

# Olanzapine Versus Placebo in the Treatment of Acute Mania

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**Objective:** The primary intent of this study was to compare the efficacy and safety of olanzapine and placebo in the treatment of acute mania. **Method:** The design involved a random-assignment, double-blind, placebo-controlled parallel group study of 3 weeks' duration. After a 2- to 4-day screening period, qualified patients were assigned to either olanzapine (N=70) or placebo (N=69). Patients began double-blind therapy with either olanzapine, 10 mg, or placebo given once per day. After the first day of treatment, the daily dose could be adjusted upward or downward, as clinically indicated, by one capsule (olanzapine, 5 mg/day) within the allowed range of one to four capsules. The primary efficacy measure in the protocol was defined as a change from baseline to endpoint in total score on the Young Mania Rating Scale. Clinical response was defined a priori as a decrease of 50% or more from baseline in Young Mania Rating Scale total score. **Results:** The olanzapine group experienced significantly greater mean improvement in Young Mania Rating Scale total score than the placebo group. On the basis of the clinical response criteria, significantly more olanzapine-treated patients (48.6%) responded than those assigned to placebo (24.2%). Somnolence, dizziness, dry mouth, and weight gain occurred significantly more often with olanzapine. There were no statistically significant differences between the olanzapine-treated and placebo-treated patients with respect to measures of parkinsonism, akathisia, and dyskinesias. No discontinuations of treatment due to adverse events occurred in the olanzapine treatment group. **Conclusions:** The results from this study suggest that compared with placebo, olanzapine has superior efficacy for the symptoms of acute mania.

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**B**ipolar disorder (manic-depressive illness) is a chronic episodic disorder with a lifetime prevalence between 0.8% and 1.6% (1-3). Over the past several decades, substantial progress has been made in the pharmacologic treatment of the manic phase of bipo-

lar disorder. Numerous authorities and treatment guidelines presently recognize that three individual agents—lithium, valproate, and carbamazepine (typically referred to as mood stabilizers)—and one class of agents—the conventional antipsychotics—have proven efficacy in the short-term treatment of acute mania (4-10).

However, it is also well recognized that a substantial proportion of patients with mania fail to respond adequately to these agents, whether they are used alone or in various combinations, or are unable to tolerate them (9, 10). Moreover, all of these agents are characterized by safety concerns that necessitate regular monitoring (e.g., renal and thyroid toxicity with lithium and tardive dyskinesia and neuroleptic malignant syndrome with typical antipsychotics). Novel medical treatments for the manic phase of bipolar disorder are therefore needed.

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The success of the novel antipsychotic agent clozapine for treatment-resistant schizophrenia has resulted in its use for bipolar patients unresponsive to the usual treatment strategies (11–15). However, caution must be applied in interpreting these data, since the numbers of patients evaluated in controlled trials were small. Nonetheless, clozapine appears to benefit patients with rapid-cycling illness and those who do not respond to standard treatment. On the other hand, the use of clozapine in bipolar illness is limited by the relatively high incidence of agranulocytosis (annual rate=0.8%), which is tenfold higher than the rate for traditional antipsychotic agents (16). Furthermore, clozapine has other troublesome side effects (e.g., excessive salivation and sedation) that are likely to limit its use in bipolar patients. Another recently released antipsychotic agent, risperidone, has also been studied in open-label designs, with some studies suggesting a favorable response when it is combined with mood-stabilizing agents (17, 18). Accordingly, there continues to be a medical need for controlled studies to identify novel pharmacologic agents for use in bipolar disorder.

Olanzapine, a recently introduced novel antipsychotic, demonstrates a pharmacologic profile that most closely resembles that of clozapine (19). In a series of double-blind controlled trials in patients with schizophrenia and schizoaffective disorder, olanzapine appeared superior to the conventional antipsychotic haloperidol on measures of overall psychotic symptoms, negative symptoms, comorbid mood symptoms, and quality of life (20–25). Recent reports of open-label studies suggest that olanzapine may be efficacious in patients with bipolar disorder (26–28), including those with manic or mixed symptoms inadequately responsive to lithium, anticonvulsants, and typical antipsychotics. Thus, on the basis of these reports and the findings of mood stabilization with olanzapine among both depressed schizophrenic patients (20) and schizoaffective bipolar patients (29), we decided to study olanzapine's efficacy in the treatment of acute manic and mixed episodes in bipolar I disorder with and without psychotic features. We report on a double-blind study that included 139 patients and was conducted in the United States at 16 study sites between October 1996 and August 1997.

