Comparison of Rapid-Cycling and Non–Rapid-Cycling Bipolar I Manic Patients During Treatment With Olanzapine: Analysis of Pooled Data

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Introduction: Rapid-cycling (RC) bipolar disorder patients experience high levels of morbidity, typically respond unsatisfactorily to available treatments, and, so, require additional studies of novel treatments. We report on the first controlled study comparing acute and continuous clinical outcomes in RC and non-RC manic patients treated with olanzapine.

Method: We analyzed data pooled from 2 placebo-controlled, double-blind, 3- to 4-week trials of olanzapine in mania (N = 254), 1 with an open-label extension up to 1 year (N = 113) and controlled supplementation with lithium or fluoxetine as needed, to compare demographic, clinical, and outcome measures between RC and non-RC subgroups of 254 DSM-IV bipolar I manic subjects.

Results: RC (N = 90, 35%) versus non-RC subjects (N = 164, 65%) were younger at intake ($p = .02$), less often psychotic ($p < .0001$), and more likely to have familial bipolar disorder ($p < .0001$), abused substances ($p = .01$), more previous hospitalizations ($p = .004$), and many more illness episodes ($p < .001$). In initial blinded trial outcomes, relative responses (≥ 50% improvement of mania) to olanzapine/placebo were similar in RC and non-RC subjects, though early responses to olanzapine favored RC over non-RC subjects ($p = .003$), and long-term outcomes favored non-RC subjects ($p = .05$). Fewer RC subjects achieved strictly defined initial symptomatic remission ($p = .014$) within a year; RC subjects were more likely to experience recurrences ($p = .002$), especially of depressive illness (< .001), and had more rehospitalizations ($p = .01$) and suicide attempts ($p = .03$).

***Conclusions*:** RC bipolar I patients showed major initial differences and more rapid initial clinical changes, especially toward depression, with less favorable long-term outcomes than non-RC cases during treatment with olanzapine. Inclusion of RC bipolar disorder patients can complicate therapeutic trials, but these patients require further study for differential responsiveness to innovative treatments with methods of assessing clinical response that take their mood instability into account.

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Rapid-cycling (RC) in bipolar (manic-depressive) disorder, involving at least 4 recurrent episodes of acute illness within 1 year, was defined by Dunner and Fieve in 1974[1] and included as a course specifier in DSM-IV.[2] Characteristics of RC patients and their responses to treatment have been reviewed recently.[3–13] Point-prevalence estimates of RC among bipolar disorder patients range from about 12% to 24%, and average about 16%, in recent studies of bipolar disorder patients not selected for cycling rates.[5,6,9,12] Risk of RC usually is found to be somewhat greater among bipolar II patients, women, and juvenile cases, and RC patients may have a relatively early age at onset of bipolar disorder.[6,9,10,12,14,15] Although response to treatment in RC patients is widely believed to be compromised, controlled comparisons of treatment responses among RC versus non-RC patients are quite limited. A recent comprehensive meta-analysis of available trials comparing RC and non-RC cases with various

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mood-stabilizing treatments found that RC was consistently associated with substantially inferior responses to all types of treatment that have been studied.[13] A major clinical challenge is to develop more effective long-term treatments for the RC forms of both types I and II bipolar disorder.[11,13]

Two recent randomized placebo-controlled trials that examined the efficacy of olanzapine for the treatment of acute mania[17,18] identified RC and non-RC subjects and provided an opportunity to compare their responses to a novel treatment. We analyzed a pooled dataset[19] from these trials that allowed us to compare clinical characteristics and treatment outcomes in large samples of DSM-IV RC and non-RC type I bipolar disorder patients not designed to be selective for RC cases. Comparisons included the initial 3- to 4-week, randomized, placebo-controlled phases of both trials,[17,18] as well as a long-term, open-label treatment with olanzapine up to a year in one of the trials.[17]

METHOD

Subjects

Methods for the trials from which data were pooled, including diagnostic and clinical assessment methods, procedures for review by human studies committees, and requirements for written, informed consent by participants, are detailed in their primary reports.[17,18] The data-pooling process and its justification also are detailed elsewhere.[19] The process of pooling data from 2 separate randomized clinical trials may yield combined samples that are no longer strictly randomized; nevertheless, detailed comparisons of many salient demographic and clinical factors supported pooling of the samples and treatment arms as highly similar.[19] Moreover, in the analyses reported here, statistical adjustments in multivariate regression modeling procedures provide for reliable estimates of treatment effects even with imperfectly randomized pooled samples.

