Original Article

Recovery and functional outcomes following olanzapine treatment for bipolar I mania

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Background: Typical experimental categorizations of treatment responses in bipolar disorder (BPD) patients may have limited relationship to clinical recovery or functional status, and there is inadequate research on such clinically important outcomes.

Methods: We analyzed data from a study of open continuation of olanzapine treatment following a 3-week placebo-controlled trial involving initially hospitalized adult subjects with DSM-IV BP-I mania to estimate rates and times to *symptomatic remission* (low scores on standardized symptomatic assessments) and *clinical recovery* (remission sustained ≥8 weeks), associated clinical factors, and functional outcomes.

Results: During treatment with olanzapine for 27.9 ± 20.1 weeks, *symptomatic remission* was attained by 70% of subjects, half by 8 weeks (95% CI 6–10) weeks, and later lost by 82% of remitted subjects; remitted (versus non-remitted) subjects had slightly lower baseline clinical global impression scores and greater trial-completion. *Sustained clinical recovery* was attained by only 40 of 113 (35%) of subjects, half by 36 (95% CI 20–40) weeks, and later lost by 45%. Subjects with above-median (>12) initial Hamilton-Depression rating scale depression scores were half as likely to recover ($p = 0.016$) and did so much later (36 versus 12 weeks) than those with lower scores. At final assessment, self-rated well being (SF-36 psychosocial functioning scores) improved substantially more among recovered versus non-recovered subjects (mean changes: 87% versus 23%), and two-thirds of recovered subjects remained unemployed-for-pay while half received disability-compensation.

Conclusions: Clinically meaningful symptomatic remission and recovery in relatively severely ill adult bipolar I manic patients were achieved slowly and sustained by only some patients within an average of 7 months of continuous treatment. These clinically relevant outcomes were worse with relatively high initial dysphoria ratings. Well-being was rated higher by recovered subjects, but their ability to work and live independently were markedly impaired. These findings underscore the emerging view that BPD can often be severe, slow to remit, and disabling, particularly in association with prominent depression-dysphoria symptoms. Improved treatments for BPD are needed, guided by longitudinal assessments of clinically meaningful measures of symptomatic recovery and functional outcome.

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Categorizations of response in treatment trials for patients diagnosed with bipolar disorder (BPD) remain unsatisfactory (1–3). For instance, improvement by 50% from baseline scores on a standard symptom-rating scale during a short-term trial is a statistically convenient measure of improvement,

but may have little bearing on predicting rates of clinical recovery or planning for aftercare (2–4). Given the need for better definitions of morbid states and clinical changes in BPD, there is growing interest in improving the precision and predictive value of various outcome criteria for manic, mixed, and depressive episodes for subsyndromal morbidity in BPD particularly the highly prevalent dysthymic morbidity (5–7). Recently, Chengappa and his colleagues proposed stringent remission criteria (3) based on pooled data from two short-term, placebo-controlled, randomized trials of olanzapine as an antimanic agent (8, 9). We now report on further analyses arising from the open, 1-year extension phase of the first trial (8, 10).

We addressed several hypothesis-generating, research questions of clinical importance, based on outcomes defined as meeting the criteria proposed by Chengappa et al. (3) for remission (significant reductions in standardized symptom-ratings) and sustained clinical recovery (**remission sustained for at least 8 weeks**), during open continuation treatment with olanzapine up to 1 year. We specifically tested the hypothesis that subjects who recovered from mania would achieve greater improvements in ratings of psychosocial functioning or occupational status. Additional *post hoc*, hypothesis-generating questions considered clinical and demographical factors that might be associated with achieving recovery or its latency.

Methods

Subject sample

Details of the 3-week double-blind and 49 week open extension study, including their approval by human studies review committees and the provision of written, informed, subject-consent for experimental treatment, were reported previously (8, 10, 11). De-identified (numerically coded) data were provided to the authors by Lilly Research Laboratories, and the present analyses and reporting were approved as an exempt-from-consent study by the University of Pittsburgh Institutional Review Board. Briefly, 139 acutely manic patients (age ± SD, 39.5 ± 11.0 years, 52% men) met DSM-IV diagnostic criteria for BP I disorder, based on initial Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) assessments (8, 12). Of the 139 subjects, 115 (82.7%) were considered to have 'pure' mania and 24 (17.3%) met DSM-IV requirements for a mixed state (full criteria for both mania and major depression) (12); 74 (53.2%) had psychotic features, and 45 (32.4%) showed rapid-cycling with ≥4 full DSM-IV episodes of mania, mixed-state, or depression within 12 months of study-entry (8, 10, 11).

