Differential Efficacy of Olanzapine and Lithium in Preventing Manic or Mixed Recurrence in Patients With Bipolar I Disorder Based on Number of Previous Manic or Mixed Episodes

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Introduction: Bipolar disorder outcome worsens as number of manic episodes increases, suggesting that prevention of recurrent episodes early during the disorder could improve patient prognosis. We investigated treatment efficacy in prevention of mood episodes in patients subgrouped by number of prior manic episodes.

Method: This study was a post hoc analysis of data from a multicenter, double-blind, 12-month clinical trial of relapse/recurrence in 431 initially euthymic patients with at least 2 prior manic/mixed episodes and a DSM-IV diagnosis of bipolar I disorder randomly assigned to olanzapine (5–20 mg/day) or lithium (serum concentration 0.6 to 1.2 mEq/L). Data were collected between August 1999 and June 2002. Patients were subcategorized by illness stage according to number of prior manic/mixed episodes—early stage: 2 prior episodes (N = 53, lithium; N = 48, olanzapine), intermediate stage: 3 to 5 prior episodes (N = 80, lithium; N = 98, olanzapine), and later stage: more than 5 prior episodes (N = 81, lithium; N = 71, olanzapine)—and were evaluated for rates of relapse/recurrence.

Results: There were significant effects for treatment ($p < .001$) and illness stage ($p = .006$) but no significant interaction ($p = .107$) on rate of manic/mixed relapse/recurrence. Rates of manic/mixed relapse/recurrence for olanzapine versus lithium were 2.1% versus 26.4% ($p = .008$), 13.3% versus 23.8% ($p = .073$), and 23.9% versus 33.3% ($p = .204$) for early-, intermediate-, and later-stage groups, respectively. There was no significant effect for treatment ($p = .096$) or illness stage ($p = .731$) for depressive relapse/recurrence.

Conclusions: Early-stage (but not intermediate- or later-stage) patients had a significantly lower rate of relapse/recurrence of manic/mixed episodes with olanzapine compared to lithium. Thus, olanzapine maintenance therapy may be particularly effective early in the course of bipolar illness.

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Bipolar disorder is characterized by recurrent episodes of mania and depression. The majority of studies of bipolar disorder that have examined frequency of affective episodes across the course of illness have reported that the time to recurrence shortens with increasing number of previous episodes,[1–4] although this finding is not without exceptions.[5,6] The episodic and progressive nature of bipolar disorder has led to neurobiological theories of the disorder that suggest the clinical progression of bipolar disorder is related to sensitization to psychosocial stressors, with recurrent affective episodes leading to increased vulnerability to subsequent episodes and progressive behavioral dysfunction.[7–9] A potential consequence is that pharmacologic response may vary over the course of the illness.

However, few studies have examined whether there is differential effectiveness of prophylactic therapy of bipolar disorder over the course of the illness. In a secondary analysis of a double-blind study of 154 inpatients with acute mania,[10] a history of many affective episodes was associated with decreased lithium response for acute mania, whereas the efficacy of divalproex for acute mania

showed a positive relationship with history of previous episodes. Similar relationships may occur with maintenance treatment. For example, lithium prophylaxis may be less effective in patients with bipolar disorder with 3 or more prior affective episodes.[11,12] In a 10-year follow-up of a prospective study of 277 patients with bipolar I disorder, Maj[12] reported that overall there was no difference in the prophylactic effect of lithium over time, although a minority of patients who displayed an optimal response to lithium for several years subsequently had multiple recurrences. It is unclear whether this finding was the result of a loss of efficacy of lithium over time in a subset of patients or the result of the progressive course of the illness independent of treatment.[12] Few studies have examined relationships between newer bipolar maintenance therapies such as olanzapine and number of prior episodes.

In a randomized, double-blind, 12-month clinical trial of olanzapine versus lithium in the prevention of relapse/recurrence to mood episode (manic, mixed, or depressive) in patients stabilized on a combination of olanzapine and lithium,[13] olanzapine-treated compared to lithium-treated patients tended to have lower risk of symptomatic relapse/recurrence to any episode and had significantly lower risk of symptomatic relapse/recurrence to manic and mixed episodes.[13] The primary objective of the present post hoc analysis of the above maintenance study[13] was to determine whether there is a difference, by treatment, in prevention of mood episodes in patients subgrouped by number of prior manic/mixed episodes. Below, we will use the term *recurrence* to refer to relapse/recurrence.

