across Western Europe, South Africa, and North and South America from November 1, 1998, through October 31, 1999. The mean, median, and range of number of patients enrolled per site were 5, 3, and 1 through 17 for the olanzapine group and 5, 3, and 1 through 19 for the haloperidol group, respectively. Before randomization, patients underwent a 2- to 7-day screening period, consisting of 2 visits (visits 1 and 2). All psychotropic medication, with the exception of benzodiazepines, was tapered at least 1 day before randomization. Patients who met enrollment criteria were randomly assigned to a unique drug kit number via a call-in interactive voice response system in a 1:1 ratio to treatment with olanzapine or haloperidol. All patients, study site personnel, and Lilly Research Laboratories employees were blinded to randomization codes.

The 12-week trial consisted of 2 phases, a 6-week, double-blind, short-term therapy phase (visits 3 to 8) and a subsequent 6-week, double-blind, continuation phase (visits 9 to 14). Clinical visits were conducted on a weekly basis throughout the 12-week trial. Patients who completed the short-term phase and showed at least a 1-point improvement from baseline in the Clinical Global Impressions–Severity of Bipolar Disorder scale (CGI-BP) overall score<sup>15</sup> were eligible for entry into the continuation phase.

Patients received flexible dosing of either olanzapine (5, 10, 15, or 20 mg/d) or haloperidol (3, 5, 10, or 15 mg/d). Following 1 day of taking the initial dose (olanzapine, 15 mg/d, or haloperidol, 10 mg/d), treating physicians could adjust the daily dose level upward or downward, as clinically indicated, by 1-level increments. Dose reductions due to adverse events could occur at any time by any number of decrements to the minimum dosage level. Concomitant medications with primary central nervous system activity were restricted to benzodiazepines (lorazepam up to 4 mg/d for a maximum of 14 cumulative days); anticholinergics (biperiden or benztropine mesylate up to 6 mg/d) were also permitted.

## ASSESSMENTS

Severity of illness and psychopathology were measured by YMRS<sup>16</sup> and the 21-item Hamilton Rating Scale for Depression (HAM-D-21).<sup>17</sup> Quality of life was assessed with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).<sup>18</sup> Laboratory tests and vital signs were assessed as specified in the protocol and as determined by the investigator. The EPSs were assessed with the Simpson-Angus Rating Scale,<sup>19</sup> the Barnes Akathisia Scale,<sup>20</sup> and the Abnormal Involuntary Movement Scale (AIMS).<sup>21</sup> Treatment-emergent EPSs based on rating scale criteria were defined as follows: parkinsonism, a score of 3 or lower at baseline to higher than 3 at any time after baseline on the Simpson-Angus scale<sup>19</sup>; akathisia, a score of lower than 2 at baseline to 2 or higher at any time after baseline on the Barnes Akathisia Scale<sup>20</sup>; and dyskinesia, 3 or higher on any of AIMS items 1 through 7 or a score of 2 or higher on any 2 of AIMS items 1 through 7 without meeting either criteria at baseline.<sup>22</sup>

Protocol-defined categorical definitions included symptomatic remission of mania and depression, defined as a YMRS score of 12 or lower and a HAM-D-21 score of 8 or higher at week 6, and syndromic remission of mania and/or depression, as previously defined in the literature.<sup>23-27</sup> Symptomatic relapse into an affective episode (depression, mania, or mixed) was defined as a YMRS score of 15 or higher and/or a HAM-D-21 score of 15 or higher in patients previously meeting symptom-

atic remission criteria, and syndromic relapse into an affective episode was defined as first achieving syndromic remission in both mania and depressive criteria, then relapsing into either DSM-IV defined mania or depression. Time to first remission was determined when patients first met criteria for remission. Secondary efficacy assessments included mean changes in YMRS and HAM-D-21 total scores and clinical response based on 50% or higher, 70% or higher, or 80% or higher reduction in YMRS scores. The incidence of switch into depression was a nonprotocol-defined assessment performed in the subset of patients who were not clinically depressed at study entry (HAM-D-21 score of 8 or lower at baseline) but who became depressed (HAM-D-21 score of 15 or higher) at some point during the trial.

Efficacy assessments, vital signs, and weight were assessed at each visit, and clinical laboratory testing was performed at baseline and weeks 6 and 12 or when the patient discontinued randomized therapy. Adverse events were recorded at every visit through nondirected, open-ended questioning, spontaneous report, and clinical observation. Quality of life was assessed at baseline and weeks 6 and 12.