Treatment and assessment

Patients were hospitalized initially and after a week, could be discharged when they met the following criteria: (i) Clinical Global Impression, bipolar version (CGI-BP) (13) severity score ≤3; or (ii) ≥50% reduction of Young Mania Rating Scale (YMRS) (14) score; and (iii) the local psychiatric investigator considered discharge clinically appropriate. Of the 139 subjects entering the initial controlled trial, 113 (81.3%) continued into a 49-week extension that provided open-label treatment with olanzapine regardless of initial treatment or response (8, 10). Patients were eligible to participate in the open-label phase if they completed at least 1 week of double-blind treatment with olanzapine or placebo during the 3-week initial controlled phase of the trial.

Olanzapine was started at 10 mg daily in the double-blind trial and, for subjects initially randomized to placebo, in the open-label phase, and could be adjusted clinically between 5 and 20 mg/day. Investigators were encouraged to use olanzapine monotherapy for at least 3 weeks before adding either fluoxetine hydrochloride (for emerging depression) or lithium carbonate (for breakthrough manic symptoms), based on clinical judgment. Adjunctive use of lorazepam to a daily maximum dose of 4 mg also was permitted throughout the study (8, 10).

Patients were assessed at baseline and then weekly during the 3-week double-blind phase, then at the end of the first week of the open-label extension, every 2 weeks for the next month, and then finally monthly up to a year. Psychiatric assessments included the CGI-BP (13), YMRS (14), and the 21-item Hamilton-Depression rating scale (HAMD) (15). Functional outcomes were assessed with the self-reported Medical Outcomes Study

These analyses were conducted through an academic-industry partnership, and the data were provided at the level of the individual subjects. Some of the authors (KNRC, JH, RJB, DJK, LNY) have served as consultants to or received research grant support from Lilly Research Laboratories. Furthermore, two of the authors (MT, RWB) are employees of Lilly Research Laboratories. Dr Gershon has no conflicts of interest to disclose with regards to this manuscript. The readers should note that as both editors are authors on this manuscript – key decisions regarding acceptance or rejection were made by senior editorial board members, independent of the editors.

SF-36 psychosocial function and health-rating questionnaire (16) to assess limitations in physical, social and major role activities because of poor health, as well as by reported occupational status and receipt of welfare benefits. Medical status was evaluated by regularly scheduled physical examinations, monitoring of vital signs and body-weight, clinical laboratory assessments and electrocardiograms, as detailed elsewhere (8, 10, 11).

In a recent paper, based on the pooled data from this trial and a similar short-term (4 week), randomized, double-blind, placebo-controlled trial of olanzapine for acute mania (9), we operationally defined *symptomatic remission* as: endpoint YMRS-total score ≤7, HAMD ≤7, and CGI-BP severity ≤2, with four YMRS items (irritability, speech, content, and aggressive-disruptive behavior) all ≤2, and the remaining seven items on the YMRS scale scored ≤1 (3). *Clinical recovery* was defined as remission sustained ≥8 weeks for purposes of this report.

Statistical methods

We compared rates of symptomatic remission and sustained clinical recovery between median-split components of selected subgroups, using Cox proportional hazards modeling methods. In applying these models to analyses involving recovery as the outcome, we identified time-to-recovery as weeks to the assessment at which the 8-week period of sustained recovery started. We also estimated Cox hazard ratios (HR) and their 95% confidence intervals (95% CIs), with associated *z*-statistics and p-values, for several preidentified explanatory factors. We checked model-fit and adherence to proportional hazards assumptions using graphical methods. Selected covariates, including age, sex, and presentation-type (manic or mixed), were added to Cox models that yielded significant effects to check whether the covariates modified outcomes. We checked for interactions among explanatory factors and covariates. Non-parametric log-rank comparison methods were used for some binary time-to-remission and time-to-recovery contrasts.

We examined functional outcomes, including summary self-report measures derived from the SF-36 scale (16), and self-reported occupational and disability-support status, using random effects modeling methods. For these analyses, we limited comparisons with baseline and endpoint observations. We contrasted recovered versus non-recovered subjects on the SF-36 psychosocial functioning sub-scale, work-status and disability-support measures, using random effects modeling procedures, with the interaction between recovery versus non-recovery and endpoints versus baseline as the primary effect of interest. Three different random effects modeling methods were used, including ordinary least-squares (SF-36 psychosocial functioning self-report sub-scale), ordered probit [self-reported work status, on a five-point scale, ranging from zero (not working) to four (fully employed)], and logistic regression methods (self-report, yes/no 'not employed for pay' and 'disability compensation' measures).