## METHOD

Patients between the ages of 18 and 65 years were enrolled in the study. All study subjects met the DSM-IV criteria for bipolar disorder, either manic or mixed episode (with or without psychotic features), on the basis of the Structured Clinical Interview for DSM-III-R (SCID) (30). Manic or mixed episodes were of at least 2 weeks' duration. A minimum total score of 20 on the Young Mania Rating Scale (31) was required. Patients were excluded if any of the following criteria were met: serious, unstable illness such that hospitalization was anticipated within 3 months or death was anticipated within 3 years; DSM-IV-defined substance dependence (except nicotine or caffeine) within the past 3 months; and serious risk of suicide. The study was fully explained to each patient, and written informed consent was obtained before their participation in the study.

**TABLE 1. Disposition of Patients With Bipolar Disorder Treated With Olanzapine or Placebo**

Variable	Placebo Group (N=69)		Olanzapine Group (N=70)		p (Fisher's exact test)
	N	%	N	%	
Completed treatment	24	34.8	43	61.4	0.002
Reason treatment was discontinued					
Adverse event	2	2.9	0	0.0	0.25
Lack of efficacy	33	47.8	20	28.6	0.02
Other	10	14.5	7	10.0	0.45

This was a randomized, double-blind, placebo-controlled parallel group study. Severity of illness and psychopathology was measured by the following rating scales: the Young Mania Rating Scale (31), the 21-item Hamilton Depression Rating Scale (32), the Positive and Negative Syndrome Scale (33), and the Clinical Global Impression (CGI), Bipolar Version (34). Quality of life was assessed with the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) (35, 36). Change from baseline to endpoint in total score on the Young Mania Rating Scale was the primary efficacy measure. Interrater reliability assessments with the Young Mania Rating Scale were conducted before the study began by measuring the correlation of each rater's scoring with the groupwise median score for each item. The correlation coefficients ranged between 0.76 and 0.99, with a median of 0.94. Extrapyramidal symptoms were assessed with the Simpson-Angus Rating Scale (37), the Barnes Akathisia Scale (38), and the Abnormal Involuntary Movement Scale (39).

After a 2- to 4-day washout period of all medications except benzodiazepines, qualified patients were randomly assigned to one of two treatment groups, olanzapine or placebo, in a 1:1 ratio. Seventy patients were assigned to olanzapine and 69 to placebo. To ensure patient safety, a minimum of 1 week of hospitalization was required. After 1 week, patients with a CGI, Bipolar Version, severity of mania score of 3 or lower and a reduction of 50% or more in Young Mania Rating Scale total score could be discharged, if clinically appropriate.

Double-blind acute therapy lasted for 3 weeks. Patients began double-blind therapy with either olanzapine, 10 mg (two 5-mg tablets), or placebo (two placebo tablets), given once per day, preferably in the evening. After the first day of treatment, the daily dose could be adjusted upward or downward, as clinically indicated, by 5-mg increments/decrements within the allowed dosage range of 5–20 mg/day. Decreases in dosage because of adverse events could occur at any time by any number of one-tablet (5-mg) decrements (at the investigator's discretion), to a minimum of one tablet per day.

Use of concomitant medications was limited to lorazepam, up to 4 mg/day, if necessary, to alleviate severe agitation during the first 7 days of therapy; then, during the next 3 days, 2 mg/day could be used. Also, benztropine, up to a maximum dose of 2 mg/day, could be used for treatment-emergent extrapyramidal symptoms. The prophylactic use of benztropine for extrapyramidal symptoms was not allowed.

A total of 139 patients were enrolled in the study; 70 were randomly assigned to olanzapine and 69 to placebo. The treatment groups did not significantly differ with respect to baseline patient characteristics or severity of illness ratings. Patients were generally in their late 30s (mean age=39.5 years, SD=11.0), the majority (72.7%) were Caucasian, and half (51.8%) were male. The majority of the patients (82.7%) were experiencing a manic episode, while the rest (17.3%) were experiencing a mixed episode. Overall, 53.2% displayed psychotic features. Of those with psychotic symptoms, 85.1% displayed mood-congruent psychotic features. A DSM-IV-defined rapid-cycling course was present in 32.4% of the patients. Comparisons of the treatment groups at baseline on efficacy variables demonstrated no evidence of any statistically significant differences.