METHOD

The data for this investigation were collected between August 1999 and June 2002 during a multicenter, randomized, double-blind, 12-month clinical trial of olanzapine versus lithium in the prevention of recurrence of mood episodes (manic, mixed, or depressive) in patients initially stabilized on a combination of olanzapine and lithium. A brief description of the original study[13] is provided here. The protocol was approved by ethical review boards responsible for study sites, and all patients gave written, informed consent prior to entering the study.

Study Design

Patients who entered the open-label stabilization period had a DSM-IV diagnosis of bipolar I disorder and displayed an acute manic or mixed episode. Patients must have had a Young Mania Rating Scale (YMRS)[14] total score ≥ 20. Patients who had a history of intolerance or lack of response to an adequate trial of treatment with either lithium or olanzapine were excluded from the trial per study protocol. Eligible patients were enrolled in the open-label period and received olanzapine and lithium cotherapy for a minimum of 6 weeks and a maximum of 12 weeks. Patients began open-label therapy with olanzapine 15 mg/day and lithium 600 mg/day. Concomitant psychotropic medications were gradually discontinued over the first 3 weeks of the open-label period. Oral or intramuscular haloperidol and zuclopenthixol were permitted for extreme agitation during the open-label period. Patients who met the symptomatic remission criteria (YMRS score ≤ 12 and 21-item Hamilton Rating Scale for Depression [HAM-D-21][15] score ≤ 8) between weeks 6 and 12 were randomly reassigned in a 1:1 ratio to either olanzapine (5–20 mg/day) or lithium monotherapy. During the taper period, patients remained on their current dose of randomized treatment, and the dose of the discontinued drug was tapered over 4 weeks. Plasma lithium concentrations were monitored every 2 weeks during the taper period and monthly during the monotherapy period. Plasma lithium concentrations ranging from 0.6 to 1.2 mEq/L were considered within normal limits.

Benzodiazepines were permitted within specified dosing guidelines (maximum dosage of 2-mg lorazepam equivalents/day during the double-blind period). Patients were allowed medication for treatment-emergent extrapyramidal symptoms (EPS); however, prophylactic use of anticholinergics for EPS was not allowed.

Assessments

Recurrence and severity of illness were assessed with the YMRS and the HAM-D-21. A priori categorical definitions of remission included symptomatic remission of mania, YMRS total score ≤ 12 and symptomatic remission of depression, HAM-D-21 score ≤ 8. A priori categorical definitions of symptomatic recurrence included recurrence of mania, YMRS score ≥ 15; recurrence of depression, HAM-D-21 score ≥ 15; recurrence of mixed episodes, YMRS score ≥ 15 and HAM-D-21 score ≥ 15; and recurrence of any mood episode, YMRS score ≥ 15 or HAM-D-21 score ≥ 15.

The primary objective of the current post hoc analysis was to assess the efficacy of olanzapine compared to lithium in preventing recurrence of manic/mixed and depressive episodes in patients subgrouped by the number of prior manic/mixed episodes. Patients were subcategorized based on number of prior manic/mixed episodes—early stage: 2 prior manic/mixed episodes (N = 53, lithium; N = 48, olanzapine), intermediate stage: 3 to 5 prior manic/mixed episodes (N = 80, lithium; N = 98, olanzapine), and later stage: more than 5 prior manic/mixed episodes (N = 81, lithium; N = 71, olanzapine). Prior episodes were categorized rather than treated as continuous data since the accuracy of reported prior episodes likely decreases with an increasing number of prior episodes. The specific bipolar disorder stages were selected for their ability to provide comparably sized groups for statistical analysis and to reflect different clinical stages of this progressive condition. Demographic characteristics

were compared for the disease state subgroups and treatment groups.