For some analyses, a baseline depression status indicator defined as having relatively high (> 12) or low (≤12) initial HAMD-21 scores (ratings of dysphoria) based on median-split, was added as a covariate. Some continuous variables were log-transformed to obtain more nearly Gaussian distributions. Robust standard error estimates were used when feasible. Averaged continuous data are reported as mean with standard deviations (± SD) or 95% CI. Statistical significance required two-tailed $p < 0.05$. Analyses employed commercial microcomputer programs (Stata®, Stata Corp., College Station, TX, USA; and Statview-5®, SAS Institute, Cary, NC, USA).

Results

Sample characteristics

In the initial, 3-week blinded trial, 139 subjects were randomized to olanzapine (n = 68) or placebo (n = 69); of these 113 elected to continue in the open-label extension for up to a full year. The overall sample included substantial fractions with psychotic (50%) and rapid-cycling features (30%). Their baseline YMRS scores (28.2 ± 6.5, range 20–56) were consistent with relatively severe illness and the need for initial hospitalization. Average total baseline HAMD scores (13.2 ± 6.9, range 1–34) were somewhat elevated, consistent with the presence of dysphoria in some manic patients as well as a 17.3% prevalence of mixed states meeting full DSM-IV criteria for a major depressive episode. Lifetime duration of BPD illness was 14.9 ± 10.0 years, following estimated onset at age 28.2 ± 6.5 (range 20–56) years in subjects entering the study at age 39.5 ± 10.8 years.

The 113 subjects who continued in the open extension study and the 26 who did not were similar in: sex, current age and estimated age-at-onset, manic versus mixed current episode, presence of psychotic features, rapid-cycling, prior hospitalization count, and lifetime substance-abuse or other comorbidity, as well as baseline YMRS, HAMD, and CGI-BP total scores (Table 1). However, those

Table 1. Characteristics of 139 acute manic trial (3 week) subjects in an acute trial of olanzapine versus placebo continuing or not in an open-label treatment with olanzapine up to 49 weeks

Characteristic[a]	Continuing	Not-continuing
Number (%)	113 (81%)	26 (13%)
Sex (n, % men)	58 (51%)	14 (54%)
Intake age (years)[b]	38.6 ± 10.8 (18–64)	43.3 ± 10.9 (23–63)
Years of illness	14.3 ± 10.0 (0.2–40)	17.4 ± 10.6 (0.7–43)
Manic versus mixed (% manic)	82.3	84.6
Psychotic features (% present)	54.0	50.0
Rapid cycling (%)[c]	34.5	23.0
Baseline total YMRS	28.0 ± 6.3 (20–56)	28.9 ± 7.6 (12–50)
Baseline total HAMD	13.5 ± 6.9 (0–31)	11.8 ± 7.0 (4–34)

YMRS = Young Mania Rating Scale; HAMD = Hamilton-Depression rating scale.
[a]Measures are percentages for binary, or mean ± SD (range) for continuous, measures.
[b]Continuing versus not-continuing data differed significantly only on intake age ($z = 1.99$, $p = 0.048$); no other comparisons differed significantly.
[c]Having had ≥4 DSM-IV episodes within 12 months of entering the study.

who continued with long-term treatment were 4.7 years younger at intake (Table 1).

The long-term subjects (n = 113) of the present study included 58 men and 55 women of average age 38.6 ± 10.8 years, with a past history of 43.1 ± 78.7 (0–464) episodes/subject over an average of 14.3 ± 10.0 years of illness, averaging three episodes/year. Presenting illnesses were 'pure' mania in 82.3%, and mixed-states in 17.7%; 54.0% had psychotic features; 34.5% had at least four discrete episodes of illness within 12 months of entering (DSM-IV rapid-cycling); and 64.6% had a lifetime history of DSM-IV substance use. Of the 113 long-term subjects, 44 (38.9%) completed the entire 52-week protocol, and exposure to olanzapine averaged 27.9 ± 20.1 weeks, with a mean daily dose of olanzapine *at endpoint* of 13.2 ± 5.5 (median 15.0, range 5.0–20.0 mg/day).