RC was defined by DSM-IV criteria as ≥ 4 mood episodes within 12 months of study entry.[2,17–19] The pooled sample[17–19] included 254 bipolar I (DSM-IV) patients not selected for RC status, presenting initially in acute manic or mixed episodes requiring hospitalization, and assigned to 3 or 4 weeks of double-blinded treatment with olanzapine or placebo monotherapy (with moderate doses of lorazepam permitted as needed clinically). Of these 254 subjects, 113 subjects elected to continue open-label treatment with olanzapine for up to 12 months, with controlled treatment supplementation with lithium carbonate or fluoxetine hydrochloride, permitted as indicated clinically.[17]

Clinical Assessments

Clinical assessments were performed weekly in both short-term blinded trials, and, in the open-label continuation trial, assessments were performed every 2 weeks for 3 months, and monthly thereafter up to a year. Clinical outcomes were defined in various ways in order to explore potential differences in treatment responses between RC and non-RC patients. Since changes in standard clinical rating scale scores have been a widely employed outcome measure, we included analyses based on percentage change in Young Mania Rating Scale (YMRS)[20] scores (from a required entry criterion score of ≥ 20), the proportion of subjects reaching at least 50% improvement in such mania ratings, and the latency to this ≥ 50% improvement criterion.

In addition, we included much stricter criteria for initial symptomatic remission and sustained clinical recovery recently proposed by Chengappa and colleagues[21] that make use of YMRS scores together with Hamilton Rating Scale for Depression (HAM-D)[22] scores and the Clinical Global Impressions scale for bipolar disorder (CGI-BP)[23] scores. By these strict criteria, initial symptomatic remission was defined as a YMRS score of ≤ 7; a HAM-D score of ≤ 7; a CGI-BP score of ≤ 2; the YMRS irritability, speech, content, and aggressive disruptive behavior items scored at ≤ 2; and all 7 other YMRS items scored at ≤ 1.[21] Sustained clinical recovery was defined as strict remission sustained for at least 8 weeks[21] and so was relevant only to long-term treatment.

Times to event in the open-label extension were assessed as weeks from the onset of olanzapine treatment. That is, for short-term blinded trial subjects initially given placebo, olanzapine treatment was dated from the end of the blinded trial period so that the times to recovery for all subjects were assessed as weeks of olanzapine treatment prior to recovery.

Postbaseline relapses or recurrences of affective illness were operationally defined as follows: (a) for new mania, occurrence of a YMRS score of ≥ 20 following a prior score of ≤ 10; (b) for depression, occurrence of a HAM-D score of ≥ 15 following a prior score of ≤ 8; (c) for a new mixed state, occurrence of a YMRS score of ≥ 20 and simultaneous HAM-D score of ≥ 15 following prior scores of ≤ 10 and ≤ 8, respectively; and (d) for hypomania, occurrence of a YMRS score of 15 to 19 following a prior score of ≤ 10.

Data Analyses

For continuous/binary measures assessed over time, we used generalized-estimating-equation (GEE)-based methods, with adjustment for clustering within subjects, except that, for some contrasts, last-observation-carried-forward (LOCF) methods were used. For categorical measures, we used contingency tables (yielding χ^2 [df = 1] summary statistics) to compare RC and non-RC subjects or the Fisher exact statistic (and associated p value) with tables having < 10 subjects per cell. For single timepoint continuous measures, including measures of previous morbidity, we

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used generalized linear modeling (GLM) methods with Gaussian family for continuous measures and binomial family and logarithmic link for binary measures; these analyses yield a z statistic (and associated p value) for each explanatory effect examined. Data for some measures of previous morbidity were first logarithmically transformed to provide more nearly Gaussian distributions. In GLM analyses of binary outcomes, we obtained estimated risk ratios (RR) and their 95% confidence intervals (CIs). For CGI contrasts, we employed ordered logistic regression modeling methods, yielding χ^2 (df = 1). For counts of new illness episodes and severe adverse events postbaseline, we used Poisson models, with adjustment for times of exposure (both yielding χ^2 [df = 1]).

Survival analytic methods were used for time-to-event contrasts. Discrete-time analytic methods were used for time to ≥ 50% improvement in YMRS score in the blinded trials.[24] Cox proportional hazards modeling methods were used to contrast RC versus non-RC subjects on weeks to strictly defined recovery in the open-label extension. These survival analysis models permitted adjustment for effects of specified covariate risk factors. For regression and proportional hazards modeling, goodness-of-fit and applicability of proportional hazards assumptions were checked graphically.

Robust standard error estimates were used wherever feasible. Categorical data are reported as number and percentage of subjects, and continuous or count data are reported as mean ± SD or mean and 95% CI, unless stated otherwise. Statistical significance required 2-tailed $p < .05$. Computations employed standard statistical programs (Stata, Stata Corporation, College Station, Tex., or Statview-5, SAS Institute, Cary, N.C.).

RESULTS

Subject Characteristics

The pooled sample of 254 bipolar I manic subjects included 90 RC (35.4%) and 164 non-RC (64.6%) patients. These subgroups differed in several ways (Table 1). RC patients were 3 years younger at intake and 2 years younger (not significant) at estimated onset of bipolar disorder. Among first-degree relatives including children of the patients, RC subjects also had significantly higher rates of mood (1.9 times more bipolar, 1.6 times more depressive) and substance use disorders (1.4 times). RC and non-RC subjects both averaged 15 to 16 years of total illness, but, as expected, RC cases had many (4 times, based on medians) more prior episodes and a 4.2-fold higher mean annual recurrence rate, as well as a 1.9 times higher mean hospitalization rate, on average. However, the RC and non-RC subgroups differed very little in measures of psychiatric or medical comorbidity (Table 1).

