Efficacy of Olanzapine in Combination With Valproate or Lithium in the Treatment of Mania in Patients Partially Nonresponsive to Valproate or Lithium Monotherapy

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Background: A 6-week double-blind, randomized, placebo-controlled trial was conducted to determine the efficacy of combined therapy with olanzapine and either valproate or lithium compared with valproate or lithium alone in treating acute manic or mixed bipolar episodes.

Methods: The primary objective was to evaluate the efficacy of olanzapine (5-20 mg/d) vs placebo when added to ongoing mood-stabilizer therapy as measured by reductions in Young Mania Rating Scale (YMRS) scores. Patients with bipolar disorder (n=344), manic or mixed episode, who were inadequately responsive to more than 2 weeks of lithium or valproate therapy, were randomized to receive cotherapy (olanzapine + mood-stabilizer) or monotherapy (placebo + mood-stabilizer).

Results: Olanzapine cotherapy improved patients' YMRS total scores significantly more than monotherapy (−13.11 vs −9.10; $P=.003$). Clinical response rates (≥50% improvement on YMRS) were significantly higher with cotherapy (67.7% vs 44.7%; $P<.001$). Olanzapine cotherapy improved 21-item Hamilton Depression Rating Scale (HAMD-21) total scores significantly more than monotherapy (4.98 vs 0.89 points; $P<.001$). In patients with mixed-episodes with moderate to severe depressive symptoms (*DSM-IV* mixed episode; HAMD-21 score of ≥20 at baseline), olanzapine cotherapy improved HAMD-21 scores by 10.31 points compared with 1.57 for monotherapy ($P<.001$). Extrapyramidal symptoms (Simpson-Angus Scale, Barnes Akathisia Scale, Abnormal Involuntary Movement Scale) were not significantly changed from baseline to end point in either treatment group. Treatment-emergent symptoms that were significantly higher for the olanzapine cotherapy group included somnolence, dry mouth, weight gain, increased appetite, tremor, and slurred speech.

Conclusion: Compared with the use of valproate or lithium alone, the addition of olanzapine provided superior efficacy in the treatment of manic and mixed bipolar episodes.

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THE EXPERT Consensus Guidelines Series, published in the year 2000, recommends lithium and valproate as first-line treatments for bipolar mania.[1] However, up to 40% of patients respond poorly to monotherapy with either treatment.[2] When monotherapy fails, the guidelines recommend combination therapies. A number of authors have recently reviewed the use of such cotherapies for bipolar mania. Freeman and Stoll[3] concluded that the combination of lithium and valproate is better tolerated and more efficacious in maintenance therapy than other combination treatments.

Typical neuroleptics have been suggested to be superior in efficacy to lithium monotherapy.[4] Conversely, the addition of a mood stabilizer to conventional antipsychotic therapy seems superior to antipsychotic agents alone.[5] In support of this, Müller-Oerlinghausen et al[6] compared the efficacy of combined therapy with conventional antipsychotics and valproate vs valproate monotherapy in patients with bipolar or schizoaffective disorder and found combination therapy to be superior to monotherapy.

Olanzapine, an atypical antipsychotic, has been shown in 2 placebo-controlled studies to have acute antimanic effects.[7,8] Moreover, a previous report has suggested that olanzapine is effective when used in combination with other psychotropic agents.[9] The present study was conducted to investigate the efficacy and safety of combined therapy with olanzapine and either valproate or lithium compared with valproate or lithium monotherapy.

A list of the Principal Investigators appears in the box on page 69. Author affiliations appear in the acknowledgment section.
Drs Tohen, Feldman, Tollefson, and Breier and Mr Risser and Ms Keeter are stockholders in Eli Lilly & Co.

SUBJECTS AND METHODS

SUBJECTS

All patients were diagnosed as having bipolar disorder, manic or mixed episode, with or without psychotic features, using the Structured Clinical Interview for the *DSM-IV*[10] (SCID).[11] Patients had to have at least 2 previous depressed, manic, or mixed episodes as well as a Young Mania Rating Scale[12] (YMRS) total score of 16 or greater at visit 1 and visit 2 (2-7 days later). Patients were required to have had a documented trial of treatment, with a therapeutic blood level of lithium (0.6-1.2 mmol/L) or valproate (50-125 μg/mL), for at least 2 weeks immediately prior to visit 1. Patients were included only if they showed inadequate response to monotherapy (YMRS total score ≥16). Prior to participation, all patients signed an informed consent document approved by their study site's institutional review board.