Characteristics of patients achieving symptomatic remission

Criteria for *symptomatic remission* of mania (2) were met by 79 of 113 (69.9%) subjects at some time during the 1-year trial. Half achieved remission by week 8 (95% CI 6–10 weeks), taking censoring at the time of dropout into account. Characteristics of remitted versus non-remitted patients were very similar by most measures (as in Table 1) used to compare the long- and short-term sub-samples (data not shown). The only significant difference found at baseline was a slightly lower initial CGI-BP score among remitted subjects (4.38 ± 0.76 versus 4.85 ± 0.86; $z = 2.73$, $p = 0.006$). There was also a plausible, nearly ninefold, greater rate of trial-completion among subjects achieving remission versus those who did not [53% versus 6%; χ^2 ($df = 1$) = 33.9, $p < 0.001$].

Of the 79 subjects who achieved symptomatic remission, 65 (82.3%) became symptomatic again at some time and 39 (49.4%) failed to sustain remission for at least 2 months so that only 40 of 113 (35.4%) achieved recovery. Time-in-remission averaged 19.3 ± 15.3 weeks (median 16, range 1–48 weeks) representing 52.2 ± 26.5% (range 4.2–92.3%) of total treatment-exposure.

Characteristics of patients achieving sustained clinical recovery

Over two-thirds of manic subjects (79/113 = 69.9%) attained symptomatic remission within 1 year of treatment with olanzapine, but only about one-third (40/113 = 35.4%) sustained such remission for ≥8 weeks to be considered *clinically recovered*. Time-in-sustained-recovery measured from the first week at which the criteria were achieved, averaged 31.65 ± 13.7 (median = 38; range, 8–50) weeks. Achieving recovery, and time-to-recovery, were contrasted between subgroups defined by selected clinical factors by estimated HRs (with 95% CIs; Table 2). As with remission, most contrasts (notably, age and sex, presence of initial psychotic features, rapid-cycling and other indices of prior morbidity) did not indicate differences between recovered and non-recovered subjects.

An exception was that above-median baseline HAMD scores (>12) were followed by a more than two-fold lower likelihood of recovery (HR: 2.13; 95% CI: 1.15–3.93; Table 2). Among the 63 subjects presenting with relatively high HAM-D scores >12, 49 (78%) were manic and only 22% were in mixed states, suggesting that many manic patients had dysthymic features. Of the 40 subjects who recovered, 37 (92.5%) presented initially

Table 2. Demographic and illness characteristics of bipolar manic patients who did (A) or did not (B) achieve sustained clinical *recovery* within 52 weeks of treatment with olanzapine

Characteristics A versus B	Group A versus B[a]	HR (95% CI) [b]	*z*-score	p-value
Initial YMRS-total: >26 versus ≤26[c]	22/54 (40.7%) versus 18/59 (30.5%)	–[d]	–	–
Initial HAMD: >12 versus ≤12[c]	14/53 (26.4%) versus 26/60 (43.3%)	2.13 (1.15–3.93)	2.40	0.02
Rapid cycling: present versus absent	11/39 (28.2%) versus 29/74 (39.2%)	1.84 (0.94–3.58)	1.79	0.07
Index episode: manic versus mixed	37/93 (39.8%) versus 3/20 (15.0%)	0.38 (0.12–1.25)	1.59	0.11
Prior episodes: >15 versus ≤15[c]	21/60 (35.0%) versus 19/53 (35.8%)	1.41 (0.77–2.55)	1.12	0.26
Any comorbidity: present versus absent	30/77 (39.0%) versus 10/36 (27.8%)	0.71 (0.36–1.39)	1.00	0.32
Sex: women versus men	22/55 (40.0%) versus 18/58 (31.0)	0.75 (0.41–1.37)	0.94	0.35
Randomized: olanzapine versus placebo	23/59 (39.0%) versus 17/54 (31.5%)	0.78 (0.43–1.43)	0.80	0.42
Initial PANSS-total: >69 versus ≤69[c]	18/52 (34.6%) versus 22/61 (36.1%)	1.21 (0.67–2.20)	0.64	0.52
Substance use: present versus absent	24/73 (32.9%) versus 16/40 (40.0%)	1.10 (0.61–2.01)	0.33	0.74
Onset age: >20 versus ≤20 years	24/61 (39.3%) versus 16/50 (32.0%)	0.91 (0.49–1.66)	0.32	0.75
Initial CGI-BP: >4 versus ≤4[c]	19/53 (35.8%) versus 21/60 (35.0%)	0.96 (0.53–1.73)	0.14	0.89
Age: ≤38 versus >38 years[c]	20/53 (37.7%) versus 20/60 (33.3%)	0.99 (0.55–1.80)	0.02	0.98