RC subjects were significantly (1.3 times) more likely to have abused alcohol or drugs (Table 1). For individual substances, data are limited, but rates of abuse for each of several types of substances were higher among RC subjects. Specifically, prevalence of abuse of alcohol, sedatives, or hypnotics was 12/90 (13.3%) in RC versus 5/163 (3.1%) in non-RC cases ($\chi^2 = 9.75$, df = 1, $p = .002$). Stimulants were abused by 17/90 (18.9%) RC versus 14/163 (8.6%) non-RC subjects ($\chi^2 = 5.72$, df = 1, $p = .017$). Use of tobacco also was more common in RC (67/90, 74.4%) than non-RC subjects (92/164, 56.1%; $\chi^2 = 8.36$, df = 1, $p = .004$).

RC and non-RC patients were similarly likely to present in pure manic or mixed states at study intake (Table 1). RC subjects were less likely to be considered to have psychotic features (35.6% vs. 64.6%), although Positive and Negative (Psychotic) Syndrome Scale (PANSS)[25] scores were similar in RC and non-RC cases (74.5 vs. 72.9). Ratings of presenting manic and depressive symptoms showed moderate, but significant, differences between RC and non-RC subjects, including lower YMRS scores and higher HAM-D scores in the RC patients.

In summary, by strength of univariate association, RC subjects (a) had many more past illness episodes, (b) were less likely to have psychotic features at intake, (c) were more likely to have had a history of substance use, (d) were more likely to have a family history of bipolar disorder, (e) were younger at intake, and (f) were more likely to have experienced previous hospitalizations (Table 1). In a multivariate logistic regression analysis, all but 1 of these factors (substance use) independently and significantly correlated with RC status, ranking: (a) previous illness episodes (adjusted OR = 5.45, 95% CI = 2.8 to 10.5), (b) lack of psychotic features at intake (OR = 3.32, 95% CI = 1.7 to 6.4), (c) younger age at intake (OR = 3.32, 95% CI = 1.7 to 6.6), (d) family history of bipolar disorder (OR = 2.88, 95% CI = 1.5 to 5.5), and (e) more hospitalizations (OR = 1.54, 95% CI = 1.2 to 2.0).

Short-Term, Blinded Treatment

In the 3- to 4-week blinded trial protocols,[17,18] a total of 44 RC subjects were assigned to olanzapine and 46 to placebo; 81 non-RC subjects were assigned to olanzapine versus 83 to placebo (Table 2). RC subjects had marginally lower mean initial YMRS scores than non-RC subjects, with a mean difference of about 8% at baseline in both the olanzapine and placebo subgroups. Initial percentage improvements in mean YMRS scores were similar in RC and non-RC cases, but the proportion of subjects with ≥ 50% improvement in YMRS scores was higher among RC (63.5%) than non-RC (49.1%) subjects ($\chi^2 = 4.68$, df = 1, $p = .030$). Moreover, RC patients attained ≥ 50% improvement in mania ratings significantly earlier than non-RC cases (hazard ratio = 1.50). Olanzapine had significant efficacy in both RC and non-RC subgroups, even though psychotic features were nearly twice

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Table 1. Characteristics of 254 Rapid-Cycling and Non–Rapid-Cycling Bipolar I Disorder Patients Treated With Olanzapine

Characteristic	Rapid-Cycling (N = 90)	Non–Rapid-Cycling (N = 164)	Statistic	p Value
Subjects, N/N (%)				
Continued long-term[a]	39/113 (34.5)	74/113 (65.5)	$\chi^2 = 1.26$	.26
Women, N (%)[b]	38 (42.2)	87 (53.0)	$\chi^2 = 2.73$	.10
Age, mean ± SD, y				
At onset	22.3 ± 8.8	24.1 ± 9.7	z = 1.51	.13
At intake	37.2 ± 9.4	40.2 ± 11.2	z = 2.30	.022
Family history, N (%)				
Substance use	58 (64.4)	78 (47.6)	$\chi^2 = 6.66$	.010
Depression	43 (47.8)	50 (30.5)	$\chi^2 = 7.49$	.006
Bipolar disorder	51 (56.7)	48 (29.3)	$\chi^2 = 18.3$	< .001
Mood episode at intake, N (%)[c]				
Manic	58 (64.4)	123 (75.0)	…	…
Mixed	32 (35.6)	41 (25.0)	$\chi^2 = 3.16$	.075
Psychotic	32 (35.6)	106 (64.6)	$\chi^2 = 19.8$	< .001
Past illness				
Time ill, mean ± SD, y	14.9 ± 9.8	16.1 ± 10.5	z = 0.92	.36
No. of episodes/case, median ± SD[d]	33.5 ± 100.5	8.0 ± 40.8	z = 6.79	< .001
No. of episodes/year, mean ± SD				
All types	7.7 ± 13.6	1.5 ± 2.4	z = 4.33	< .001
Depression	3.4 ± 7.0	0.6 ± 1.6	z = 3.41	.001
Mania/mixed	4.8 ± 7.5	0.9 ± 1.5	z = 4.93	< .001
No. of hospitalizations/case, mean ± SD	1.6 ± 2.0	0.8 ± 1.1	z = 2.92	.004
Comorbidity				
Psychiatric, N (%)	33 (36.7)	65 (39.6)	$\chi^2 = 0.22$	.64
Substance use ever, N (%)	63 (70.0)	91 (55.5)	$\chi^2 = 5.13$	.024
Medical (conditions/case), mean ± SD	1.64 ± 1.84	1.68 ± 2.01	z = 0.17	.87
Prior treatment response, N/N (%)				
Lithium	15/75 (20.0)	36/147 (24.5)	$\chi^2 = 0.57$	.45
Valproate	9/24 (37.5)	23/39 (59.0)	$\chi^2 = 2.74$	.098
Antipsychotics	17/25 (68.0)	35/48 (72.9)	$\chi^2 = 0.19$	.66
Initial morbidity scores, mean ± SD				
YMRS	27.6 ± 5.1	29.8 ± 6.5	z = 2.98	.003
HAM-D	17.2 ± 7.3	14.5 ± 8.1	z = 2.70	.007
PANSS	74.5 ± 16.9	72.9 ± 22.6	z = 0.65	.52
CGI-BP	4.7 ± 0.7	4.8 ± 0.9	z = 1.10	.27