STUDY DESIGN

Participants in the study initially entered a 2- to 7-day screening and washout period (study period 1) during which all concomitant medications other than lithium or valproate were discontinued. Patients already receiving valproate or lithium continued to do so throughout the study. Patients receiving other forms of treatment started receiving either lithium or valproate at investigator discretion for the 2 weeks immediately prior to visit 1. Plasma levels of the medications were documented to be within the therapeutic ranges. Only patients scoring greater than or equal to 16 on the YMRS were randomized to receive concurrent treatment combined with either olanzapine or placebo (study period 2).

Study period 2 consisted of a 6-week acute, double-blind phase, during which levels of lithium or valproate were maintained within the therapeutic range. Patients were assessed weekly. Patients were randomized 2:1 to receive either olanzapine (flexible dose range of 5, 10, 15, or 20 mg/d) added to valproate or lithium or placebo added to valproate or lithium. Olanzapine therapy was initiated at 10 mg/d. To maintain blinding, treatment took the form of two 5-mg capsules (either olanzapine or placebo), titrated up in increments of 1 capsule or down by any number of decrements at investigator discretion as indicated by each patient's tolerance. Patients unable to tolerate the minimum dose were discontinued. Patients were permitted adjunctive use of benzodiazepine (≤2 mg/d of lorazepam equivalents) for no more than 14 days cumulatively. Anticholinergic therapy (benztropine mesylate, ≤2 mg/d) was permitted throughout the study for treatment of extrapyramidal symptoms but not for prophylaxis. Aside from study drugs, benzodiazepines, and anticholinergics, no other drugs were permitted during the study.

ASSESSMENTS

Patient assessments were conducted by mental health care professionals, including psychiatrists, psychologists, nurses, and other mental health caregivers with a clinical degree or certification. Raters were trained in the use of the SCID and symptom-rating scales before study initiation. To ensure high interrater reliability, investigators were required to achieve a reliability coefficient of 0.75 or greater. The primary measure of efficacy to assess severity of manic symptoms was the mean change from baseline to end point in the YMRS total score. Secondary measures included the 21-item Hamilton Depression Rating Scale[13] (HAMD-21); the Positive and Negative Syndrome Scale[14]; and the Clinical Global Impressions Severity of Bipolar Disorder scale[14] (CGI-BP) total scores, and mania and depression subscale scores. Clinical responses on the YMRS and HAMD-21 were defined a priori as an improvement of 50% or greater. Clinical remission (euthymia) was defined a priori as achievement of a YMRS total score of less than or equal to 12. A subsample of patients with moderate to severe depressive symptoms was defined by a current mixed episode and a HAMD-21 total score of 20 or greater at baseline. Secondary assessments, also defined a priori, included analyses of treatment differences following stratification by the current course of illness, the presence or absence of psychotic features, and the use of lithium or valproate.

Scales for the assessment of neurologic adverse events included the Simpson-Angus Scale,[15] the Barnes Akathisia Scale,[16] and the Abnormal Involuntary Movement Scale.[14] Assessment of vital signs, weight, and clinical laboratory analytes (including prolactin, nonfasting glucose, and electrolyte levels and hematologic analysis) was performed at each visit. Serum concentrations of mood stabilizers were collected at every visit.

STATISTICAL ANALYSES

Data were analyzed on an intent-to-treat basis,[17] included all patients who met the entry criteria (including inadequate responsiveness to the minimum 2-week prior treatment with lithium or valproate), and provided both a baseline and at least 1 postbaseline data measurement. Total scores from rating scales were derived from the individual items; if any item was missing, the total score was treated as missing. All tests were 2-sided, with an α level of .05. Analysis of variance (ANOVA) models were used to evaluate continuous data, including terms for treatment, investigator, and treatment-investigator interaction. The linear model for this analysis included terms for baseline, treatment, investigator, treatment-investigator interaction, visit, and treatment-visit interaction. The Fisher exact test was used for categorical analyses, including laboratory values, vital signs, and treatment-emergent adverse events. Data are given as mean (SD) unless otherwise indicated.