## STATISTICAL METHODS

The planned sample size of 218 patients per group (based on a 5% type I error rate and 80% power for a 2-sided test of proportions) was derived assuming 39% and 26% remission for olanzapine-treated and haloperidol-treated patients, respectively. Baseline characteristics were compared between groups with the Fisher exact test for categorical data, and, for continuous data, an analysis of variance (ANOVA) was used. The proportions of patients using benzodiazepines and anticholinergics were compared using the Fisher exact test, and the mean doses of these medications were compared with ANOVA. The proportion of patients meeting remission criteria was analyzed with the Cochran-Mantel-Haenszel test using country as a stratification variable. Remission was further analyzed for subgroups of patients with the Breslow-Day test, examining differential treatment effects for remission based on subgroup stratification; treatment differences within strata were compared with the Fisher exact test. Incidences of response and relapse following remission were compared between groups using the Fisher exact test. Analyses of time to events were performed using Kaplan-Meier estimated survival curves, and the curves were compared using the log-rank test.

Analysis of the change from baseline in efficacy rating scales (YMRS and HAM-D-21 total scores) and the quality-of-life scale (SF-36 dimension and composite scores) was performed using a mixed-effects model, repeated-measures ANOVA. The linear model used in this analysis included terms for the treatment, country, treatment-by-country interaction, visit, and treatment-by-visit interaction, with the score at baseline used as a covariate. All of these terms were considered fixed effects in the model. An unstructured covariance matrix was specified for the within-patient error. Treatment groups were compared using a *t* test based on least-squares mean estimates.

ANOVA was used to analyze the last-observation-carried-forward changes from baseline to end point for the continuous safety measures (laboratory analytes, vital signs and weight, and EPS rating scales). Categorical safety data were evaluated with the Fisher exact test.

Analyses were performed on an intent-to-treat basis, meaning patients were retained in the analysis as randomized even if the patient did not strictly adhere to the protocol during the trial. For analysis of scale scores and quantitative measurements, patients were included only if they had at least 1 post-baseline assessment. Linear models used in ANOVA generally contained terms for treatment, country, and the treatment-country interaction, unless otherwise specified. SAS statistical

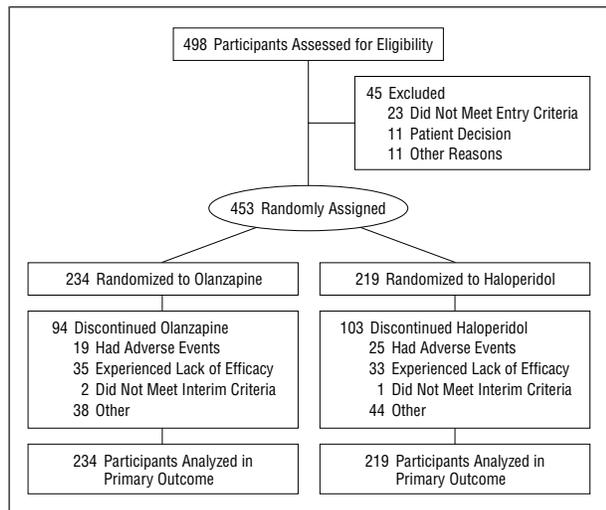


Figure 1. Patient flowchart.

Table 1. Patient Illness and Characteristics at Randomization

Characteristic	Olanzapine (n = 234)	Haloperidol (n = 219)	P Value	F Test (df)
Age, mean (SD), y	41 (13)	40 (13)	.21	1.57 (1,442)
Sex, No. (%) female	148 (63.2)	125 (57.1)	.21	NA
Bipolar index episode, No. (%) manic	221 (94.4)	207 (94.7)	>.99	NA
Psychotic features, No. (%) present	130 (55.6)	130 (59.4)	.45	NA
YMRS total score, mean (SD)	31.1 (7.57)	30.6 (7.68)	.57	0.32 (1,442)
HAMD-21 total score, mean (SD)	8.03 (6.34)	8.05 (6.42)	.72	0.13 (1,440)

Abbreviations: HAMD-21, 21-item Hamilton Rating Scale for Depression; NA, not applicable; YMRS, Young-Mania Rating Scale.

software was used to perform all analyses<sup>28</sup>; treatment effects were tested at the 2-sided  $\alpha$  level of .05 and all interactions at a level of .10 as protocol specified.

## RESULTS

### PATIENT CHARACTERISTICS AND DISPOSITION

A total of 498 patients were screened and 453 were randomized to treatment (**Figure 1**). Most randomized patients were female (60.3%) and had a mean age of 40 years (range, 18-86 years). Based on *DSM-IV* criteria using the *SCID-P*, 94.5% of patients had a manic index episode and 57.4% of patients were experiencing psychotic features. At study entry, 79% of randomized patients were hospitalized (olanzapine, 77.3%; haloperidol, 80.7%;  $P = .42$ ), and at week 6, 8.3% remained hospitalized (olanzapine, 10.1%; haloperidol, 6.3%;  $P = .37$ ). There were no significant differences in any demographic or illness baseline characteristic between treatment groups at randomization (**Table 1**). Approximately 44% of the patients withdrew during the 12-week trial, most frequently for lack of efficacy. The rate of withdrawals and completions and the specific reasons for withdrawals did not dif-