[a]Proportion of the 113 subjects continuing in long-term open treatment.
[b]Rapid-cycling risk by sex: 38/125 (30.4%) women vs. 52/129 (49.3%) men ($\chi^2 = 2.72$, df = 1, p = .099).
[c]Mania is used as the comparator for Mixed and Psychotic.
[d]Median ± SD for highly skewed numbers of past episodes; analyses and rating methods are described in text.
Abbreviations: CGI-BP = Clinical Global Impressions scale for bipolar disorder, HAM-D = Hamilton Rating Scale for Depression, PANSS = Positive and Negative Syndrome Scale, YMRS = Young Mania Rating Scale.

as common among non-RC than RC subjects (Table 1). Relatively few subjects attained initial symptomatic remission[21] within the 3 to 4 weeks of blinded treatment, and these rates were similar in RC (14/85, 16.5%) and non-RC (37/161, 23.0%) subjects ($\chi^2 = 1.44$, df = 1, p = .23).

Remission and Recovery During Long-Term Treatment

Of the 113 subjects electing to continue open, long-term treatment with olanzapine, 39 (34.5%) were RC and 74 (65.5%) were non-RC; 44 subjects (38.9%) completed a full 12 months of treatment (17 RC and 27 non-RC). Subjects who continued open treatment were similar to those who stopped after the initial blinded trials by sex, presenting syndrome type, baseline rating scale scores, initial treatment with olanzapine or placebo, and degree of initial symptomatic improvement (data not shown). The total daily dose of olanzapine was 12.4 ± 5.9 mg at endpoint after 27.8 ± 20.0 weeks (7 months) of treatment with olanzapine, and neither doses nor treatment exposure times differed significantly between RC and non-RC subjects.

A large majority of RC (37/39, 94.9%) and non-RC (62/74, 83.8%) subjects achieved the criterion of a ≥ 50% improvement in YMRS score at some point during the 52-week open-label extension, and these proportions did not differ significantly between RC and non-RC subgroups (Table 3). Strictly defined initial symptomatic remission[20] during the open-label extension period was achieved by 69.9% (79/113) of subjects at 1 or more assessment times. A higher proportion of non-RC than RC subjects attained this rigorous outcome criterion. On average over all postbaseline assessments, RC versus non-RC rates of remission were 36.6% of 370 assessments versus 52.5% of 630 assessments, respectively (Table 3). This 1.5-fold difference, assessed over time by GEE-based

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Table 2. Response to Treatment for Manic Episode at Intake Among 254 Rapid-Cycling and Non–Rapid-Cycling Bipolar I Disorder Patients Treated in Short-Term (3–4 weeks) Randomized, Blinded Trials With Olanzapine or Placebo[a]