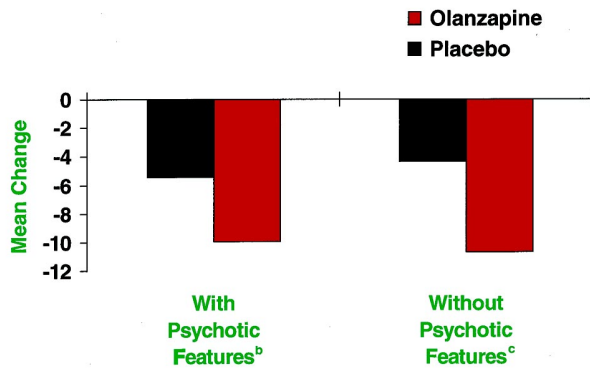
All statistical analyses were done on an intent-to-treat basis; that is, data on all randomly assigned patients were included in the analysis. Patients' data were included in the analysis of change if they had both a baseline and a postbaseline observation. For the analysis of baseline efficacy and extrapyramidal symptom scores, only the patients with a baseline and a postbaseline observation were included,

**TABLE 2. Endpoint Change in Severity of Illness Scores (Last Observation Carried Forward) of Patients With Bipolar Disorder Treated With Olanzapine or Placebo**

Measure	Placebo Group (N=69)					Olanzapine Group (N=70)					Analysis <sup>a</sup>		
	N	Baseline		Change From Baseline		N	Baseline		Change From Baseline				
		Mean	SD	Mean	SD		Mean	SD	Mean	SD	F	df	p
Young Mania Rating Scale total score	66	27.65	6.46	-4.88	11.64	70	28.66	6.71	-10.26	13.43	5.64	1, 108	0.02
Hamilton 21-item depression scale total score	65	13.98	6.69	-3.00	6.00	69	12.58	7.15	-2.90	6.74	0.03	1, 106	0.87
Positive and Negative Syndrome Scale													
Total symptom score	64	70.97	21.04	-3.09	18.37	70	71.04	18.74	-11.06	16.98	5.64	1, 106	0.02
Positive symptom score	64	20.72	7.01	-2.00	7.10	70	20.90	6.59	-4.67	6.57	4.30	1, 106	0.04
Negative symptom score	64	13.94	5.69	-0.19	4.23	70	13.51	5.45	-0.90	4.26	0.72	1, 106	0.40
Clinical Global Impression, Bipolar Version													
Severity of mania rating	66	4.62	0.87	-0.48	1.37	70	4.51	0.86	-1.07	1.60	5.69	1, 108	0.02
Severity of depression rating	66	2.11	1.29	-0.30	1.15	70	1.71	0.97	0.06	1.17	2.17	1, 108	0.14
Severity of overall bipolar illness rating	66	4.68	0.83	-0.59	1.30	70	4.46	0.88	-0.89	1.39	2.10	1, 108	0.15

<sup>a</sup> Changes from baseline means were analyzed with an F test from an ANOVA model with treatment, investigator, and interaction. No statistically significant differences were observed between baseline values of the two groups for any measure.

**FIGURE 1. Change in Total Scores on the Young Mania Rating Scale of Patients With Bipolar Disorder Treated With Olanzapine or Placebo<sup>a</sup>**



<sup>a</sup> There was no significant difference in the treatment advantage of olanzapine and placebo for patients with and without psychotic features (therapy-by-subgroup:  $F=0.02$ ,  $df=1$ ,  $106$ ,  $p=0.88$ ).

<sup>b</sup>  $N=33$  for the placebo group;  $N=38$  for the olanzapine group. Mean baseline score=29.0 for the placebo group; mean baseline score=29.6 for the olanzapine group. Within strata,  $F=2.32$ ,  $df=1$ ,  $56$ ,  $p=0.13$ .

<sup>c</sup>  $N=33$  for the placebo group;  $N=32$  for the olanzapine group. Mean baseline score=26.3 for the placebo group; mean baseline score=27.6 for the olanzapine group. Within strata,  $F=3.73$ ,  $df=1$ ,  $52$ ,  $p<0.06$ .

to be consistent with the analysis of change from baseline. All patients randomly assigned to double-blind therapy were included in the analysis of baseline patient and illness characteristics as well as the analysis of the incidence of treatment-emergent adverse events. Total scores from rating scales were derived from the individual items; if any single item was missing, the total score was treated as missing.