Table 2. Patient Disposition

Variable	Patients, No. (%)			P Value
	Olanzapine	Haloperidol	Total	
Patients randomized	234 (100)	219 (100)	453 (100)	...
Completed 6 weeks of treatment	166 (70.9)	141 (64.4)	307 (67.8)	.16
Entered continuation period (week 7)	160 (68.4)	138 (63.0)	298 (65.8)	...
Completed 12 weeks of treatment	140 (59.8)	116 (53.0)	256 (56.4)	.15
Discontinued treatment				
Adverse events	19 (8.1)	25 (11.4)	44 (9.8)	.27
Lack of efficacy	35 (15)	33 (15.1)	68 (15)	>.99
Lost to follow-up	3 (1.3)	3 (1.4)	6 (1.3)	>.99
Entry criteria not met/ noncompliance	9 (3.8)	6 (2.7)	15 (3.3)	.60
Interim criteria not met	2 (0.9)	1 (0.5)	3 (0.7)	>.99
Patient decision	15 (6.4)	17 (7.8)	32 (7.1)	.59
Physician decision	7 (3.0)	15 (6.8)	22 (4.9)	.08
Sponsor decision	2 (0.9)	1 (0.5)	3 (0.7)	>.99
Satisfactory response	2 (0.9)	2 (0.9)	4 (0.9)	>.99

Table 3. Summary of Drug Dose

Therapy	Drug Dose, mg/d	
	Mean (SD)	Median
Week 1		
Olanzapine	15.1 (2.7)	15
Haloperidol	9.6 (2.4)	10
Week 6		
Olanzapine	15.0 (5.1)	15
Haloperidol	7.1 (4.3)	5
Week 12		
Olanzapine	11.4 (5.3)	10
Haloperidol	5.2 (3.3)	3

fer between treatment groups (**Table 2**). At the end of 6 weeks, only 2 olanzapine-treated patients and 1 haloperidol-treated patient did not meet the criteria for entry into the 6-week, double-blind continuation phase.

### STUDY DRUG DOSE AND CONCOMITANT MEDICATION

The mean and median doses of olanzapine and haloperidol during the short-term and continuation periods of the trial are given in **Table 3**. Thirty-three patients in the haloperidol group and 35 patients in the olanzapine group discontinued the study because of a lack of efficacy. The mean dose of haloperidol for these 33 patients was 10.0 mg (SD=4.7 mg), and 25 of these 33 patients had received the maximal dose of haloperidol. The mean dose of olanzapine for the 35 patients was 17.4 mg (SD=4.0 mg), and 32 of 35 patients had received the maximal dose of olanzapine.

Benzodiazepines were used at least once during the 12-week study period by 60.3% and 64.8% of patients

**Table 4. Rates of Remission and Response**

Variable	Patients, No./Total No. (%)		P Value	OR (95% CI)
	Olanzapine	Haloperidol		
Remission based on				
Symptomatic rating scale criteria at week 6	122/234 (52.1)	101/219 (46.1)	.15	1.27 (0.88-1.84)
Symptomatic rating scale criteria at weeks 5 and 6	100/234 (42.7)	85/219 (38.8)	.29	1.18 (0.81-1.71)
Symptomatic rating scale criteria at week 6 in those patients who completed more than 1 week of therapy	122/227 (53.7)	101/201 (50.2)	.38	1.19 (0.89-1.75)
DSM-IV syndromic criteria at week 6	116/234 (49.4)	97/219 (44.3)	.17	1.24 (0.85-1.79)
Response based on				
≥70% Improvement in YMRS total score at week 6	127/231 (55.0)	132/213 (62.0)	.15	0.75 (0.51-1.09)
≥80% Improvement in YMRS total score at week 6	106/231 (45.9)	110/213 (51.6)	.25	0.79 (0.55-1.15)

Abbreviations: CI, confidence interval; OR, odds ratio; YMRS, Young-Mania Rating Scale.

in the olanzapine and haloperidol groups, respectively ( $P = .33$ ), and the average daily dose was 1.5 and 1.1 mg, respectively ( $F_{1,267} = 0.85$ ,  $P = .35$ ). The incidence of anticholinergic use was significantly greater among haloperidol-treated patients (60.3%) compared with olanzapine-treated patients (18.4%) ( $P < .001$ ). The average daily dose of anticholinergics was also significantly greater among patients randomized to the haloperidol group (2.9 vs 1.6 mg/d,  $F_{1,158} = 15.8$ ,  $P < .001$ ).

