Cognitive Change in the Year After a First Manic Episode: Association Between Clinical Outcome and Cognitive Performance Early in the Course of Bipolar I Disorder

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ABSTRACT

Objective: Cognitive impairments are present immediately following recovery from a first episode of mania, although at a lesser severity than those seen in more chronic patients with bipolar I disorder. Little is known about how deficits evolve over the course of illness, however, and whether these changes are associated with disease progression.

Method: Patients with bipolar I disorder (*DSM-IV-TR*) receiving naturalistic clinical follow-up from the Systematic Treatment Optimization Program for Early Mania (STOP-EM) from July 2004 to May 2013 completed a comprehensive cognitive battery following recovery from their first manic episode and again 1 year later. Performance was compared between patients who experienced a recurrence of a mood episode (BD_{recur}) (n = 26) versus those that maintained remission (BD_{well}) (n = 27) over follow-up, as well as healthy comparison subjects (HS) (n = 31).

Results: While both BD_{recur} and BD_{well} had impairments in overall cognitive performance relative to HS at baseline (mean difference = –0.59, $P < .001$; mean difference = –0.43, $P < .05$, respectively), at follow-up BD_{recur} showed deficits compared to both HS (mean difference = –0.62, $P = .001$) and BD_{well} (mean difference = –0.41, $P = .05$), with BD_{well} cognition similar to that in HS (mean difference = –0.21, $P > .4$). BD_{well} showed larger improvements over follow-up relative to both other groups ($P < .05$). While changes in BD_{recur} did not differ from HS, in this group more days in a manic or hypomanic episode was associated with performance declines ($r = –0.40$, $P < .05$).

Conclusions: While cognitive function improves in patients who sustain remission in the year following a first manic episode, those who experience a recurrence remain impaired, with performance declines being most apparent in those who experienced longer manic or hypomanic episodes.

J Clin Psychiatry 2014;75(6):e587–e593

Submitted: *December 11, 2013; accepted February 24, 2014 (doi:10.4088/JCP.13m08928).*
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Bipolar I disorder has a progressive course, with recurrence of each mood episode hypothesized to lead to a subsequent decrease in interepisodic recovery and functioning, higher frequency and severity of relapse, and reduced treatment response.[1] Even patients early in the course of illness suffer from alarming rates of recurrence, with over half of patients in recovery from their first manic episode experiencing another mood episode within 1 year of follow-up.[2] These patients also suffer from cognitive impairments of comparable severity to those seen in first-episode schizophrenia[3,4] that persist following pharmacologic treatment.[5] Indeed, the level of dysfunction during periods of euthymia is only modestly less severe than that seen during acute episodes,[6] with longitudinal studies consistently indicating that cognitive variability cannot be predicted by changes in mood symptoms.[7–10] Cognition may also decline with illness course: cross-sectional studies often report correlations with number of prior episodes, particularly of mania,[11] with direct comparisons of patients with a single versus multiple prior manic episodes also indicating that deficits progress.[12,13] While a previous report from the Systematic Treatment Optimization Program for Early Mania (STOP-EM) indicated that cognition does improve in the year following a first manic episode,[14] there have been no prospective studies examining how this relates to illness progression. As such, this study will compare changes in cognitive function between patients who remain well over follow-up, those who experience recurrence of a mood episode, and healthy subjects. We hypothesized that while continued recovery would be associated with improvements in cognitive function, recurrence would be accompanied by performance declines.

METHOD

Participants

Patients were identified immediately (≤ 3 months) following recovery from their first manic episode through the STOP-EM[15] at the University of British Columbia Hospital and affiliated sites. A *DSM-IV-TR*[16] diagnosis of bipolar I disorder was confirmed by an academic research psychiatrist using a comprehensive clinical assessment and structured diagnostic interview.[17] Participants were required to be 17–35 years of age and clinically stable, and subjects with premorbidity or comorbidity were not excluded as long as the primary diagnosis was bipolar I disorder.

From July 2004 to May 2013, 88 patients were enrolled in the STOP-EM program. Of these, 70 underwent the baseline neurocognitive assessment. Of these, 53 also had follow-up data available (11 patients withdrew, 6 did not complete the follow-up visit). There were no differences between patients who did and did not complete follow-up testing in terms of age, gender, education, mood symptoms, or cognitive functioning (all P values > .1). Twenty-six patients experienced at least 1 mood episode over follow-up (BD_{recur}) (depressive [n = 13], manic or hypomanic [n = 5], both depressive and manic or hypomanic episode[s] [n = 8]; 73% with

Clinical Points

- Cognitive impairments are an important feature of bipolar I disorder and are found in patients early in the course of illness.
- Impairments seen following the first manic episode may be reversible, as patients who remain well over 1 year follow-up show noticeable improvements.
- Episode recurrence, particular of a hypomania or mania, is associated with further performance declines.