YMRS = Young Mania Rating Scale; HAMD = Hamilton-Depression rating scale; CGI-BP = Clinical Global Impression, bipolar version.
[a]Tabulated are ratios (recovered versus at risk) and percentages for subjects within contrasting subgroups [A (n = 40) versus B (n = 73)] for defined characteristics in descending order of significance of differences in recovery rates. Note that only 40 of 113 subjects (35.4%) attained sustained clinical recovery, with half achieving recovery by 36 (95% CI 20–40) weeks, and 45% of these (18/40) later became symptomatic again.
[b]HR = Hazard Ratio [with 95% confidence interval (CI)] computed by Cox proportional hazards regression methods.
[c]Split at approximate medians.
[d]HR not computed as YMRS is critical in defining *recovery*.

in manic episodes, but those presenting in a mixed-state were 2.6-times less likely than manic patients to recover during long-term treatment with olanzapine (HR: 0.38; CI: 0.12–1.25; statistically not significant, Table 2). Indeed, no patient with a diagnosis of mixed manic-depressive episode and an initial HAMD score ≥12 (n = 14) recovered.

The time at which 50% of the subjects remaining in the study achieved recovery, taking censoring into account, was 36 weeks (95% CI 20–40 weeks). Subjects with relatively high baseline HAMD scores (>12) not only were significantly less likely to achieve recovery (26.4% versus 43.3%) during long-term treatment with olanzapine, but their Kaplan–Meier survival-analysis-computed time-to-40% of subjects attaining recovery was thrice longer [36 (95% CI 20–52) versus 12 (CI 10–32) weeks; $z = 2.40$, $p = 0.016$; Fig. 1]. We also found that, at endpoint, mean improvements in YMRS scores (94.4% versus 62.3%, a 1.52-fold difference), and especially HAMD scores (72.1% versus 29.2%, 2.47-fold difference) were much greater among patients who attained sustained clinical recovery versus those who did not (data not shown; statistical tests were not applied as these ratings were used in the definition of remission and recovery). Finally, of the 40 patients who achieved and sustained recovery for at least 2 months, 18 (45.0%) later failed to meet the required symptomatic criteria. Time in clinical recovery (measured from the first week at which criteria were achieved)

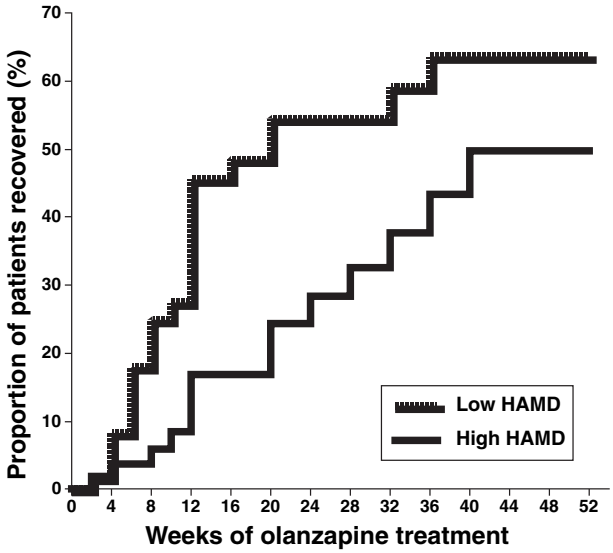

Fig. 1. Latency to the start of sustained recovery from an acute manic or mixed episode in 113 bipolar I patients in subgroups with relatively high (>12; n = 53; solid line) or low (≤12; n = 60; dotted line) baseline HAMD ratings of initial dysphoria. Times by which 40% of the sub-samples achieved recovery were 36 weeks (95% CI: 20–52) in the high baseline HAMD subgroup and 12 weeks (CI: 10–32) in the low HAMD subgroup; Cox HR 2.13, (95% CI: 1.15–3.93; $z = 2.40$, $p = 0.016$). Weeks to recovery by 40% of subjects were used as the outcome criterion in this contrast rather than weeks until 50% recovered because fewer than half of the subjects in the high baseline HAMD subgroup achieved recovery, even after taking censoring into account. Including age and sex as covariates in this Cox modeling did not appreciably alter the outcome.

averaged 31.6 ± 13.7 (median 38, range 8–50) weeks.