## EFFICACY

### Remission

The protocol-defined primary efficacy measure in this study was the proportion of patients who met the criteria for symptomatic remission of both manic and depressive symptoms, defined as a YMRS score of 12 or lower and a HAMD-21 score of 8 or lower at week 6. Rates of symptomatic remission were not different between groups (**Table 4**). Time to symptomatic remission was also not different (log-rank test  $\chi^2_1 = .001$ ,  $P = .98$ ); the estimated median time to first remission was 34 and 29 days for the olanzapine and haloperidol groups, respectively. Remission was also assessed 3 additional ways: as meeting the symptomatic remission criteria for 2 successive visits (weeks 5 and 6), based on symptomatic remission criteria in patients who completed more than 1 week of therapy, and based on DSM-IV criteria for syndromic remission. Irrespective of the criteria used to define remission, rates of remission were not statistically different; approximately 47% of patients achieved remission by week 6 (Table 4). Considering those patients who were not in remission at week 6, significantly more olanzapine-treated patients (28 [68%] of 41) met symptomatic remission criteria at week 12 compared with haloperidol-treated patients (16 [41%] of 39,  $P = .02$ ).

A statistically significant interaction was found for protocol-defined subgroup analysis based on the presence or absence of psychotic features ( $P = .09$ , Breslow-Day test), suggesting a differential treatment response. The proportion of patients without psychotic features who achieved symptomatic remission was significantly greater for the olanzapine group compared with the haloperidol group (56.7% vs 41.6%, respectively;  $P = .04$ ). Time

to symptomatic remission for patients without psychotic features was not significantly different between treatment groups (log-rank test  $\chi^2_1 = 0.21$ ,  $P = .88$ ). Among patients with psychotic features, olanzapine and haloperidol were not significantly different in treating mania; approximately half the patients in each group met the criteria for symptomatic remission (48.5% vs 49.2%, respectively;  $P > .99$ ). Of note, there was no significant interaction for the treatment by manic or mixed subtypes ( $P = .33$ , Breslow-Day test).

To examine the relationship between treatment efficacy and severity of illness, a nonprotocol-defined analysis was performed of remission rates stratified by baseline scores of the overall CGI-BP. Patients were separated into a moderate illness category (overall CGI-BP score  $\leq 4$ ) or a severe illness category (overall CGI-BP score  $\geq 5$ ). For both therapy groups, remission rates were similar among patients moderately ill at baseline (58.9% for olanzapine and 57.0% for haloperidol) but somewhat disparate among those severely ill at baseline (47.9% for olanzapine and 40.0% for haloperidol); overall, the differential effect between therapy groups based on baseline severity was not statistically significant ( $P = .54$ , Breslow-Day test).

### Maintenance of Response

Maintenance of response was characterized as the proportion of patients who met the remission criteria based on symptomatic rating scales at week 6 and then relapsed into any affective episode (manic, depressive, or mixed) during the continuation phase (YMRS score  $\geq 15$  and/or HAMD-21 score  $\geq 15$  at any time after week 6) and as the proportion of patients who met the remission criteria based on the DSM-IV criteria for syndromic remission at week 6 and then had a DSM-IV affective syndromic relapse.

Rates of relapse based on symptomatic criteria were not different; 16 (13.1%) of 122 patients in the olanzapine group and 15 (14.8%) of 101 patients in the haloperidol group ( $P = .56$ ) relapsed into an affective episode. Time to relapse was also not statistically different between groups (log-rank test  $\chi^2_1 = 0.15$ ,  $P = .70$ ). Relapses were further categorized as manic (olanzapine,  $n = 7$ ; haloperidol,  $n = 7$ ), depressive (olanzapine,  $n = 8$ ; halo-

**Table 5. Tests of Fixed Effects in Mixed-Effects Model, Repeated-Measures Analyses of Variance for Change From Baseline in the YMRS and HAMD-21 Total Scores**

Effect	Change in YMRS Total Score			Change in HAMD-21 Total Score		
	F Test	df	P Value	F Test	df	P Value
Baseline	265.37	1,423	<.001	303.54	1,422	<.001
Therapy	7.10	1,423	.008	2.05	1,422	.15
Country	2.38	9,423	.01	5.50	9,422	<.001
Visit	112.91	11,423	<.001	7.15	11,422	<.001
Therapy by country	1.28	11,423	.24	2.41	9,422	.01
Therapy by visit	2.40	11,423	.007	0.75	11,422	.69

Abbreviations: HAMD-21, 21-item Hamilton Rating Scale for Depression; YMRS, Young-Mania Rating Scale.

**Table 6. Secondary Efficacy End Points for the Short-term and Continuation Phases\***

End Point	Week 6 Change	Week 12 Change	Change From Week 6 to Week 12
<b>YMRS</b>			
Olanzapine, least squares mean (SE)	-21.3 (0.72)	-26.5 (0.60)	-5.2 (0.55)
Haloperidol, least squares mean (SE)	-23.5 (0.73)	-26.8 (0.57)	-3.3 (0.59)
P value	.03	.72	.02
t Test	2.12	0.35	-2.33
df	423	423	423
<b>HAMD-21</b>			
Olanzapine, least squares mean (SE)	-2.8 (0.41)	-2.6 (0.54)	0.2 (0.47)
Haloperidol, least squares mean (SE)	-1.8 (0.42)	-1.7 (0.57)	0.1 (0.51)
P value	.09	.24	.92
t Test	-0.99	-0.91	0.11
df	422	422	422