Condition	Rapid-Cycling (N = 90)	Non–Rapid-Cycling (N = 164)	Statistic	p Value
Subjects, N (%)				
Olanzapine[b]	44 (48.9)	81 (49.4)	$\chi^2 = 0.01$	.94
Placebo	46 (51.1)	83 (50.6)		
Continued long-term[c]	39 (34.5)	74 (65.5)	$\chi^2 = 1.26$	.26
Initial YMRS total score, mean ± SD				
Olanzapine	27.1 ± 5.1	30.3 ± 6.6	z = 3.02	.003
Placebo	27.6 ± 4.3	29.2 ± 6.6	z = 1.63	.10
YMRS score decrease, mean ± SD (%)	11.2 ± 10.3 (42.0)	8.9 ± 14.4 (30.9)	z = 1.44	.15
Olanzapine	14.8 ± 8.7 (55.0)	11.6 ± 15.2 (38.9)	z = 1.50	.13
Placebo	7.5 ± 10.6 (28.6)	6.2 ± 13.2 (22.9)	z = 0.60	.55
Drug effect, z score (p value)	3.51 (< .001)	2.45 (.014)	NA	NA
YMRS score improved ≥ 50%, N/N (%)	54/85 (63.5)	79/161 (49.1)	$\chi^2 = 4.68$	.03
Olanzapine	33/43 (76.7)	49/81 (60.5)	$\chi^2 = 3.31$	.069
Placebo	21/42 (50.0)	30/80 (37.5)	$\chi^2 = 1.77$	.18
Drug effect, χ^2 (p value)	6.56 (.010)	8.52 (.004)	NA	NA
Time to 50% improvement, median ± SD, wk[d]	2.0 ± 0.18	3.0 ± 0.20	z = 2.20	.03
Olanzapine	1.0 ± 0.13	2.0 ± 0.13	z = 1.87	.06
Placebo	2.0 ± 0.16	3.0 ± 0.17	z = 1.34	.18
Drug effect, χ^2 (p value)	5.30 (.021)	6.36 (.012)	NA	NA

[a]Denominators are subjects (total N = 246) with at least 1 postbaseline YMRS score. Statistics are χ^2 for categorical comparisons and z for continuous variables and hazard ratio contrasts.
[b]χ^2 and p values for this 2 × 2 comparison (olanzapine vs. placebo crossed with rapid-cycling vs. non–rapid-cycling) appear in the olanzapine row.
[c]Subjects are the 113 who continued in long-term, open-label treatment with olanzapine.
[d]Median latency, or weeks to 50% of subjects achieving ≥ 50% reduction of YMRS score. The corresponding hazard ratio (with 95% CI), based on discrete-time survival analysis methods, was rapid-cycling vs. non–rapid-cycling = 1.50, 95% CI = 1.05 to 2.14, z = 2.20, p = .03 and olanzapine vs. placebo = 2.00, 95% CI = 1.40 to 2.86, z = 3.79, p < .001.
Abbreviations: NA = not applicable, YMRS = Young Mania Rating Scale.

time series modeling methods, was statistically significant (z = 2.78, p = .006; Table 3). These RC versus non-RC differences in strictly defined clinical response rates over time are shown graphically (Figure 1).

Sustained clinical recovery (initial symptomatic remission sustained for at least 8 continuous weeks) was achieved by 40/113 (35.4%) participants in the open-label extension. Recovery rates were substantially higher among non-RC (29/74, 39.2%; 95% CI = 27.8% to 50.6%) than RC subjects (11/39, 28.2%; 95% CI = 13.4% to 43.0%). Median time to recovery in RC subjects (12 weeks) was 1.5 times longer than in the non-RC subgroup (8 weeks; Cox z = 1.76, p = .078; Table 3).

Use of Adjunctive Treatments, Long-Term

Adjunctive fluoxetine and lithium were permitted in the open-label extension protocol: 14/113 long-term subjects (12.4%) received fluoxetine, and 16/113 (14.2%) received supplemental lithium with olanzapine. Fluoxetine was used 4.7 times more often by RC patients, whereas lithium was given only to non-RC subjects. Rates of initial symptomatic remission were marginally higher in subjects taking adjunctive fluoxetine or lithium, but these differences were not statistically significant, nor did they vary between RC and non-RC subjects (data not shown). Subjects given fluoxetine were much more likely to experience depressive episodes during the study (8/14, 57.1% vs. 24/99, 24.2%; $\chi^2 = 6.54$, df = 1, p = .011), suggesting that emerging depression led to elective addition of the antidepressant. New depressive illness may well have limited sustained clinical recovery.

This hypothesis was supported by the finding that rates of sustained clinical recovery were 2.4 times higher among fluoxetine-treated subjects than those treated with olanzapine alone (10/14 [71.4%] vs. 30/99 [30.3%]; RR = 2.36, 95% CI = 1.51 to 3.69). This association did not differ between RC and non-RC subjects. Indeed, when considered together in a trivariate GLM model, both RC and adjunctive fluoxetine use were significantly correlated (in opposite directions) with recovery (data not shown). When adjusted for covariates (sex, current age, age at onset, baseline YMRS and HAM-D scores, presence of psychotic features, substance use history, and number of previous episodes or hospitalizations), the adjusted RR estimates for adjunctive fluoxetine all remained statistically significantly different from 1.0 (data not shown). Indeed, disregarding RC status, these RR estimates all exceeded 2.0, suggesting that use of adjunctive fluoxetine was associated with at least a 2-fold better chance of attaining clinical recovery. Lithium augmentation was not correlated with recovery (data not shown).