Analysis of variance (ANOVA) was used to evaluate the continuous efficacy and safety variables; the models included the terms for treatment, investigator, and treatment-by-investigator interaction. Data were pooled from investigators who did not have at least two patients per treatment. Fisher's exact test, two-tailed, was used to analyze treatment effects for categorical efficacy and safety variables. For selected efficacy variables, weekly changes from baseline were

analyzed. The protocol established the primary efficacy analysis as the mean change from baseline to endpoint (last observation carried forward) in Young Mania Rating Scale total score.

All cited  $p$  values were two-tailed, with a significance level of 0.05 as specified in the protocol. SAS (40) was used for all analyses.

**RESULTS**

The disposition of the study group during the acute phase of the trial is shown in table 1. Almost twice as many olanzapine-treated patients as placebo-treated patients completed the acute phase of the study. Nearly one in two patients receiving placebo had to discontinue because of lack of efficacy, compared to one in four olanzapine-treated patients.

The mean modal and median modal doses of olanzapine were 14.9 mg/day ( $SD=5.0$ ) and 15 mg/day, respectively. The modal dose was defined as the daily dose most often taken.

There were no statistically significant differences between the two treatment groups in the number of patients who used anticholinergic medication, benzodiazepines, or any other concomitant medications during the study. Of all patients, 86.3% ( $N=120$ ) took at least one dose of a benzodiazepine, and 9.4% ( $N=13$ ) took at least one dose of an anticholinergic medication. Of the patients receiving benzodiazepines, the placebo-treated patients received a significantly greater mean daily dose than the olanzapine-treated patients (placebo: mean=1.7 mg/day,  $SD=1.3$ ; olanzapine: mean=1.1 mg/day,  $SD=1.2$ ;  $F=10.42$ ,  $df=1$ ,  $102$ ,  $p=0.002$ ). There was no significant difference between the two groups in mean daily dose of anticholinergics.

*Efficacy*

*Endpoint analysis.* Mean change from baseline to endpoint (last observation carried forward) of the 3-

**TABLE 3. Endpoint Change in Individual Item Scores on the Young Mania Rating Scale (Last Observation Carried Forward) of Patients With Bipolar Disorder Treated With Olanzapine or Placebo**

Item	Placebo Group (N=66)				Olanzapine Group (N=70)				Analysis <sup>a</sup>		
	Baseline		Change From Baseline		Baseline		Change From Baseline				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p
Elevated mood	2.30	0.96	-0.47	1.08	2.29	0.97	-0.76	1.27	3.64	1, 108	0.06
Increased motor activity-energy	2.58	0.84	-0.62	1.39	2.56	0.88	-0.96	1.47	2.44	1, 108	0.12
Sexual interest	1.82	1.18	-0.32	1.49	1.67	1.18	-0.63	1.36	3.22	1, 108	0.08
Sleep	2.03	1.16	-0.61	1.39	2.04	1.17	-1.09	1.45	4.45	1, 108	0.04
Irritability	3.94	1.61	-0.24	2.59	3.97	1.72	-1.20	2.88	4.51	1, 108	0.04
Speech	4.00	1.79	-0.70	2.26	4.46	1.67	-1.54	2.41	1.85	1, 108	0.18
Language-thought disorder	2.05	0.77	-0.41	1.10	2.06	0.70	-0.70	1.08	1.26	1, 108	0.26
Content	4.55	2.37	-0.91	2.63	4.86	2.45	-1.86	3.05	3.07	1, 108	0.08
Disruptive aggressive behavior <sup>b</sup>	1.91	1.38	-0.09	1.97	2.31	1.62	-0.83	2.25	2.69	1, 108	0.10
Appearance	1.21	1.00	-0.26	1.06	1.23	0.95	-0.50	1.16	1.82	1, 108	0.18
Insight	1.27	1.34	-0.26	0.85	1.21	1.40	-0.20	1.31	0.42	1, 108	0.52

<sup>a</sup> Changes from baseline means were analyzed with an F test from an ANOVA model with treatment, investigator, and interaction.