RESULTS

PATIENT CHARACTERISTICS AND DISPOSITION

A total of 501 patients entered the screening phase and 344 patients were randomized and enrolled (33 US centers, 5 Canadian), with a mean enrollment of 9 patients per site. Patients were recruited from both academic and nonacademic sites from existing clinical patient populations seeking treatment at those sites. Of the 344 randomized patients, 322 came from outpatient centers. The other 20 (cotherapy, n=16; monotherapy, n=4) came from inpatient settings. Patients were initially screened on the basis of face-to-face interviews, medical record re-

Table 1. Patient Characteristics

Characteristic	Mood Stabilizer	Olanzapine Cotherapy (*n* = 229)	Monotherapy (*n* = 115)	*P* Value*
Age, mean ± SD, y		40.7 ± 11.2	40.4 ± 10.8	.9
	Lithium	40.8 ± 12.4	43.4 ± 11.0	.2
	Valproate	40.7 ± 10.7	38.9 ± 10.5	.25
Male, No. (%)		101 (44.1)	64 (55.6)	.05
	Lithium	41 (54.0)	26 (63.4)	.34
	Valproate	60 (39.2)	38 (52.1)	.08
White, No. (%)		196 (85.6)	97 (84.4)	.75
	Lithium	65 (85.5)	34 (82.9)	.79
	Valproate	131 (85.6)	63 (86.3)	>.99
Current course, No. (%)				.21
Manic		104 (45.4)	61 (53.0)	
Mixed		125 (54.6)	54 (47.0)	
	Lithium			.03
Manic		38 (50.0)	12 (29.3)	
Mixed		38 (50.0)	29 (70.7)	
	Valproate			>.99
Manic		87 (56.9)	42 (57.5)	
Mixed		66 (43.1)	31 (42.5)	
Without psychotic features, No. (%)†		154 (67.3)	76 (66.1)	.90
	Lithium	54 (71.1)	28 (68.3)	.83
	Valproate	100 (65.4)	48 (65.8)	>.99
Cotherapeutic agent, No. (%)				.63
Lithium		76 (33.2)	41 (36.0)	
Valproate		153 (66.8)	73 (64.0)	

*Treatment difference, olanzapine cotherapy vs monotherapy; derived from analysis of variance for age and from the Fisher exact test otherwise.
†Based on n = 114 for monotherapy.

views, and information obtained from family members and referring clinicians. Reasons for lack of enrollment included entry criteria not met (86 patients, including 24 failing to meet the YMRS total score criterion of ≥16); patient decision or loss to follow-up during the screening phase (58); investigator decision (8); protocol violation (4); and a single death that occurred before completion of screening or exposure to the study drug. Ultimately, 229 patients were randomized to receive olanzapine cotherapy and 115 to receive monotherapy (**Table 1**). One patient in the monotherapy group received both valproate and lithium and accordingly was excluded from the subgroup analyses. The median duration of mood-stabilizer therapy prior to randomization was 67 days; 203 patients had a duration of therapy longer than 6 weeks. One patient in the monotherapy group and 9 in the cotherapy group had no postbaseline measures and were excluded from all efficacy analyses.

The percentage of patients completing the study was roughly equal in the 2 treatment groups (cotherapy, 69.9%; monotherapy, 71.3%). Significantly more patients in the monotherapy group discontinued treatment due to lack of efficacy (12.2% vs 3.1%; $P=.002$), whereas significantly more patients in the cotherapy group withdrew due to adverse events (10.9% vs 1.7%; $P=.002$) (**Table 2**).

Patient demographics and illness characteristics were not significantly different between the cotherapy and monotherapy treatment groups overall (Table 1). In the overall study group (n=344), the mean age was 40.6 (11.1) years. One hundred sixty-five patients (48.0%) had mixed episodes at enrollment; the remainder had pure manic episodes. Overall baseline mean YMRS total scores for the olanzapine cotherapy (n=220) and monotherapy (n=114) groups were 22.31 (5.39) and 22.67 (5.15), respectively, and mean HAMD-21 scores were 14.52 (8.46) and 13.54 (7.63), respectively (**Table 3**).

Mean modal dose of olanzapine in the cotherapy group (n=224) was 10.4 (4.9) mg/d). Mean plasma levels of lithium among the cotherapy (n=74) and monotherapy (n=41) patients were 0.76 (0.16) and 0.82 (0.19) ($F_{1,86}=4.26$; $P=.04$) mEq/L, respectively, while mean plasma levels of valproate for cotherapy (n=145) and monotherapy (n=73) were 63.6 (18.4) µg/mL and 74.7 (18.6) µg/mL, respectively ($F_{1,188}=18.38$; $P<.001$). Benzodiazepine use was not statistically different between patients in the cotherapy (66/229 [28.8%]) and monotherapy (39/115 [33.9%]) groups ($P=.38$).