New Morbidity During Long-Term Treatment

During long-term, unblinded treatment with olanzapine, 50/113 subjects (44.2%) had a total of 98 new mood episodes within 12 months; 56 episodes occurred in 39

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Table 3. Response Among Rapid-Cycling and Non–Rapid-Cycling Bipolar I Patients to Treatment With Olanzapine up to 1 Year (N = 113)[a]

Condition	Rapid-Cycling (N = 39)	Non–Rapid-Cycling (N = 74)	Risk Ratio (95% CI)[b]	Statistic[b]	p Value
Adjunctive treatment, N (%)					
Lithium[c]	0 (0.0)	16 (21.6)	…	exact	.001
Fluoxetine	10 (25.6)	4 (5.4)	4.74 (1.59 to 14.2)	exact	.005
Both	10 (25.6)	20 (27.0)	0.95 (0.49 to 1.83)	z = 0.025	.87
Long-term outcomes[d]					
Initial YMRS total score, mean ± SD	27.0 ± 4.1	29.2 ± 6.2	…	z = 2.25	.02
≥ 50% Improvement in YMRS score, N (%)	37 (94.9)	62 (83.8)	1.13 (1.00 to 1.28)	z = 1.96	.050
Symptomatic remission, N/N (%)	128/370 (34.6)	331/630 (52.5)	0.68 (0.51 to 0.92)	z = 2.78	.006
Sustained recovery, N (%)	11 (28.2)	29 (39.2)	0.70 (0.39 to 1.25)	z = 1.21	.23
Time to onset of recovery, median ± SE, wk	12.0 ± 17.6	8.0 ± 15.0	0.52 (0.25 to 1.08)	z = 1.76	.078
New illness, N (%)					
Any episode	27 (69.2)	23 (31.1)	2.28 (1.38 to 3.80)	z = 3.10	.002
Depression	21 (53.8)	11 (14.9)	3.42 (1.71 to 6.80)	z = 3.48	< .001
Hypomania	11 (28.2)	13 (17.6)	1.37 (0.64 to 2.90)	z = 0.82	.42
Mania	11 (28.2)	10 (13.5)	2.02 (0.87 to 4.70)	z = 1.64	.10
Mixed state	3 (7.7)	2 (2.7)	2.56 (0.45 to 14.6)	z = 1.06	.29
Suicide attempted, N/N (%)	8/36 (22.2)	5/71 (7.0)	3.16 (1.11 to 9.00)	z = 2.15	.03
Hospital contacts, N (%)					
Rehospitalization	15 (38.5)	12 (16.2)	2.37 (1.23 to 4.57)	z = 2.58	.01
Emergency unit visited	29/38 (76.3)	44/74 (59.5)	1.28 (0.99 to 1.66)	z = 1.88	.06

[a]Subjects with ≥ 1 YMRS score during open-label, long-term treatment or otherwise providing pertinent data.
[b]Statistics are χ^2 (df = 1) (or Fisher exact p value) for categorical variables (including proportion of subjects with new episodes) and z for continuous variables.
[c]Lithium is used as the base category in estimating the risk ratios for Fluoxetine and Both.
[d]Symptomatic remission and sustained recovery (defined in text) in long-term, open-label extension. Symptomatic remission rates are averaged over all postbaseline assessments. Risk ratios estimated by generalized linear modeling–based methods (binary outcomes) or by Cox proportional hazards regression modeling (time-to-recovery outcomes).
Abbreviation: YMRS = Young Mania Rating Scale.

RC subjects, and 42 occurred in 74 non-RC subjects (Table 3). Among the 50 patients with at least 1 recurrence, 21 subjects had 2 and 9 subjects had ≥ 3 new mood episodes. Mean counts of recurrent episodes of all modalities were 2.98 ± 3.92 (RC) and 1.51 ± 3.67 (non-RC) episodes. The corresponding RR, estimated by Poisson modeling methods adjusting for exposure time, was 2.28 (95% CI = 1.39 to 3.80; Table 3). There was an excess of all types of new episodes among the RC subjects, including new depressive, hypomanic, manic, and mixed states, although only for depression did the corresponding RRs differ statistically significantly from the null value of 1.0 (Table 3). The RC/non-RC RR for patients with new depression was 3.42 (95% CI = 1.71 to 6.80; Table 3), with a corresponding relative incidence of 20 new depressive episodes/39 RC patients (51.3%) versus only 11 episodes/74 non-RC cases (14.9%).

Hospitalizations and Suicide Attempts

Among 113 subjects continuing in the open-label extension, 27 (23.9%) had to be rehospitalized at least once (Table 3). Rates of rehospitalization were much higher among RC (15/39, 38.5%) than non-RC (12/74, 16.2%) subjects, with an associated RR, adjusted for time of exposure, of 2.37 (95% CI = 1.23 to 4.57; Table 3). There was also an excess of emergency service visits among the RC subjects (Table 3). Suicide attempt data were available for 107 subjects, among whom there were 13 attempts and no deaths, with a significant excess of attempts among RC subjects, at an exposure-adjusted RR of 3.16 (95% CI = 1.11 to 9.00; Table 3). Neither suicide attempts nor rehospitalizations were associated with adjunctive lithium or fluoxetine use.