<sup>b</sup> Significant difference between baseline means (F=4.55, df=1, 108, p<0.04).

week acute phase was used to compare the efficacy of the two treatments (table 2). In the primary efficacy analysis, change from baseline to endpoint in total scores on the Young Mania Rating Scale, the olanzapine group experienced significantly greater mean improvement than the placebo group. The mean difference between the olanzapine and placebo groups was -5.38 points (95% confidence interval=-10.31 to -0.93). Subgroup analyses were performed on the basis of the presence or absence of psychotic features and the presence or absence of a rapid-cycling course as well as between patients with pure and mixed mania. When patients with and without psychotic features were compared (figure 1), there was no difference in the treatment advantage of olanzapine relative to placebo (F=0.02, df=1, 106, p=0.88). The olanzapine-treated patients with a rapid-cycling course showed a significantly greater mean change from baseline in Young Mania Rating Scale total scores (mean=-13.89, SD=7.97) than did the placebo-treated patients (mean=-4.12, SD=11.45) (F=7.25, df=1, 35, p=0.01). There was no significant difference in mean change from baseline between the patients with pure and mixed mania who were treated with olanzapine (mean=-10.84, SD=13.72, and mean=-7.42, SD=12.06, respectively; F=0.01, df=1, 55, p=0.91).

Analyses of scores on the secondary efficacy scales were also performed. The olanzapine patients had a significantly greater mean decrease from baseline in CGI, Bipolar Version, severity of mania scores compared with the placebo patients (table 2). They also had a significantly greater reduction in total scores and positive symptom scores on the Positive and Negative Syndrome Scale.

As expected with the relatively low baseline values in both treatment groups, the analysis of mean change from baseline to endpoint in Hamilton depression scale total scores showed no significant treatment advantages for improvement of depressive symptoms (table 2). Olanzapine was not associated with a significant baseline-to-endpoint worsening in Hamilton depression

scale total score relative to placebo. There was also no difference in mean change from baseline in Hamilton depression scale total scores between patients with pure and mixed mania who were treated with olanzapine (mean=-2.95, SD=6.10, and mean=-2.67, SD=9.55, respectively; F=0.14, df=1, 54, p=0.71).

*Weekly analysis.* The olanzapine group consistently showed greater mean improvement in total scores on the Young Mania Rating Scale; the difference was statistically significant at week 3 (F=5.64, df=1, 108, p=0.02). For the olanzapine-treated patients, 81% of the last-observation-carried-forward improvement in mean Young Mania Rating Scale total score was achieved after the first week of treatment. Visitwise analyses of the CGI, Bipolar Version, ratings of overall severity of illness and severity of mania and the Positive and Negative Syndrome Scale total, positive, and negative symptom scores were also performed. At weeks 2 and 3, the olanzapine group demonstrated significantly greater improvement relative to the placebo group in severity of mania (F=4.36, df=1, 108, p=0.04, and F=5.69, df=1, 108, p=0.02, respectively) and in Positive and Negative Syndrome Scale total scores (F=5.30, df=1, 106, p=0.02, and F=5.64, df=1, 106, p=0.02, respectively), and at week 3 in Positive and Negative Syndrome Scale positive scores (F=4.30, df=1, 106, p=0.04). In comparison with the olanzapine group, the placebo group did not show significantly greater mean improvement on any scale at any visit.

*Response analysis.* The protocol defined a responder a priori as any patient achieving a 50% or greater decrease in total score on the Young Mania Rating Scale from baseline to endpoint. Significantly more patients responded to olanzapine than to placebo (olanzapine: N=34 of 70, 48.6%; placebo: N=16 of 66, 24.2%; p=0.004, Fisher's exact test).

*Young Mania Rating Scale individual items.* The olanzapine group demonstrated a numerically greater mean improvement relative to the placebo group on all items except insight (table 3). Importantly, the difference for elevated mood nearly reached statistical sig-

**TABLE 4. Treatment-Emergent Adverse Events<sup>a</sup> in Patients With Bipolar Disorder Treated With Olanzapine or Placebo**

Adverse Event	Placebo Group (N=69)		Olanzapine Group (N=70)		p (Fisher's exact test)
	N	%	N	%	
Somnolence	12	17.4	23	32.9	0.05
Dry mouth	6	8.7	18	25.7	0.01
Dizziness	4	5.8	16	22.9	0.007
Agitation	16	23.2	13	18.6	0.54
Asthenia	5	7.2	13	18.6	0.08
Headache	11	15.9	12	17.1	1.00
Anxiety	7	10.1	10	14.3	0.61
Depression	8	11.6	9	12.9	1.00
Constipation	2	2.9	8	11.4	0.10
Pain	3	4.3	8	11.4	0.21
Weight gain	1	1.4	8	11.4	0.03
Hostility	8	11.6	6	8.6	0.59
Nervousness	9	13.0	6	8.6	0.43
Personality disorder	8	11.6	5	7.1	0.40

<sup>a</sup> Events that occurred in 10% or more of either group or that showed a significant difference between groups.

nificance. The olanzapine group's greater mean improvement in the sleep and irritability items did achieve statistical significance.