Statistical Methods

Recurrence rates for mood episodes were predicted using 2 logistic regression models: first, recurrence rates were predicted by therapy and illness stage and then by a model containing an interaction between the 2. Time to recurrence was analyzed using Kaplan-Meier estimated survival curves, and comparisons were made using the log-rank test. A stratified proportional hazards model was used to compare therapies within the 3 illness stage groups. Categorical baseline characteristics were compared between the illness stages and treatment groups with Fisher exact test and continuous baseline data using analysis of variance. Analyses were completed on an intent-to-treat basis, and SAS software version 8 (SAS Institute, Inc., Cary, N.C.) was used to perform all analyses. All tests of hypotheses were considered statistically significant if the p value was equal to or less than .050.

RESULTS

Patient and Illness Characteristics After Remission

A total of 431 euthymic (YMRS score ≤ 12 and HAM-D-21 score ≤ 8) patients entered into the maintenance monotherapy phase of the study. Baseline characteristics after remission by illness stage and treatment are shown in Table 1. The vast majority of patients (93%) had an index episode of pure mania, and there was no difference in the number of patients with an index mixed episode or in the number of patients with rapid cycling (4 or more affective episodes in the prior year) between illness stages or treatment groups. As expected, there were significant differences in age ($p < .001$), illness duration ($p < .001$), and time since first manic/mixed episode ($p < .001$) based on illness stage. Also, there were significant differences in age at illness onset ($p = .012$) and YMRS total score ($p = .004$) based on illness stage. In general, advancing illness stage was associated with increased age and illness duration and with a younger age at bipolar disorder onset. Baseline characteristics did not significantly differ between treatments adjusted for illness stage.

The olanzapine mean (SD) daily dose was 11.9 (4.4) mg and the lithium daily dose was 1102.7 (270.3) mg during the maintenance phase of the trial. The mean (SD) plasma concentration for lithium was 0.765 (0.142) mEq/L during the maintenance phase of the trial. Both olanzapine- and lithium-treated patients had a median of 4 prior manic episodes, 2 prior depressive episodes, and zero prior mixed episodes.

Rate of Recurrence

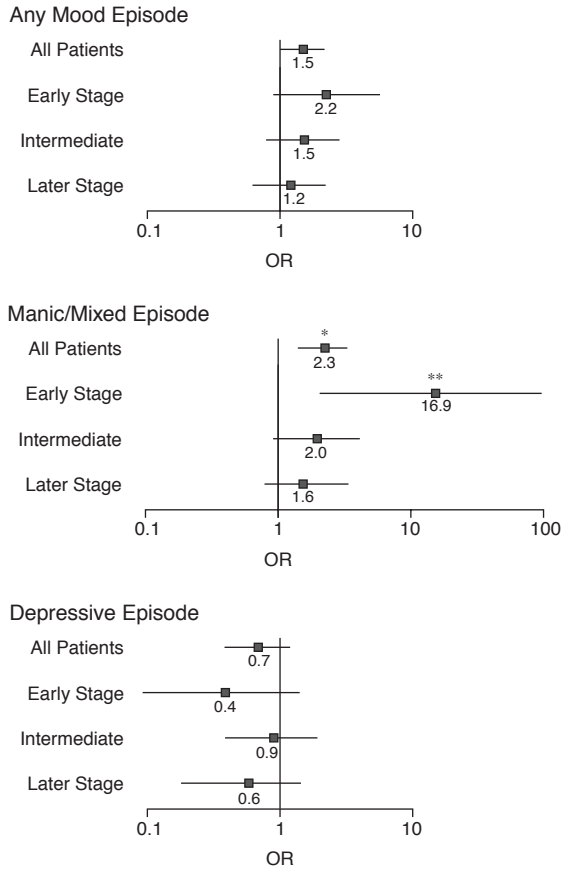
Advancing illness stage was related to a higher rate of recurrence of manic/mixed episodes ($p = .017$) and any

Table 1. Baseline Patient and Illness Characteristics After Remission of 431 Patients With Bipolar I Disorder