PRIMARY OUTCOMES

Both groups of patients improved during the course of treatment as indicated by the primary measure of efficacy, the YMRS total score (Table 3). However, the olanzapine cotherapy group (n=220) showed a mean decrease in YMRS total score of 13.1 (8.53) points, corresponding to a 58.8% improvement from baseline compared with a decrease of 9.10 (9.36) points ($F_{1,276}=9.08$; $P=.003$) for the monotherapy group (n=114), which corresponded to an improvement of 40.1%.

Itemwise analysis of the YMRS revealed that, compared with monotherapy, olanzapine cotherapy brought about significantly greater improvement at end point on the items of Irritability (cotherapy, −1.82 [2.09], n=220;

Table 2. Patient Disposition*

Characteristic	Mood Stabilizer	Olanzapine Cotherapy (n = 229)	Monotherapy (n = 115)	P Value†
Completed study, No.	Full sample	160 (69.9)	82 (71.3)	.80
	Lithium	58 (76.3)	32 (78.1)	>.99
	Valproate	102 (66.7)	50 (68.5)	.88
Reasons for discontinuation				
Adverse event	Full sample	25 (10.9)	2 (1.7)	.002
	Lithium	5 (6.6)	0	.16
	Valproate	20 (13.1)	2 (2.74)	.02
Lack of efficacy	Full sample	7 (3.1)	14 (12.2)	.002
	Lithium	2 (2.6)	4 (9.8)	.18
	Valproate	5 (3.3)	9 (12.3)	.02
Lost to follow-up	Full sample	5 (2.2)	3 (2.6)	>.99
	Lithium	2 (2.6)	2 (4.9)	.61
	Valproate	3 (2.0)	1 (1.4)	>.99
Patient decision	Full sample	13 (5.7)	2 (1.7)	.16
	Lithium	3 (4.0)	1 (2.4)	>.99
	Valproate	10 (6.5)	1 (1.4)	.12
Criteria not met/compliance	Full sample	12 (5.2)	5 (4.3)	.8
	Lithium	3 (4.0)	1 (2.4)	>.99
	Valproate	9 (5.9)	4 (5.5)	>.99
Sponsor decision	Full sample	1 (0.4)	1 (0.9)	>.99
	Lithium	0	1 (2.4)	.35
	Valproate	1 (0.7)	0	>.99
Physician decision	Full sample	5 (2.2)	6 (5.2)	.19
	Lithium	2 (2.6)	0	.54
	Valproate	3 (2.0)	6 (8.2)	.06
Satisfactory response	Full sample	1 (0.4)	0	>.99
	Lithium	1 (1.3)	0	>.99
	Valproate	0	0	

*Data are given as number (percentage) unless otherwise indicated.
†Treatment difference, olanzapine cotherapy vs monotherapy; derived from the Fisher exact test.

monotherapy, −1.02 [2.37], n=114; $F_{1,276}$=5.69; P=.02); Speech (cotherapy, −2.45 [2.03], n=220; monotherapy, −1.63 [2.53], n=114; $F_{1,276}$=5.24; P=.02); Language/Thought Disorder (cotherapy, −0.94 [0.91], n=220, monotherapy, −0.72 [1.00], n=114; $F_{1,276}$=5.34; P=.02); and Disruptive/Aggressive Behavior (cotherapy, −1.18 [1.64], n=220; monotherapy, −0.46 [1.77], n=114; $F_{1,276}$=10.16; P=.002).

Clinical response was defined a priori in the protocol as improvement of 50% or greater from baseline to end point in the YMRS total score. On this basis, 149 (67.7%) of the 220 patients in the olanzapine cotherapy group responded to treatment compared with 51 (44.7%) of the 114 patients in the monotherapy group (P<.001). In addition, time to response was significantly shorter for cotherapy (P=.002, log rank test), with a median response time of 18 days for cotherapy vs 28 days for monotherapy.

SECONDARY OUTCOMES

Clinical remission was defined a priori in the protocol as achievement of a YMRS total score of less than or equal to 12. On this basis, 173 (78.6%) of the 220 patients in the olanzapine cotherapy group demonstrated evidence of remission. In the monotherapy group, 75 (65.8%) of the 114 evaluated patients demonstrated evidence of remission. This difference in remission rates was also significant (P=.01). Time to remission was significantly shorter in the cotherapy group (log rank test, P=.002), with a median remission time of 14 days for cotherapy vs 22 days for monotherapy.