Treatment discontinuation

Treatment discontinuation during long-term, open-label treatment was much more common among non-recovered subjects than among those achieving recovery. Among the 40 recovered subjects, 30 (75.0%) continued treatment with olanzapine to the week 52 study-endpoint, but of the 73 non-recovered subjects, only 14 (19.2%) continued for a year [χ^2 (df = 1) = 33.9, p < 0.001]. Specific reasons for discontinuation [available for 49 of the 113 subjects, of whom 28 (57.1%) failed to complete a full year of treatment] ranked: physician or patient-perceived lack of efficacy (34.7%); patient decision (8.2%); loss-to-follow-up (6.1%); physician decision (4.1%); averse event (2.0%); or extension entry criteria not met (2.0%). The remaining 21 subjects (42.9%) completed the protocol.

Treatment options and recovery

For varying periods of time, 15 of 113 subjects treated long-term with olanzapine had lithium added clinically (744 ± 443 mg/day), 14 received supplemental fluoxetine (23.5 ± 12.2 mg/day), and none received both. Recovery rates were 2.6-times higher among those given adjunctive fluoxetine treatment (71.4%) versus olanzapine alone (27.4%) and 1.5-times greater than with lithium added to olanzapine (46.7%). However, by Cox proportional hazard modeling (with limited statistical power because of the small numbers of subjects given adjunctive treatments), recovery rates with olanzapine + fluoxetine ($z = 1.60$, $p = 0.11$) as well as olanzapine + lithium ($z = 0.30$, $p = 0.76$) did not differ significantly from recovery rates among subjects treated with olanzapine alone. Use of lorazepam was not related to recovery rates (data not shown).

Functional outcomes

Symptomatic recovery was associated with substantial improvement in some self-ratings of general health or physical, psychological, and psychosocial well-being, as assessed using the SF-36 scale. Sub-scale scores for physical vigor at baseline and end-point did not differ between recovered and non-recovered subjects (data not shown). However, on average, baseline-to-end-point percentage improvements in self-assessed general psychosocial functioning were rated as being 3.3-times larger among recovered than non-recovered subjects (Table 3).

Table 3. Functional outcomes in manic subjects within 52 weeks of olanzapine treatment versus achieving sustained clinical recovery[a]

Characteristic[b]	Recovered	Not recovered	*z*-score[c]	p-value
Subjects [n (%)]	40 (35.4)	73 (65.6)	–	–
SF-36 Psychosocial functioning[d]				
Baseline	42.2 ± 28.0 (40)	46.7 ± 31.0 (69)	0.79	0.43
Endpoint	78.8 ± 25.2 (40)	57.5 ± 28.9 (72)	4.07	<0.001
Mean percentage-change	86.7%	22.9%	3.90	<0.001
Doing any work[e]				
Baseline	2.69 ± 1.40	2.07 ± 1.40	2.15	0.032
Endpoint	2.62 ± 1.33	1.57 ± 1.40	3.99	<0.001
Employed for pay				
Baseline	26/38 (68.4%)	38/69 (55.1%)	1.28	0.20
Endpoint	13/40 (32.5%)	22/73 (30.1%)	0.26	0.80
Receiving disability compensation				
Baseline	24/40 (60.0%)	35/71 (49.3%)	1.04	0.30
Endpoint (LOCF)	20/40 (50.0%)	34/71 (47.9%)	0.21	0.83

[a]Endpoint is the last subject-specific assessment, not the last assessment at the end of the trial. Thus, there are 'employed for pay' data at endpoint for essentially all subjects. Baseline data for 'employed for pay' might be missing a few observations because some subjects may have declined to answer this question at the beginning of the trial.
[b]Data are n (%) or mean percentage-change ± SD; data were missing for some subjects.
[c]Random effects modeling methods were used to examine baseline and endpoint differences between recovered versus not recovered subjects, and for recovery × time interactions (none of which was significant: all $z \leq 1.55$, all $p \geq 0.12$). We tested 'Doing any work' with an ordered-probit random-effects model, and 'Employed for pay' and 'Receiving disability compensation' with random-effects logistic regression models.
[d]SF36 items (scaled at 0–100) provide self-assessments of functioning; data are means from psychosocial function items of this broad health-survey questionnaire.
[e]'Work' was rated on a 5-point scale (4 highest, 0 lowest); means ± SD are provided (all scores ranged from 0 to 4).