	Early Stage (2 prior manic/mixed episodes)			Intermediate (3–5 prior manic/mixed episodes)			Later Stage (> 5 manic/mixed episodes)		
Variable	Lithium (N = 53)	Olanzapine (N = 48)	Total (N = 101)	Lithium (N = 80)	Olanzapine (N = 98)	Total (N = 178)	Lithium (N = 81)	Olanzapine (N = 71)	Total (N = 152)
Sex, % male	50.9	50.0	50.5	47.5	41.8	44.4	42.0	54.9	48.0
Age, mean ± SD, y*	37.77 ± 13.17	39.45 ± 13.71	38.57 ± 13.39	41.33 ± 12.24	40.71 ± 12.89	40.99 ± 12.57	46.28 ± 10.72	47.04 ± 12.01	46.64 ± 11.31
Race, % white	100	100	100	100	99.0	99.4	100	97.2	98.7
Rapid cycle, %	3.8	0	2.0	0	2.0	1.1	6.2	5.6	5.9
Index mixed episode, N (%)	3 (5.66)	2 (4.17)	5 (4.95)	6 (7.50)	10 (10.20)	16 (8.99)	3 (3.70)	3 (4.23)	6 (3.95)
Age at illness onset, mean ± SD, y*	30.0 ± 12.2	31.2 ± 11.8	30.5 ± 12.0	29.2 ± 10.3	29.5 ± 12.7	29.4 ± 11.6	26.9 ± 9.8	26.3 ± 8.7	26.6 ± 9.3
Time since first mood episode, mean ± SD, y*	7.26 ± 8.18	7.92 ± 7.59	7.57 ± 7.87	11.64 ± 8.38	10.63 ± 8.01	11.08 ± 8.17	18.93 ± 9.59	20.25 ± 11.47	19.55 ± 10.50
Time since first manic/mixed episode, mean ± SD, y*	3.70 ± 2.92	3.98 ± 4.94	3.83 ± 3.99	9.68 ± 6.72	8.40 ± 7.23	8.97 ± 7.01	17.19 ± 9.30	18.66 ± 10.85	17.87 ± 10.04
Psychotic features, %	20.8	31.3	25.7	20.0	22.4	21.3	32.1	31.0	31.6
Time in remission prior to randomization, mean ± SD, d	20.3 ± 21.8	20.5 ± 19.6	20.4 ± 20.7	22.3 ± 19.3	20.5 ± 19.4	21.3 ± 19.3	21.7 ± 17.8	21.0 ± 18.4	21.4 ± 18.0
YMRS total score, mean ± SD*	5.36 ± 4.29	4.06 ± 3.94	4.74 ± 4.16	3.20 ± 3.48	4.04 ± 3.59	3.66 ± 3.55	3.57 ± 3.53	2.76 ± 3.03	3.19 ± 3.32
HAM-D-21 total score, mean ± SD	1.58 ± 1.95	1.29 ± 1.82	1.45 ± 1.88	1.47 ± 1.84	1.53 ± 1.82	1.51 ± 1.83	1.63 ± 2.05	1.80 ± 2.30	1.71 ± 2.16

*Patient age, age at illness onset, time since first mood and first manic/mixed episode, and YMRS total score significantly differed by illness stage ($p < .05$). There were no significant differences between treatments adjusted for illness stage.
Abbreviations: HAM-D-21 = 21-item Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.

Figure 1. Odds Ratios (ORs) With 95% Confidence Intervals (CIs) for Bipolar Recurrence in Patients Treated With Lithium Versus Olanzapine[a]



[a]Odds ratios for recurrence in all patients were constructed using a model that included therapy and illness stage as predictors. Odds ratios for the specific illness stage groups were constructed using a model that included an interaction between therapy and illness stage.
*OR = 2.3, 95% CI = 1.4 to 3.8, p < .001.
**OR = 16.9, 95% CI = 2.1 to 134.1, p = .008.

mood episode (p = .050) but not depressive episodes (p = .829) when controlling for treatment. When the interaction between illness stage and treatment was modeled, there was an overall effect for treatment (p < .001) and illness stage (p = .007) on rate of manic/mixed recurrence but no significant interaction between treatment and illness stage (p = .107) with respect to rate of manic/mixed recurrence. Although the interaction between treatment and illness stage was not significant, we still compared treatments for each of the illness stages, because the classifications may be clinically relevant, and there was an overall effect of illness stage on recurrence. Odds ratios (ORs) with 95% confidence intervals (CIs) for recurrence of manic/mixed episode or depressive episode in patients treated with olanzapine versus lithium are shown in Figure 1.