Adverse Effect Reports

Symptomatic complaints considered to be possibly indicative of adverse effects of treatment were reported at 3 levels of severity—severe, moderate, and mild. Most of these complaints involved nonspecific effects, including excessive sedation, dizziness, increased appetite or weight, or diminished sexual interest. Among 246 subjects with at least 1 postbaseline assessment, 99 (40.2%) reported at least 1 severe adverse effect. There were 242 such events in all, with a mean of 2.4 ± 3.2 per affected person. Severe adverse effects were reported nearly twice as frequently among RC (48/85, 56.5%) than non-RC (51/161, 31.7%) subjects; the corresponding RR, adjusted for exposure time, was 1.64 (95% CI = 1.15 to 2.33, z = 2.76, p = .006; data not shown).

DISCUSSION

In this analysis of data derived from 2 recent trials of olanzapine treatment for acute mania, we examined RC versus non-RC differences in clinical characteristics and clinical outcomes. Compared with non-RC patients at

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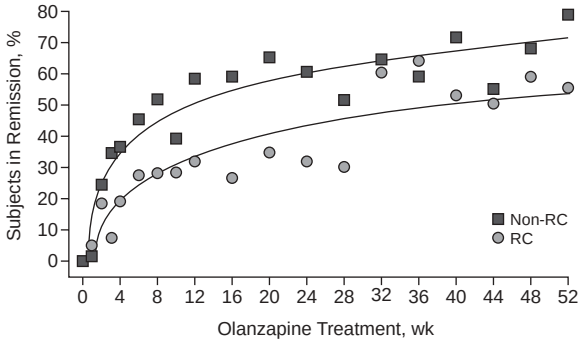
Figure 1. Proportion of 39 Rapid-Cycling (RC) or 74 Non–Rapid-Cycling (non-RC) Bipolar I Patients in Strictly Defined Remission Versus Weeks of Treatment With Olanzapine for Acute Mania[a]



[a]Lines represent best fit to the raw datapoints based on exponential function modeling. Clinical improvement among RC subjects was more erratic owing to sometimes-frequent shifting among morbid mood states over time. These differences between RC and non-RC subjects were highly statistically significant based on random-effects logistic regression modeling ($z = 3.64$, $p < .001$).

baseline, RC subjects (a) were more likely to have a family history of bipolar disorder, (b) were younger at intake, (c) were less likely to have psychotic features, (d) were more likely to have (lifetime) substance use histories, (e) were more likely to have experienced previous hospitalizations, and, as expected, (f) had many more past mood episodes. Both early and later outcomes also differed substantially between these RC and non-RC subgroups.

In the short-term blinded trials, RC subjects were more likely to achieve symptomatic improvement (≥ 50% improvement in YMRS score), in which they showed a significantly superior drug/placebo difference compared with non-RC subjects (Table 2). In the open-label extension involving treatment with olanzapine up to 1 year, RC subjects were significantly less likely than non-RC subjects to achieve strictly defined initial symptomatic remission or sustained clinical recovery. When adjusted for time of exposure using Poisson distribution based methods, the rate of recovery in RC versus non-RC subjects was 46.8%/year (95% CI = 23 to 84) versus 72.2%/year (95% CI = 48 to 100), respectively. Also, times to recovery were shorter for non-RC subjects than for RC subjects (Table 3). These differences in recovery rates are likely to be of clinical significance. RC subjects were more likely to require addition of the antidepressant fluoxetine but less likely to have lithium added. They also were more likely to experience recurrences of illness, especially depressive episodes, as well as to become suicidal and to require rehospitalization.

These findings convey several important impressions. First, over time, RC subjects suffered substantially more morbidity than non-RC subjects during long-term treatment with olanzapine (Table 3). This difference occurred even though both subgroups were reasonably well matched at baseline for illness severity and past duration of illness, current illness severity, and other salient demographic and clinical factors (Table 1). The greater morbidity among RC patients during a year of treatment parallels their generally more severe illness histories. Notably, the RC patients had over 6 times more prior mood episodes and 5 times greater risk of substance use than non-RC subjects (Table 1). RC patients also had more than 4 times higher average annual cycling rates, but it is not certain in what proportion of years of illness the RC subjects would have met the DSM-IV RC diagnostic criterion of ≥ 4 discrete episodes/year. Nevertheless, their mean recurrence frequency of 7.7 episodes/year (Table 1) suggests that they may well have cycled rapidly in most years. Previous studies suggest that RC status is not necessarily a sustained characteristic in all cases of RC bipolar disorder, and that some patients shift in and out of RC status at different times, either spontaneously or with exposure to prescribed or abused agents that may tend to increase (antidepressants, stimulants) or decrease (lithium, anticonvulsants, antipsychotics, and perhaps sedatives) cycling.[3,10,12]

There also were substantially higher rates of mood and substance use disorders among first-degree relatives of RC patients (Table 1), suggesting possibly higher heritability of RC forms of bipolar disorder. Nevertheless, it remains uncertain whether RC itself is an inherited trait separate from general risk of bipolar disorder or other related disorders, and data on cycling patterns among relatives were not available for analysis. We did not find a higher risk of RC among women (Table 1), and this outcome is both unexpected[14] and not readily explained. In addition, there was only a nonsignificant tendency toward expected[4–11] earlier onset of illness in the samples considered here (Table 1).