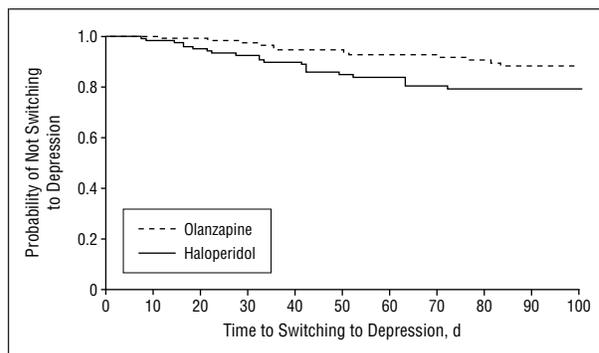
Abbreviations: HAMD-21, 21-item Hamilton Rating Scale for Depression; YMRS, Young-Mania Rating Scale.

\*Negative values indicate improvement from baseline for YMRS and HAMD-21 total scores.

peridol, n=8), or mixed or cycling course (olanzapine, n=1; haloperidol, n=0). Rates of relapse based on DSM-IV criteria for syndromic remission did not differ between groups; 40 (34.5%) of 116 patients in the olanzapine group and 30 (30.9%) of 97 patients in the haloperidol group ( $P=.95$ ) relapsed into an affective episode. Time to syndromic relapse was also not statistically different between treatment groups (log-rank test  $\chi^2_1=0.34$ ,  $P=.56$ ). Relapses were further categorized as manic (olanzapine, n=14; haloperidol, n=13), depressive (olanzapine, n=18; haloperidol, n=17), or mixed or cycling course (olanzapine, n=8; haloperidol, n=0).

### Secondary Measures of Efficacy

**Manic Symptoms.** Overall, patients manifested a clinically severe manic symptom profile at baseline as indicated by the baseline YMRS scores (Table 1). For change in the YMRS scores, the significant therapy-by-visit in-



**Figure 2.** Time to switch to depression for patients who were not clinically depressed at baseline (21-item Hamilton Rating Scale for Depression [HAMD-21] score  $\leq 8$ ). Time to switch into depression (HAMD-21 score  $\geq 15$ ) was significantly longer (log-rank test  $\chi^2_1=4.1$ ,  $P=.04$ ) for the olanzapine group (dashed line) compared with the haloperidol group (solid line). During the 12-week period, 22 haloperidol- and 12 olanzapine-treated patients switched into depression. The number of patients who experienced a switch to depression by days 15, 30, and 60 were 3, 9, and 18 for the haloperidol group and 1, 3, and 8 for the olanzapine group, respectively.

teraction suggests differential treatment effects among visits; baseline and country also were associated with improvement in YMRS scores (Table 5). At the end of the 6-week phase, improvement in manic symptoms was statistically significantly greater for haloperidol-treated patients, whereas improvement in manic symptoms was statistically significantly greater for olanzapine-treated patients from weeks 6 to 12 (Table 6). At the end of 12 weeks, there was no statistical difference between groups in YMRS total scores. Clinical response, defined as a 50% or greater improvement from baseline in YMRS total score, was 72.3% and 74.2% ( $P=.67$ ) during the short-term period and 96.3% and 94.1% ( $P=.42$ ) during the continuation period for olanzapine- and haloperidol-treated patients, respectively. When response was defined as either a 70% or 80% reduction in YMRS scores, no differences were observed between groups (Table 4).

**Depressive Symptoms and Switch Into Depression.** On average, HAMD-21 total scores at baseline were low (Table 1). For changes in the HAMD-21 scores, there were significant visit effects but no significant therapy effects; baseline and country were associated with improvement in depressive symptoms (Table 5). The small changes observed in HAMD-21 total scores were not likely clinically relevant (Table 6). Therefore, to assess the effects of treatment on depressive symptoms, nonprotocol-defined analyses were performed in patients who entered the study in a mixed manic state and in patients who exhibited severe depressive symptoms at baseline (ie, HAMD-21 score  $\geq 20$ ). Both therapies were effective in reducing depressive symptoms among these subgroups of patients. For patients presenting with a mixed manic index episode, the mean change from baseline to week 12 was -7.15 (SD, 10.2; n=13) and -1.92 (SD, 9.21; n=12) for the olanzapine and haloperidol groups, respectively ( $F_{1,11}=0.01$ ,  $P=.94$ ). For those patients who were considered severely depressed at study entry, the mean change from baseline to week 12 was -8.22 (SD, 11.0; n=9) and -12.5 (SD, 9.07; n=10) for the olanzapine and haloperidol groups, respectively ( $F_{1,10}=0.18$ ,  $P=.68$ ).