Rates of manic/mixed recurrence in patients treated with olanzapine versus lithium were 2.1% versus 26.4% (p = .008), 13.3% versus 23.8% (p = .073), and 23.9% versus 33.3% (p = .204) for early, intermediate, and later-stage groups, respectively (Table 2). There was no significant overall effect for treatment (p = .096), illness stage (p = .731), or interaction (p = .593) for depressive recurrence. Rates of depressive recurrence in patients treated with olanzapine versus lithium were 16.7% versus 7.6% (p = .167), 15.3% versus 13.8% (p = .770), and 15.5% versus 9.9% (p = .300) for early-, intermediate-, and later-stage groups, respectively. Rates for recurrence of any mood episode did not differ by treatment or illness stage (Table 2).

Rates of recurrence to manic/mixed episode, depressive episode, or any mood episode were also analyzed by treatment and illness stage, with illness stage defined by number of prior manic episodes only (excluding prior mixed episodes). Rates of manic/mixed recurrence in patients treated with olanzapine versus lithium were 3.4% versus 26.5% (p = .003) for early-stage patients defined by prior manic episodes only. The odds ratio for manic/mixed recurrence in early-stage patients changed from 16.9, 95% CI = 2.1 to 134.1, p = .008 when illness stage was defined by prior manic or mixed episodes to 10.3, 95% CI = 2.3 to 46.4, p = .003 when illness stage was defined by only prior manic episodes. Rates of recurrence were similar, and lack of statistical significance was the same for recurrence rates in the intermediate and later-illness–stage groups as when recurrence was analyzed with illness stage defined by prior manic/mixed episodes (data not shown).

Time to Recurrence

There was a significant treatment difference in time to recurrence of manic/mixed episodes in early-stage patients (p < .001, log-rank test; Figure 2). The hazard ratio for estimated probability of manic/mixed recurrence was 16.7, 95% CI = 2.1 to 129.5, p = .007 when comparing lithium with olanzapine. Survival curves for intermediate- and later-stage patients are also shown in Figure 2. Although the curves for olanzapine-treated patients and lithium-treated patients were significantly different for later-stage patients, this difference was not as robust as for the early-stage patients and is difficult to interpret since the curves cross.

Effect of Previous Depressive Episodes

Patients were similarly categorized as early (2 prior episodes), intermediate (3–5 prior episodes), and later stage (> 5 prior episodes) based on number of previous depressive episodes, and rates of recurrence were examined using logistic regression. There was no significant effect of treatment (p = .081), previous depressive episodes (p = .111), or interaction (p = .067) on recurrence to

Table 2. Rates of Recurrence to Any Mood Episode, Manic/Mixed Episode, or Depressive Episode by History of Previous Manic/Mixed Episodes Among 431 Patients With Bipolar I Disorder[a]

	Any Episode, N (%)			Manic/Mixed Episode, N (%)			Depressive Episode, N (%)		
Stage	Olanzapine	Lithium	p	Olanzapine	Lithium	p	Olanzapine	Lithium	p
Early (2 manic/mixed episodes)	9 (18.8)	18 (34.0)	.088	1 (2.1)	14 (26.4)	.008	8 (16.7)	4 (7.6)	.167
Intermediate (3–5 manic/mixed episodes)	28 (28.6)	30 (37.5)	.207	13 (13.3)	19 (23.8)	.073	15 (15.3)	11 (13.8)	.770
Later (> 5 manic/mixed episodes)	28 (39.4)	35 (43.2)	.638	17 (23.9)	27 (33.3)	.204	11 (15.5)	8 (9.9)	.300

[a]There was an overall effect for treatment (p = .039) and episode history (p = .038) but no significant interaction (p = .530) for recurrence of any mood episode. There was an overall effect for treatment (p < .001) and episode history (p = .007) but no significant interaction (p = .107) for recurrence of manic/mixed episodes. The overall effects for treatment (p = .096), episode history (p = .731), and interaction (p = .593) were not significant for recurrence of depressive episode.

depressive episodes, although there was a trend for a treatment difference in favor of lithium. There was a significant effect of treatment (OR = 2.27, 95% CI = 1.39 to 3.69 in favor of olanzapine, p < .001) but not of previous depressive episodes (p = .872) or interaction (p = .351) on recurrence to manic/mixed episodes. There was no significant effect of treatment (p = .055), previous depressive episodes (p = .413), or interaction (p = .335) on recurrence to any mood episode.