**Quality of life.** In nine of the 10 components of the SF-36 there was no statistically significant difference between the two groups over the 3-week acute phase. The olanzapine-treated patients had significantly greater improvement in their physical functioning than the placebo-treated patients, as measured by the SF-36 physical functioning subscore (olanzapine: mean=4.01, SD=13.27, placebo: mean=-1.84, SD=14.50;  $F=6.06$ ,  $df=1, 94$ ,  $p=0.02$ ).

### Safety

**Treatment-emergent adverse events (events that first appeared or worsened during double-blind therapy).** Somnolence, dry mouth, dizziness, and weight gain occurred significantly more frequently in the olanzapine group than in the placebo group (table 4). However, no olanzapine-treated patients discontinued therapy because of an adverse event, whereas two placebo-treated patients discontinued (one because of convulsions and one because of dystonia).

**Extrapyramidal symptoms.** Extrapyramidal symptoms were infrequent among the study participants, and thus anticholinergic use was negligible in both treatment groups. Table 5 shows that pseudo parkinsonism (Simpson-Angus scale), akathisia (Barnes scale), and dyskinesias (Abnormal Involuntary Movement Scale) were not significantly different between the two groups with respect to mean change from baseline to endpoint.

**Vital signs and weight.** No clinically significant changes in vital signs were observed in either treatment group. However, olanzapine-treated patients on average gained 1.65 kg (SD=2.54) of weight from baseline to endpoint, whereas there was a mean weight loss of 0.44 kg (SD=2.35) among the placebo-treated patients

( $F=11.72$ ,  $df=1, 101$ ,  $p<0.001$ ). No patients discontinued therapy because of an adverse event associated with weight.

**Laboratory values.** No clinically significant changes in laboratory values were observed in either treatment group. In the analysis of treatment-emergent laboratory values at any time during the acute phase, the occurrence of increased ALT/SGPT values at any time was significantly different between the two groups (olanzapine: 17.6%; placebo: 0%;  $p<0.001$ , Fisher's exact test). However, all of the ALT/SGPT values returned to normal during continued treatment with olanzapine, and none of the patients displayed clinical symptoms of hepatic dysfunction at any time, consistent with observations from earlier studies with olanzapine (24).

**ECG.** There were no significant differences between the groups in the analysis of mean change from baseline to endpoint in ECG heart rate and interval times.

### DISCUSSION

This randomized, placebo-controlled, double-blind study suggests that olanzapine is effective in the treatment of acute mania, as evidenced by the decreases in total scores on the Young Mania Rating Scale; in severity of mania ratings on the CGI, Bipolar Version; and in total and positive symptom scores on the Positive and Negative Syndrome Scale. Also, the percentage of patients who discontinued treatment because of lack of efficacy was significantly smaller ( $p=0.02$ ) in the olanzapine group (28.6%) than in the placebo group (47.8%). That olanzapine may have antimanic effects is further suggested by the magnitude of response to treatment as illustrated by the responder analysis, where 48.6% of the olanzapine-treated patients had an improvement of 50% or more in Young Mania Rating Scale total score, compared with 24.2% of the placebo-treated patients. Similar degrees of response were observed in two recent clinical trials in the treatment of mania (41, 42). Bowden and collaborators (41) found that 48% of divalproex-treated patients and 49% of lithium-treated patients, compared with 25% of placebo-treated patients, had an improvement of at least 50%. However, those investigators used the manic syndrome subscale of the Schedule for Affective Disorders and Schizophrenia (43) instead of the Young Mania Rating Scale to assess manic symptoms. Pope and collaborators (42), using the Young Mania Rating Scale to assess manic symptoms, found that 54% of valproate-treated patients improved at least 50%. Considering that there may be differences in study populations and efficacy measures across studies, the most appropriate study would be a head-to-head comparison trial of olanzapine against other mood-stabilizing drugs.

Regarding individual manic signs and symptoms, as shown on table 3, olanzapine was nearly significantly superior to placebo for the two Young Mania Rating

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