**Table 7. Quality of Life According to the Medical Outcomes Study 36-Item Short-Form Health Survey\***

Item	Baseline			Week 6					Week 12				
	Mean (SE)		P	Least Squares Mean (SE)		F	df	P	Least Squares Mean (SE)		F	df	P
	Olanzapine	Haloperidol		Olanzapine	Haloperidol				Olanzapine	Haloperidol			
General health	73.7 (12.6)	75.1 (11.9)	.65	-2.3 (2.1)	-7.4 (1.9)	3.2	1,280	.07	0.2 (2.4)	-7.3 (2.2)	5.5	1,280	.02
Physical functioning	85.0 (12.7)	89.8 (11.9)	.03	-1.0 (2.7)	-10.3 (2.4)	6.7	1,282	.01	-1.0 (2.8)	-9.4 (2.5)	5.0	1,282	.03
Role limitations, physical problems	65.9 (12.7)	71.6 (11.9)	.21	1.7 (4.5)	-12.6 (4.1)	5.5	1,282	.02	7.8 (4.7)	-1.7 (4.2)	2.3	1,282	.13
Vitality	75.9 (12.7)	79.2 (11.9)	.09	-8.2 (2.5)	-13.6 (2.2)	2.6	1,282	.11	-11.3 (2.7)	-17.7 (2.5)	3.1	1,282	.08
Bodily pain	79.9 (12.7)	80.8 (11.9)	.93	-0.2 (2.4)	2.0 (2.2)	0.5	1,283	.49	2.8 (2.5)	5.2 (2.2)	0.5	1,283	.48
Mental health	71.2 (12.7)	72.4 (11.9)	.70	0.6 (2.3)	-1.6 (2.1)	0.5	1,282	.48	2.5 (2.5)	-1.5 (2.3)	1.4	1,282	.24
Role limitations, emotional problems	53.3 (12.7)	49.1 (11.8)	.49	9.7 (5.1)	0.2 (4.6)	1.9	1,281	.17	28.0 (5.2)	11.6 (4.6)	5.5	1,281	.02
Social functioning	61.3 (12.7)	60.8 (11.9)	.88	10.4 (3.3)	1.7 (3.1)	3.7	1,282	.06	17.8 (3.5)	13.2 (3.1)	0.9	1,282	.33

\*Positive values indicate an improvement for all domains of the 36-Item Short-Form Health Survey.

Switch to a depressive state was a nonprotocol-defined analysis performed in the subset of patients who were not clinically depressed at study entry (HAMD-21 score  $\leq 8$  at baseline) but who became depressed (HAMD-21 score  $\geq 15$ ) at some point during the trial. Haloperidol-treated patients switched to depression significantly earlier than olanzapine-treated patients (log-rank test  $\chi^2_1 = 4.1, P = .04$ ) (Figure 2). The incidence of switch was 9.4% (12 of 128 patients) for the olanzapine group and 16.8% (22 of 131 patients) for the haloperidol group ( $P = .10$ ). For those patients who experienced a switch to depression, the mean HAMD-21 scores at baseline and at the time of the switch were 4.0 (SD, 2.13;  $n = 12$ ) and 18.6 (SD, 2.94) for olanzapine-treated patients and 5.5 (SD, 2.3;  $n = 22$ ) and 18.2 (SD, 4.0) for haloperidol-treated patients, respectively.

**Quality-of-Life Outcomes.** Dimensions of quality of life were examined at baseline and weeks 6 and 12 using the SF-36. There were no baseline differences between treatment groups with the exception of a statistically significant difference in the dimension of physical functioning (Table 7). Following 12 weeks of treatment, olanzapine-treated patients experienced statistically significantly greater improvement on the SF-36 dimension score of role limitations due to emotional problems. Haloperidol-treated patients showed a significant deterioration relative to olanzapine-treated patients in the dimensions of physical functioning and general health.

## SAFETY

### Adverse Events

Nineteen patients in the olanzapine group (8.1%) and 25 patients in the haloperidol group (11.4%) discontinued treatment because of an adverse event ( $P = .27$ ); no specific adverse event led to discontinuation significantly more frequently in one treatment group than in the other. Table 8 lists treatment-emergent adverse events that were significantly different between treatment groups or occurred more than 10% of the time.

## EPS Ratings

Extrapyramidal symptoms were monitored as patient-reported treatment-emergent events, rating scale-defined treatment-emergent events (see the "Methods" section for criteria), and mean change in scores on rating scales. Extrapyramidal symptoms, irrespective of the means of assessment, were statistically significantly worsened among haloperidol-treated patients compared with olanzapine-treated patients (Table 9 and Table 10).

## Vitals Signs, Weight, and Laboratory Measures

There were no statistically significant differences between treatment groups in the incidence rates of potentially clinically relevant changes in vital signs. For weight, both mean change and clinically relevant changes in weight were significantly greater for patients in the olanzapine group (Table 11). Moreover, change in weight for both groups was normally distributed and was not significantly correlated with baseline weight.

There were no statistically significant differences between treatment groups in the rates of potentially clinically relevant changes in laboratory measures. More detailed analyses were conducted for cholesterol and nonfasting glucose measures, which revealed no differences between therapy groups (Table 11).