1 recurrence, 15% with 2, and 12% with 3 or more), while 27 remained well (BD_{well}). Of the first 41 healthy subjects (HS) meeting inclusion criteria (aged 17–35 years, no personal or family history of mental illness), 31 had complete data available, with no significant demographic or cognitive differences between those who did and did not complete follow-up (all P values > .1)

Ethics approval for the STOP-EM study was granted from University of British Columbia Clinical Research Ethics Board, and written informed consent was obtained from all patients and healthy subjects prior to performing any study procedures.

Clinical Assessment

Patients received naturalistic follow-up from psychiatrists with expertise in mood disorders, with pharmacologic treatment prescribed according to current clinical practice guidelines.[18] Assessments were scheduled at baseline, 6-month, and 1-year time points, with additional appointments as appropriate (such as during occurrence of mood symptoms). Determination of recurrence of mood episodes was done according to *DSM-IV-TR* criteria and through clinician observation and patient self-report, with additional confirmation as necessary using health records. Hamilton Depression Rating Scale, 29-item version (HDRS-29)[19]; Young Mania Rating Scale (YMRS)[20]; and Positive and Negative Syndrome Scale (PANSS)[21] were administered to assess depressive, manic, and psychotic symptoms, with the Global Assessment of Functioning (GAF) scale[22] used to quantify overall functioning. Additional clinical variables recorded included the number of prior depressive episodes, history of psychotic symptoms, substance abuse or dependence, as well as dose and duration of current psychotropic treatment. Antipsychotic doses were standardized according to loxapine equivalents.[23] Dose for the 1 patient (BD_{recur}) taking aripiprazole at baseline was not included in analyses, as information regarding its loxapine equivalency was unavailable.

Neurocognitive Assessment

Further description of the measures used and rationale for their inclusion into domains can be found in Torres et al.[14] Measures and domains were based on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery (MCCB), developed for use in schizophrenia, but also validated and translated for use in bipolar populations.[24,25] Tests include paper and pencil as well as computerized measures from the Cambridge Automated Neurocognitive Testing Battery (CANTAB). The domains and measures are processing speed (Trail Making Test Part A time to completion, Phonemic Verbal Fluency number correct, Stroop Test Word number correct, Stroop Test Color number correct), attention (CANTAB Rapid Visual Information Processing discriminability and latency scores), verbal memory (California Verbal Learning Test, 2nd Edition; recall trials 1–5, short-delay free recall, and long-delay free recall number correct), nonverbal memory (CANTAB Spatial Recognition Memory percent correct, CANTAB Pattern Recognition Memory percent correct, and CANTAB Paired Associate Learning total errors adjusted score), working memory (Wechsler Memory Scale, 3rd Edition; Letter/Number Sequencing score; CANTAB Spatial Working Memory between errors score), and executive function (Trail Making Test Part B time to completion, Stroop Color/Word number correct, CANTAB IntraExtra Dimensional set shifting task number of extradimensional shift errors, CANTAB Stockings of Cambridge problems solved in number of moves). Additionally, premorbid (North American Adult Reading Test) intellectual functioning was assessed at baseline only.

Sessions were conducted in a quiet testing room and lasted approximately 2–2.5 hours, with breaks available as necessary. Testing was completed by graduate student research assistants under the supervision of a clinical neuropsychologist. While subjects were also tested at 6 months, only the baseline and 1-year data are reported here.

In 4 cases, testing or computer errors resulted in missing data for an individual measure; here the average of the remaining tests was used to calculate the domain score. For 1 subject, data were completely missing for 1 domain at baseline (attention). This subject was excluded from multivariate analyses only.

Statistical Analysis

All data are reported as means and standard deviations (SDs). Group comparisons and correlations were conducted using SPSS 21.0 (SPSS Inc, Chicago, Illinois). For all results, $P \leq .05$ was used as the threshold for significance. Demographic and clinical differences were examined using analysis of variance (ANOVA) or t tests for continuous and χ^2 for categorical variables.

For each neurocognitive measure, raw scores were converted into z scores using demographic-adjusted normative data from available testing manuals. The summary score for each of the domains was calculated from the mean score of all measures included, with overall cognitive performance calculated as the average of all domains. Comparisons between groups at baseline and 1 year were conducted using multivariate analysis of variance (MANOVA) with Tukey post hoc comparisons. Changes in performance between the 2 visits were examined for each group using paired sample t tests. Group × time effects for overall cognitive function were

Table 1. Clinical and Treatment Features of Patients at Baseline and 1-Year Follow-Up