Additional ratings of capacity to perform useful work, based on a five-point rating scale showed interesting, though statistically non-significant trends (Table 3). End-point ratings of capacity for work were one point on a five-point scale (20%) higher for recovered than non-recovered patients (2.6 versus 1.6). There was a moderate overall decline in these work function ratings across all subjects, but this decline was considerably smaller on average, among recovered patients (2.6 versus 1.6; $z = 3.99$, $p < 0.001$). There was a moderate overall decline in these self-reported work function ratings across all subjects, but this decline was considerably smaller on average, among recovered (2.6%) than non-recovered patients (24.2%). Rates of self-reported unemployment were high for both recovered and non-recovered subjects. Nearly one-third of all subjects reported not working for pay at endpoint, and unemployment rates were similar in both those who recovered from mania (32.5%) or did not (30.1%; Table 3).

Perhaps reflecting prolonged and severe illness, both recovered and non-recovered patients had high rates of support by disability insurance, both at baseline (40.0% versus 50.7%), and at endpoint (50.0% versus 52.1%, respectively). These proportions did not differ significantly between recovered and non-recovered subjects (Table 3), and emphasize the high level of functional disability within the sample despite marked symptomatic improvements.

Discussion

This study, based on unblinded treatment up to a year (average of 6.5 months) following a previously reported 3-week double-blind placebo-controlled trial of olanzapine for mania (8, 10), involved 113, initially hospitalized, BP-I patients recovering from an acute index episode of mania or a mixed-state, for up to 1 year. The present findings are limited by the clinical, though protocol-guided, nature of the treatment administered, by unblinded assessments during long-term treatment, the limited and largely self-reported ratings of functional changes, and the small numbers of subjects in some sub-groups of potential interest. The findings reported should be considered as largely preliminary, and in need of prospective verification in blinded long-term trials, including subjects with less severe and long-lasting illnesses that may limit treatment responsiveness (4, 27). The operational categorizations of symptomatic remission and sustained clinical recovery appear to be useful ways of evaluating outcomes of greater clinical importance than statistical differences in partially improved rating scale scores between an active drug and a placebo (1–3).

Despite their methodological limitations, the present analyses yielded some important and only partially expected observations. First, within a year of continuous treatment, remission of symptoms of acute manic or mixed episodes was achieved by nearly 70% of the patients studied, and half attained this very substantial level of improvement by 8 weeks of treatment with olanzapine. These results are consistent with the findings of another recently-reported longitudinal study, which evaluated time to initial stabilization following an index manic, depressive, or mixed/cycling episode in 151 BPD patients and assessed the effectiveness of interpersonal social rhythms therapy combined with lithium and adjunctive medicines assigned by a treatment algorithm (17). In this study, in which stable symptomatic remission on a constant medication regimen for 4 weeks was defined by score criteria on the 17-item HAMD and Bech–Rafaelsen Mania scales (15, 18), patients presenting with mania required on average, 11 weeks to stabilize initially, those presenting in BP depression required 24 weeks, and those presenting with mixed/cycling episodes needed 40 weeks (17). These findings support the impression that depressive or dysphoric components of BP psychopathology may be associated with particularly limited or slow treatment responses (17).

In the present study, symptomatic remission maintained for at least 2 months (*sustained clinical recovery*) was achieved by only 35% (40/113) of acutely manic BP-I patients, with a median latency of 36 weeks. Longer latency (Fig. 1) and lower likelihood of recovery (Table 2) were predicted by baseline HAMD scores. Moreover, 45% of the recovering patients later failed to sustain required symptomatic improvement criteria. These findings indicate strikingly sluggish, less than universal, and unevenly sustained recovery among initially hospitalized adult BP-I patients in mid-course of relatively severe and highly recurrent BP-I illnesses, and suggest further that depressive or dysthymic symptoms were unfavorable prognostic features.

Even among patients attaining sustained symptomatic recovery within a year of clinical treatment, *functional* recovery was generally uncommon: only one-third of recovered patients (32.5%, Table 3) were gainfully employed at endpoint, and half received disability compensation (Table 3). As data on premorbid levels of education or work status were not obtained, we do not know whether these levels of unemployment and

disability were recent or long-standing. Knowledge of baseline or premorbid functional status is critically important in assessing the impact of treatment on functional status.