## COMMENT

An important, clinically relevant aspect to this short-term study was that the primary efficacy measure required the remission of both manic and depressive symptoms. In both treatment groups, approximately 50% of patients met the criteria for remission at week 6. These results confirm previous studies<sup>4,29-31</sup> that have demonstrated the short-term antimanic efficacy of both these agents and extend our understanding by demonstrating that the efficacy of olanzapine and haloperidol is sustained during a 12-week period. For example, the average end point YMRS total scores of 4.4 for the olanzapine group and 3.6 for the haloperidol group from a

baseline of approximately 30 typifies a near absence of manic symptoms in those patients who completed the 12-week study. Additionally, more than 70% of patients in both treatment groups had a 50% or higher reduction in their YMRS scores after 6 weeks of therapy, and at 12 weeks, the rates exceeded 90%. These response rates at 6 weeks are higher than those previously reported after 3 weeks of monotherapy with ziprasidone (50%),<sup>32</sup> divalproex (48%), or lithium (49%).<sup>33</sup>

Another indication of the sustained efficacy of these drugs was that approximately 86% of patients who met symptomatic remission criteria remained in remission

throughout the continuation period. Interestingly, the rates of relapse varied depending on the criteria used to assess relapse. The overall rate of relapse based on symptomatic rating scale criteria was approximately 14%, whereas it was approximately 33% using DSM-IV syndromic criteria. The inconsistency in results suggests that different methods of assessing recovery and relapse need to be considered carefully in future studies.

In patients with acute mania and psychotic features, both therapies were similarly effective. Olanzapine, however, was significantly more effective than haloperidol in patients without psychotic features by a margin of 15%. Similar findings with olanzapine have been previously reported<sup>34,35</sup>; olanzapine was superior to divalproex and in combination with lithium or valproate was superior to lithium or valproate monotherapy in patients without psychotic features. These data suggest that the antimanic efficacy of olanzapine may be independent of its antipsychotic properties.

Reports in the literature suggest that typical antipsychotics may induce or worsen depression in patients with bipolar mania.<sup>5,7</sup> In this study, patients who were not depressed at study entry but became depressed during the trial experienced the switch to depression significantly more rapidly with haloperidol than olanzapine when using survival analysis techniques. Furthermore, the incidence of switch to depression was numerically higher for the haloperidol group (16.8%) compared with the olanzapine group (9.4%), but the less powerful test comparing incidence rates failed to achieve significance ( $P = .10$ ). Thus, the advantage of an atypical antipsychotic compared with a typical antipsychotic in preventing and/or delaying switch to depression requires further study.

As previously reported,<sup>30,31</sup> fewer EPS events occurred during treatment with olanzapine whether measured objectively or subjectively, whereas haloperidol-treated patients experienced significantly more EPSs and more anticholinergic use. Comparison of EPS ratings is of interest given that patients with bipolar disorder may be more susceptible to developing tardive dyskinesia when treated with typical antipsychotics than patients with schizophrenia.<sup>9,10</sup>

There were no significant differences between the groups in clinically identified treatment-emergent glucose abnormalities or mean baseline to end point changes in nonfasting glucose levels. The incidence of nonfasting glucose levels greater than 200 mg/dL ( $>11.1$  mmol/L)

**Table 8. Significant or Common Treatment-Emergent Adverse Events\***

Event	Incidence, %		P Value
	Haloperidol, % (n = 219)	Olanzapine, % (n = 234)	
Somnolence	8.7	15.0	.04
Weight gain	4.1	13.7	<.001
Infection	1.4	5.1	.03
Dizziness	0.9	4.3	.04
Fever	0.0	4.3	.002
Increased salivation	7.3	1.3	.002

\*Common events occurred at a 10% or more incidence; treatment-emergent adverse events are patient-reported events.

**Table 9. Events of Extrapyrimal Symptoms (EPSs)**

Variable	Incidence, %		P Value
	Haloperidol	Olanzapine	
Patient-reported treatment-emergent EPSs*			
Akathisia	29.7	6.4	<.001
Tremor	15.5	5.6	<.001
Hypertonia	17.8	5.1	<.001
Extrapyrimal syndrome	23.7	2.1	<.001
Dystonia	6.8	1.3	.003
Dyskinesia	3.2	0.4	.03
Hypokinesia	3.7	0.4	.02
Tardive dyskinesia	2.3	0	.03
Scale-defined treatment-emergent EPSs			
Parkinsonism	54.4 (n = 169)	12.8 (n = 187)	<.001
Akathisia	40.4 (n = 193)	9.9 (n = 203)	<.001
Dyskinesia	9.1 (n = 208)	3.1 (n = 223)	.01

\*For the haloperidol group, n = 219 for all; olanzapine, n = 234 for all.