DISCUSSION

A higher rate of manic/mixed recurrence was associated with a greater number of prior manic/mixed episodes in patients with bipolar I disorder. While olanzapine appeared to be associated with an overall lower rate of manic/mixed recurrence in comparison with lithium, this response was particularly robust in patients with fewer prior manic/mixed episodes. Thus, in patients with only 2 previous manic/mixed episodes, only 2.1% of olanzapine-treated patients experienced recurrence of manic/mixed episodes. This treatment difference diminished as the number of prior manic/mixed episodes increased. However, the overall interaction between treatment and illness stage was not significant, suggesting that treatment response diminishes with increasing number of manic/mixed episodes with olanzapine and lithium treatments.

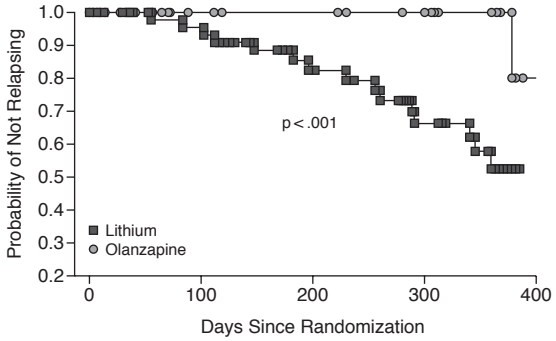
An association between longer duration of illness before the start of lithium treatment and a less favorable outcome of prophylaxis has previously been reported.[12] In addition, a decrease in response with increasing number of prior episodes has been observed for the acute treatment of mania with lithium.[10] The results of our study are consistent with longer illness duration being associated with poor response to lithium, since longer illness duration was associated with an increased number of prior manic/mixed episodes. The present results also suggest that a similar relationship may exist with olanzapine and that, in general, an increasing number of episodes and illness duration are associated with poor treatment response. Therefore, decreasing the number of episodes by instituting prophylactic treatment early in the course of the illness may be an important component of efforts to improve long-term disease prognosis. Although speculative, our results are consistent with the idea that affective episodes inflict neurobiological changes that render the illness more severe and challenging to treat. Repeated episodes may trigger new mechanisms that can overwhelm or circumvent a previously effective treatment.[8] The present data suggest that treatment response differs over the course of bipolar illness and highlight the importance of promptly initiating effective treatment in new-onset patients.

Treatments with different mechanisms of action may show differential efficacy with illness progression. Olanzapine and lithium differ in their mechanisms of action, but the therapeutic mechanisms responsible for prophylactic effects in bipolar disorder are not known with any certainty. Olanzapine binds to dopamine (D_1–D_5), serotonin (5-$HT_{2A–C}$ and 5-HT_6), muscarinic acetylcholine (M_1–M_5), histamine, and norepinephrine receptors. In addition, olanzapine may indirectly increase γ-aminobutyric acid neurotransmission and decrease glutamate transmission. Lithium interacts with a variety of intracellular signaling pathways. Much research has focused on lithium inhibition of inositol monophosphate phosphatase (IMPase) and glycogen synthase kinase-3 (GSK-3).[16] Both drugs may exert neuroprotective effects.[17–19] Why olanzapine and lithium would differentially prevent manic recurrence in early-stage patients remains to be established but may be a consequence of their different mechanisms of action.