We also considered whether subgroups of patients without a history of substance abuse, rapid-cycling, or psychotic features might fare worse, given that such features have been considered predictors of poor outcomes in BPD (19–22). Although their power was limited, our additional statistical analyses (data not shown) indicated that high episode-counts, recent rapid cycling, and initial psychotic features did not account for the relatively poor functional outcomes encountered in the present study. Moreover, time-ill before treatment and prior episode counts may not determine long-term therapeutic effects of some mood-stabilizing agents (23–25), although rapid-cycling limits response to most treatments (26).

Evidence that such poor outcomes may not be entirely be explained by severe or long-standing illness is provided by two recent *first-episode* studies of DSM-IV BP-I patients (4, 27). In one of these, syndromal recovery (defined as no longer meeting DSM-IV criteria for mania or a mixed state) was achieved by 98% of manic/mixed patients at 2 years (4). However, only 43% achieved functional recovery (defined as both occupational level and residential status returned or exceeded the preintake level). Similarly a functional recovery rate of 35.0% at 12 months was noted in another first-episode mania study (27).

Overall, these several findings are congruent with an emerging view that acute episodes of BPD often are only slowly responsive to modern treatments (4, 17, 28–30), with high levels of remaining symptoms and disability, both late in the course of the illness (5–7) and even following first lifetime manic/mixed episodes (4, 27, 28). Clinical histories and responses to treatment like those of the present subjects are commonly encountered in contemporary clinical practice, particularly in specialized or academic centers (4, 17, 28–30). This representation of contemporary BP-I disorder does not support views suggesting it is a relatively benign disorder, with high levels of treatment responsiveness and a favorable prognosis. To the contrary, we suggest that the picture presented here is clinically realistic, and that it encourages redoubled efforts to improve treatment of this very common disorder (1–7).

Symptomatic remission was predicted only by slightly lower initial global clinical ratings of illness severity, and was strongly associated with longer retention in an open trial of continuation treatment with olanzapine. Overall, the median time to the start of recovery in the present study was 36 (95% CI 20–40) weeks. These results are similar to the median latency to major clinical stabilization of acutely ill mixed episode/cycling BP-I patients of 40 weeks in another recent study (17). Among the 113 subjects in the present study, sustained clinical recovery was dependent on low initial severity of dysphoria or depression, and perhaps lack of rapid cycling (Table 2; Fig. 1). Recovery was half as likely and arrived 24 weeks later, on average, among manic subjects with initially high (HAMD ≥12) depression scores. Similarly, in an ongoing first-episode study, below-median HAMD depression rating scores were predictive of attaining functional recovery at 6 months (4). No other clinical or demographic factors predicted recovery or its latency in the present study.

The apparently deleterious impact of depressive or dysphoric features associated with initial mania as well as mixed-states calls for particular emphasis. Non-bipolar major depressive disorder is associated with significant disability (31). A series of recent studies in prospective followup of BP-I patients under standard contemporary clinical treatment regimens, is spent in depressive or subsyndromal dysthymic states, and much less in mania or hypomania (5–7). In BPD, depression appears to be associated strongly with long-term disability (31, 32) and morbidity, and contributes importantly to extraordinarily high risks of excess mortality, especially by suicide (33). It is particularly ironic, therefore, that BP depression remains one of the least well studied forms of major depressive illness, and that the status of traditional antidepressant treatment for this disorder remains surprisingly ambiguous (34–35). In short, we suggest that unresolved depressive symptoms may contribute especially importantly to incomplete symptomatic remission, lack of sustained clinical recovery, and perhaps lead to major dysfunction and disability that appear to be characteristic of presumably well-treated, modern BP-I disorder, even from the onset of the illness.

In conclusion, our findings indicate that symptomatic remission and sustained clinical recovery were achieved only by some manic patients and after months of delay. These findings accord with other studies indicating high levels of sustained morbidity and dysfunction, not only among BP-I disorder patients after many episodes and years of illness, but even following first-lifetime episodes of mania (4, 27–28). These data although requiring prospective, controlled verification should be considered in clinically realistic designs of future experimental therapeutic studies aimed at optimizing long-term symptomatic and functional recovery in BPD

patients, with particular regard to the challenge of safe and effective long-term treatment of BP depression and dysthymia. Finally, outcomes that objectively assess premorbid, illness-associated, and treatment-responsive levels of occupational productivity and role functioning are needed to assess the true clinical impact of modern treatments for BPD.

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