**Table 10. Mean Change in Extrapyrimal Symptom Rating Scale Total Scores\***

Rating Scale	Mean (SD) Change to Week 12		% Change From Baseline		P Value	F Test (df)
	Haloperidol	Olanzapine	Haloperidol	Olanzapine		
Simpson-Angus Rating Scale	1.65 (5.46)	-0.59 (3.14)	108.6	-42.8	<.001	28.8 (1,431)
Barnes Akathisia Scale	0.45 (1.35)	-0.13 (0.95)	166.7	-40.6	<.001	28.7 (1,433)
AIMS	0.19 (1.93)	-0.14 (1.19)	54.3	-37.8	.03	4.77 (1,433)

Abbreviation: AIMS, Abnormal Involuntary Movement Scale.

\*Negative values indicate improvement from baseline for all rating scales. Sample sizes for the Simpson-Angus Rating Scale patients were 211 for the haloperidol group and 231 for the olanzapine group; for the Barnes Akathisia Scale and AIMS groups, sample sizes were 213 for the haloperidol group and 231 for the olanzapine group.

**Table 11. Changes in Weight, Cholesterol Levels, and Nonfasting Glucose Levels**

Variable	Mean Change					Clinically Relevant Outcomes*		
	Patients, No.	Mean (SD) Baseline	Mean (SD) Change to End Point	P Value	F Test (df)	Patients, No.	No. (%) With Outcomes	P Value†
Weight								
Olanzapine	229	69.1 (15.6)	2.82 (4.43)	<.001	38.0 (1,429)	229	91 (39.7)	<.001
Haloperidol	211	69.0 (14.8)	0.02 (5.17)			211	34 (16.1)	
Cholesterol								
Olanzapine	217	181.3 (39.4)	14.00 (31.54)	.56	0.34 (1,395)	134	9 (6.7)	>.99
Haloperidol	198	178.3 (39.4)	9.63 (34.81)			133	8 (6.0)	
Nonfasting glucose								
Olanzapine	215	102.7 (33.7)	-0.19 (34.84)	.37	0.81 (1,389)	209	3 (1.4)	.71
Haloperidol	194	97.5 (20.4)	-0.56 (29.91)			194	4 (2.1)	

\*Clinically relevant outcomes are defined as a 7% or greater increase in weight from baseline; a baseline cholesterol level of less than 200 mg/dL (<5.17 mmol/L) and an end point cholesterol level of 240 mg/dL or higher ( $\geq 6.21$  mmol/L); and a baseline nonfasting glucose level of less than 200 mg/dL (<11.1 mmol/L) and an end point nonfasting glucose level of 200 mg/dL or higher ( $\geq 11.1$  mmol/L).

†Fisher exact test.

also did not statistically differ between groups (olanzapine, 1.4%; haloperidol, 2.1%;  $P = .71$ ). This study, however, may not have had sufficient power to determine treatment differences in rare adverse events. Furthermore, assessment of the potential impact of treatment on glucose homeostasis is limited in this study because glucose measurements were nonfasting. Measurements of the effects of atypical antipsychotics on glucose are important because of apparent increased rates of diabetes among patients with bipolar disorder<sup>36</sup> and case reports of diabetes among patients treated with the atypical antipsychotic agents.<sup>37</sup> Therefore, additional studies are needed to determine the impact of pharmacological treatment on glucose homeostasis in patients with bipolar disorder.

These findings must be viewed in light of several methodological limitations. The lack of a placebo arm raises the possibility that the response to both of the therapies reflected a placebo response rather than true efficacy. Considering that there were few patients who entered the study with a mixed index episode, the results of this study may have limited generalizability to patients with mixed mania. Another limitation of this study was the restricted maximal doses of olanzapine and haloperidol. Although the dosing regimens used in this study are consistent with those of Rifkin et al,<sup>38</sup> who suggest that doses of haloperidol in excess of 10 mg/d offer no therapeutic advantage, and previous olanzapine studies<sup>30,39</sup> in mania where the mean modal dose was 15 mg, approximately 15% of patients in this study discontinued due to a lack of efficacy and most of these patients had received the maximal dose of their respective treatment. Importantly, there were no differences between groups in the number of patients who received the maximal dose of therapy. The overall completion rates in this study are 68% at 6 weeks and 56% at 12 weeks, which may limit the generalizability of the results; however, the rates of completion are well within ranges reported in other clinical trials in patients with acute mania.<sup>35,40,41</sup> Finally, carrying forward only responders could have introduced a bias; however, only 3 patients failed to

meet the interim criteria for the double-blind continuation period.

The results of this study suggest that olanzapine does not differ from haloperidol in terms of treating acute symptoms of mania and depression in bipolar mania. Olanzapine appears to offer efficacy advantages in patients who do not experience psychotic episodes and has a lower risk of EPSs. Haloperidol-treated patients experience less weight gain compared with patients treated with olanzapine and experience a greater reduction in manic symptoms by week 6 but had a faster onset of switch into depression. The treating clinician should determine the appropriate therapy for an individual patient based on a risk-benefit assessment of the pharmacotherapy.

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