Recurrence in patients with bipolar disorder is common, and preventing recurrence is important to maintain normal patient functioning. Although long-term functional consequences of depression may be severe,[20] and patients with bipolar disorder typically spend more time experiencing depressive compared to manic symptoms,[21] recurrence of acute mania is a medical emergency that frequently requires hospitalization. Without rapid treatment, the manic patient may engage in activities affecting marriage, employment, morbidity, and even mortality.[22] Thus, the manic phase constitutes a substantial public health problem even in comparison with the more common unipolar depression.[23] Our finding that the number of prior manic, but not depressive, episodes influences

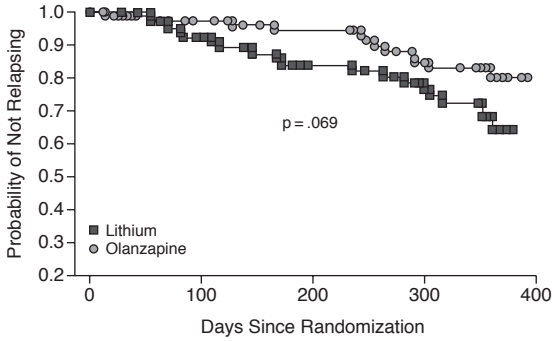
Figure 2. Time to Recurrence to Manic/Mixed Episode in Patients With Bipolar I Disorder by Illness Stage[a]

A. Early-Stage Illness (2 manic/mixed episodes)



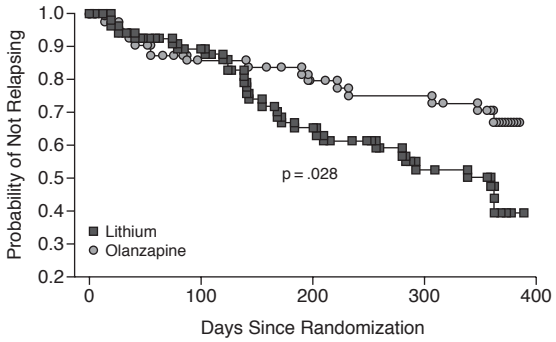
Days	0	75	150	225	300	365
Olanzapine, N	48	33	29	28	26	11
Lithium, N	53	44	33	27	19	6

B. Intermediate Illness (3–5 manic/mixed episodes)



Days	0	75	150	225	300	365
Olanzapine, N	98	76	69	63	50	18
Lithium, N	80	67	52	46	40	17

C. Later-Stage Illness (> 5 manic/mixed episodes)



Days	0	75	150	225	300	365
Olanzapine, N	71	52	43	35	34	15
Lithium, N	81	58	42	31	23	10

[a]Time to recurrence to manic/mixed episode was significantly longer for the olanzapine group compared to the lithium group for early-stage patients (log-rank test, $p < .001$) and later-stage patients (log-rank test, $p < .028$).

outcome and treatment response is consistent with the notion that manic episodes may provide particularly important contributions to illness progression and thus may be particularly important to avoid.

The present study has several important limitations. This was a post hoc analysis, so the results cannot be interpreted with the same rigor as if we had been testing an a priori hypothesis. In addition, prior episodes were evaluated by patient history, which may be inaccurate, particularly in patients with histories of many episodes. Subgroups categorized by number of prior manic/mixed episodes had significantly different age and illness onset and duration. In general, more previous episodes were associated with an increased age and illness duration and earlier illness onset. These patient characteristics may contribute to the difference in treatment response in early-stage patients independently of number of episodes. However, it was expected that these characteristics would be correlated with the number of previous episodes.

CONCLUSION

In general, olanzapine- and lithium-treated patients had similar rates of recurrence of any mood episode (30.0% vs. 38.8%), but olanzapine-treated patients, early in the course of illness, did exceedingly well with respect to prevention of mania (2.1% recurrence of mania). This treatment difference diminished as the number of prior manic/mixed episodes increased, and this suggests an efficacy advantage for olanzapine in the prevention of manic/mixed recurrences in patients with bipolar I disorder with recent onset of illness. A lower rate of depressive recurrence, which was not statistically significant, occurred with lithium versus olanzapine treatment overall and in subgroups. This lower rate did not appear to be related to number of previous manic/mixed or depressive episodes. Prospective studies are needed to confirm our preliminary findings that more prior manic (but not depressive) episodes increase the risk of manic/mixed (but not depressive) recurrence and our observation of differential prophylactic efficacy of olanzapine and lithium in the early stages of bipolar illness.

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

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