Compared with the patients in the monotherapy group, patients in the olanzapine cotherapy group showed significantly greater improvement on the HAMD-21 at each time point throughout the study. By week 6, the cotherapy group (n=220) experienced a mean last observation carried forward decrease in HAMD-21 scores of 4.98 (7.61) points, significantly greater ($F_{1,276}$=18.05; P<.001) than the decrease of 0.89 (6.90) points in the monotherapy group (n=114). An exploratory itemwise analysis showed significantly greater improvement in the dimensions of depressed mood, feelings of guilt, suicidality, early insomnia, anxiety-psychic, and paranoid symptoms.

Analysis of end point HAMD-21 scores conducted in the subset of patients experiencing a mixed episode with moderate to severe depressive symptoms at baseline (HAMD-21 total score ≥20 at baseline) showed a decrease of 10.31 (8.19) points for olanzapine cotherapy (n=51) compared with 1.57 (7.73) points ($F_{1,70}$=17.50; P<.001) for monotherapy (n=21). Within this subset, 43.1% of patients in the cotherapy group showed ≥50% improvement of depressive symptoms compared with 9.5% in the monotherapy group (P=.006).

Other secondary measures of efficacy included the Positive and Negative Syndrome Scale (total; Positive, Negative, and Cognitive clusters; and Hostility subscores) and the CGI-BP (overall, Severity of Mania, and Severity of Depression). Olanzapine cotherapy brought

Table 3. Summary of Efficacy Results, Baseline to End Point Changes*

Measurement Scale	Mood Stabilizer	Olanzapine Cotherapy (n = 220)		Monotherapy (n = 114)		Comparison		
		Baseline: mean (SD)	Change: mean (SD)	Baseline: mean (SD)	Change: mean (SD)	F Statistic†	Effect Size	P Value‡
YMRS Total	Full sample	22.31 (5.39)	−13.11 (8.53)	22.67 (5.15)	−9.10 (9.36)	9.08	0.47	.003
	Lithium	22.34 (5.26)	−13.62 (8.36)	22.22 (4.65)	−10.39 (8.69)	3.10	0.42	.08
	Valproate	22.29 (5.48)	−12.85 (8.64)	22.76 (5.31)	−8.39 (9.76)	4.51	0.50	.04
HAMD-21 Total	Full sample	14.52 (8.46)	−4.98 (7.61)	13.54 (7.63)	−0.89 (6.90)	18.05	0.58	<.001
	Lithium	14.26 (8.33)	−4.15 (8.18)	10.90 (6.54)	−1.32 (5.19)	3.58	0.40	.06
	Valproate	14.65 (8.55)	−5.40 (7.30)	15.04 (7.89)	−0.67 (7.77)	14.77	0.65	<.001
CGI-BP Overall	Full sample	4.10 (0.74)	−1.20 (1.16)	4.18 (0.72)	−0.89 (1.31)	4.48	0.27	.04
	Lithium	4.12 (0.78)	−1.23 (1.24)	4.00 (0.71)	−0.98 (1.44)	0.24	0.20	.62
	Valproate	4.10 (0.73)	−1.19 (1.12)	4.28 (0.72)	−0.82 (1.24)	2.08	0.33	.15
CGI-BP Mania	Full sample	4.06 (0.79)	−1.48 (1.25)	4.13 (0.70)	−1.16 (1.39)	2.94	0.26	.09
	Lithium	4.12 (0.72)	−1.61 (1.23)	4.02 (0.69)	−1.10 (1.55)	1.70	0.40	.2
	Valproate	4.03 (0.82)	−1.42 (1.26)	4.18 (0.70)	−1.18 (1.31)	0.10	0.20	.75
CGI-BP Depression	Full sample	2.76 (1.40)	−0.50 (1.33)	2.62 (1.37)	0.12 (1.45)	13.84	0.48	<.001
	Lithium	2.59 (1.32)	−0.35 (1.46)	2.07 (1.06)	0.10 (1.16)	0.46	0.36	.5
	Valproate	2.84 (1.43)	−0.58 (1.26)	2.93 (1.44)	0.17 (1.58)	15.79	0.57	<.001
PANSS Total	Full sample	62.10 (17.28)	−12.90 (15.72)	61.75 (15.51)	−6.96 (16.39)	8.78	0.42	.003
	Lithium	61.43 (15.85)	−14.03 (15.15)	58.63 (13.27)	−9.02 (12.59)	0.93	0.40	.34
	Valproate	62.45 (18.00)	−12.34 (16.02)	63.31 (16.50)	−5.86 (18.28)	7.80	0.42	.006
PANSS Cognition	Full sample	14.36 (4.32)	−3.08 (4.12)	14.50 (3.90)	−2.29 (4.23)	2.59	0.21	.12
	Lithium	14.12 (4.04)	−3.39 (4.10)	14.41 (3.76)	−3.37 (4.07)	0.01	0.01	.92
	Valproate	14.49 (4.46)	−2.92 (4.13)	14.50 (4.00)	−1.72 (4.24)	4.98	0.31	.03
PANSS Hostility	Full sample	9.54 (3.36)	−2.99 (3.62)	9.58 (3.11)	−1.69 (3.66)	4.95	0.39	.03
	Lithium	9.57 (2.95)	−3.49 (3.40)	9.49 (2.93)	−2.05 (3.07)	3.66	0.45	.06
	Valproate	9.53 (3.56)	−2.73 (3.71)	9.57 (3.20)	−1.49 (3.98)	1.80	0.39	.18