The present study supports the growing impression that RC patients, perhaps seemingly paradoxically, are highly responsive to various antimanic treatments in the short-term, probably owing in part to their natural tendency to move into and out of episodes more rapidly than non-RC bipolar disorder patients. A significantly higher proportion of RC (63.5%) than non-RC patients (49.1%) achieved a ≥ 50% improvement in YMRS score during the blinded trials, and they did so earlier than non-RC subjects (Table 2). RC subjects had higher early rates of achieving a ≥ 50% YMRS score improvement with olanzapine and also tended to do so with placebo.[26] In striking contrast, in long-term treatment, clinical outcomes were much less favorable for RC patients. They had lower rates of sustained remission and much higher rates of new illness, rehospitalizations, and suicide attempts than non-RC patients, despite ongoing treatment with olanzapine and sometimes with fluoxetine added (Table 3).

This striking discrepancy between outcomes in short-term versus long-term treatment suggests that outcome as-

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sessment based on the use of simple improvement in mania ratings may be seriously misleading. Although RC patients may well cycle out of mania more quickly than non-RC patients, they are also prone to shifting sooner into depressive or other new morbidity during follow-up. Early improvement in a single dimension of their morbidity misses the larger point that, overall, they spent much more time ill, even with an effective antimanic treatment supplemented with an effective antidepressant. It seems clear that much more reliable and valid measures of clinical improvement are required than a frankly arbitrary change in a single dimension of illness. Given the requirements of the strict criteria for symptomatic remission and clinical recovery that we employed,[21] it is likely that failure to achieve remission or recovery, despite substantial improvement in mania, reflects the tendency of RC patients to shift into depressive states relatively early, as reflected in their much higher risk of major depression and excess use of fluoxetine during long-term treatment (Table 3).

The dissimilarities of treatment responses in RC and non-RC subjects raise the question of whether or not to include them routinely in experimental therapeutic trials, especially in critically important, but logistically challenging and expensive, long-term trials. RC bipolar disorder patients have proved consistently to have inferior long-term responses to all mood-stabilizing treatments so far considered, including lithium and several anticonvulsants,[13] and now with olanzapine (Table 3), the first U.S. Food and Drug Administration–approved modern antipsychotic agent with proof of efficacy in mania, based largely on the trials[17,18] included in the present analyses, as well as for maintenance treatment in bipolar disorder. Similar, substantially inferior responses among RC patients have been reported for risperidone,[27] as well as olanzapine[28,29] and quetiapine[30] in other recent studies.

The striking dissimilarities in treatment response and long-term course variables between RC and non-RC bipolar I patients (Tables 1–3), including their tendency to shift directly out of mania into depression, indicate that assessments of these RC subgroups in future therapeutic trials may call for outcomes assessment methods with greater incisiveness than that provided by simple short-term improvement in mania ratings. We suggest that the multidimensional, as well as demanding, criteria for remission and recovery recommended by Chengappa and colleagues[21] may represent more appropriate outcome measures with RC patients, and indeed a more clinically relevant measure of major clinical improvement for use in trials of experimental treatments for both non-RC and RC bipolar disorder patients.

Evidence is growing that patients with bipolar I disorder spend consistently more time in depressive or dysthymic states than in mania or hypomania, especially after several years of illness.[31–33] Similar observations are arising from a study of first-episode manic patients followed up prospectively for several years.[34] There also is evidence that RC bipolar disorder is marked by a particularly striking excess of depressive morbidity over time.[35] This impression accords with the findings of this study, in which non-RC patients had similar risks of new depression and mania during long-term follow-up treatment, whereas the risk of new depressive illness (9 episodes among 39 patients) was greater than for new mania (5/39) among RC patients, while not differing among non-RC patients (5 new depressive and 5 new manic episodes among 74 persons; Table 3). Moreover, the relative annualized risk of new depression in RC/non-RC subjects was nearly 3.8, compared with 1.5 for new manic episodes (Table 3). There was also a nearly 5-fold excess of open-label use of supplemental fluoxetine treatment among RC patients (Table 3). It is important to point out that adding the antidepressant fluoxetine proved beneficial for both RC and non-RC patients in facilitating their attainment of strictly defined remission and sustained recovery during long-term treatment with olanzapine, which is at odds with claims against the use of antidepressants in rapid cyclers[36] but consistent with the results obtained with the combination of olanzapine and fluoxetine in both RC and non-RC in an 8-week controlled trial.[37]

Finally, the preceding observations support the important conclusion that, despite their potential for complicating the design and interpretation of experimental therapeutic trials, RC patients require redoubled efforts to define optimal maintenance treatments to minimize their high levels of long-term morbidity. Moreover, identifying improved, safe, and effective long-term treatments for the depressive-dysthymic phases of both types I and II bipolar disorder remains the central challenge for the therapeutics of the disorders.[38–40]

Drug names: fluoxetine (Prozac and others), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel).

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