*YMRS indicates Young Mania Rating Scale; HAMD-21, Hamilton Depression Rating, 21-Item; CGI-BP, Clinical Global Impressions–Severity of Bipolar Disorder; and PANSS, Positive and Negative Syndrome Scale.
†All tests based on 1 *df*.
‡Treatment difference, olanzapine cotherapy vs monotherapy; derived from analysis of variance.

about significantly greater improvement than monotherapy on patients' last observation carried forward, Positive and Negative Syndrome Scale total, and Hostility item scores, as well as on the CGI-BP overall and Severity of Depression scores (Table 3).

SUBGROUP ANALYSES

Subgroup analyses, defined a priori, were conducted on baseline to end point YMRS total scores. No significant interactions were seen between previous exposure to psychotropics (antidepressants, antipsychotics) and therapy (cotherapy, monotherapy). However, among all patients without psychotic features, olanzapine cotherapy was significantly more efficacious than monotherapy (cotherapy: −13.25 [7.76], n=150; monotherapy: −8.32 [8.68], n=76; $F_{1,196}=16.97$; $P<.001$). Among patients without psychotic features, olanzapine cotherapy was more effective than monotherapy regardless of whether patients received lithium or valproate. However, among patients with psychotic features, responses to treatment were not different between the cotherapy and monotherapy groups regardless of whether patients received lithium or valproate—this despite the lack of association between the presence of psychotic features and the differential effect of therapy (ANOVA test of interaction: $F_{1,274}=0.60$; $P=.44$).

Among patients with a current mixed episode, olanzapine cotherapy was superior to monotherapy (cotherapy: −12.92 [8.37], n=121; monotherapy: −7.46 [10.15], n=54; $F_{1,146}=17.31$; $P<.001$). However, among patients presenting with pure mania, the treatment difference did not achieve statistical significance (cotherapy: −13.34 [8.77], n=99; monotherapy: −10.57 [8.40], n=60; $F_{1,129}=2.95$; $P=.09$). The superiority of olanzapine cotherapy over monotherapy seen in patients with mixed episodes was found only in patients receiving valproate (cotherapy: −13.18, [8.49], n=84; monotherapy: −7.48 [10.74], n=42; $F_{1,124}=10.53$; $P=.002$), whereas the treatment difference seen with lithium did not achieve statistical significance (cotherapy: −12.32 [8.15], n=37; monotherapy: −7.42 [8.14], n=12; $F_{1,47}=3.28$; $P=.08$), again despite the lack of association between course of illness and the differential effect of therapy (ANOVA test of interaction, $F_{1,274}=0.14$; $P=.71$).

Finally, among patients receiving valproate, olanzapine cotherapy brought about significantly greater improvement in YMRS total scores compared with patients receiving valproate monotherapy (cotherapy: −12.85 [8.64], n=146; monotherapy: −8.39 [9.76], n=72; $F_{1,188}=13.44$; $P<.001$). Among patients receiving lithium, the greater improvement seen with olanzapine cotherapy relative to monotherapy did not achieve statistical significance (cotherapy: −13.62 [8.36], n=74; monotherapy: −10.39 [8.69], n=41; $F_{1,86}=3.74$; $P=.06$). The type of mood stabilizer was not associated significantly with a differential effect of cotherapy compared with monotherapy (ANOVA test of interaction, $F_{1,273}=0.74$; $P=.39$).

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