	BD_{recur} (n = 26), Mean (SD)		BD_{well} (n = 27), Mean (SD)		Group Comparison, *t* (*P*)	
Variable	Baseline	Year 1	Baseline	Year 1	Baseline	Year 1
YMRS	1.9 (3.9)	2.5 (5.4)	0.8 (1.6)	0.7 (1.9)	1.36 (>.05)	1.53 (>.05)
HDRS-29	9.1 (8.5)	4.2 (5.7)	5.1 (6.5)	2.0 (3.8)	1.94 (>.05)	1.65 (>.05)
PANSS positive symptoms	7.8 (1.6)	7.5 (2.4)	7.7 (1.6)	7.1 (0.3)	0.24 (>.05)	1.02 (>.05)
GAF	60.6 (12.2)	73.0 (11.2)	68.8 (12.4)	79.6 (8.3)	**−2.41 (<.05)**	**−2.41 (<.05)**
Antipsychotic dose[a]	17.5 (19.7)	10.0 (10.5)	23.0 (15.7)	14.8 (12.1)	−0.97 (>.05)	−1.09 (>.05)
	% (n)	% (n)	% (n)	% (n)	χ^2 (*P*)	χ^2 (*P*)
Mood stabilizer	88.5 (23)	84.6 (22)	96.3 (26)	77.8 (21)	1.17 (>.05)	0.41 (>.05)
Lithium	46.2 (12)	42.3 (11)	48.1 (13)	37.0 (10)	0.02 (>.05)	0.15 (>.05)
Valproate	46.2 (12)	46.2 (12)	48.1 (13)	44.4 (12)	0.02 (>.05)	0.02 (>.05)
Antipsychotic	76.9 (20)	61.5 (16)	77.8 (21)	40.7 (11)	0.01 (>.05)	2.29 (>.05)
Risperidone	42.3 (11)	15.4 (4)	33.3 (9)	7.4 (2)	0.45 (>.05)	9.84 (>.05)
Olanzapine	19.2 (5)	26.9 (7)	11.1 (3)	7.4 (2)	0.68 (>.05)	3.58 (>.05)
Quetiapine	15.4 (4)	19.2 (5)	37.0 (10)	25.9 (7)	3.20 (>.05)	0.34 (>.05)
Antidepressant	15.4 (4)	23.1 (6)	0.0 (0)	7.4 (2)	**4.49 (.05)**	2.54 (>.05)
Past depressive episode	57.5 (15)		40.7 (11)		1.52 (>.05)	
History of psychosis	65.4 (17)		92.6 (25)		**5.96 (<.05)**	
Substance abuse/dependence	57.7 (15)		22.2 (6)		**6.97 (.01)**	
Other Axis I comorbidity	30.8 (8)		11.1 (3)		3.11 (>.05)	

[a]In patients treated with an antipsychotic. Unit of measure is milligram loxapine equivalents.
Abbreviations: BD_{recur} = bipolar disorder patients with at least 1 mood episode over follow-up; BD_{well} = bipolar disorder patients who remained well over follow-up; BPRS = Brief Psychiatric Rating Scale; GAF = Global Assessment of Functioning; HDRS-29 = Hamilton Depression Rating Scale, 29-item version; PANSS = Positive and Negative Symptom Scale; YMRS = Young Mania Rating Scale.

examined using repeated-measures ANOVA, with repeated-measures MANOVA used to test effects with each individual domain. Additional multivariate analyses of covariance were done separately with each potential confounding variable (mood symptoms, psychosis, antipsychotic treatment, or substance use) to confirm results. Exploratory Pearson correlations and independent *t* tests were conducted within each patient group to identify potential clinical and treatment variables associated with cognitive change.

RESULTS

Demographic and Clinical Features

The mean (SD) ages for BD_{recur}, BD_{well}, and HS were 24 (4), 22 (4), and 23 (4) years, respectively ($F_{2,81} = 1.75$, $P = .18$). Groups were equivalent in terms of gender, with 42% of BD_{recur}, 44% of BD_{well}, and 42% of HS subjects being male ($\chi^2_2 = 0.09$, $P > .9$). Mean (SD) results in both premorbid intellectual functioning (BD_{recur}, intelligence quotient [IQ] = 107 [6]; BD_{well}, IQ = 106 [9]; and HS, IQ = 108 [7]; $F_{2,81} = 0.28$, $P = .76$) and education (all groups, 14 (2) years; $F_{2,81} = 0.58$, $P > .8$) were similar between groups. On average, year 1 neurocognitive assessments were done 51 (5) weeks after baseline, and did not differ across participant groups ($F_{2,81} = 0.59$, $P = .6$).

As shown in Table 1, patient groups did not differ from each other in manic or psychotic symptoms (all *P* values >.12). Depressive symptoms were somewhat higher in the recurrence group, but these differences did not reach significance at baseline ($t_{51} = 1.94$, $P = .06$) or follow-up ($t_{51} = 1.65$, $P = .11$). Most patients met criteria for syndromal recovery (HDRS, YMRS scores ≤ 12) at baseline and year 1 visits (73% and 81%, respectively, for BD_{recur} and 85% and 93%, respectively, for BD_{well} [all *P* values >.2]), and many were also fully euthymic (HDRS, YMRS scores ≤ 7; 50% and 69% for BD_{recur} and BD_{well} at baseline [$P = .2$] and 67% and 93% for BD_{recur} and BD_{well} at year 1 follow-up [$P < .05$]). Forty-one percent of patients had cognitive testing and mood symptoms assessed on the same day, 76% within 2 weeks, and 89% within a month; all had been tested and assessed within 14 weeks. Global functioning was also worse in the BD_{recur} group at both visits ($t_{51} = -2.41$, $P < .05$).

While rates of antipsychotic and mood stabilizer treatment were similar between groups at both time points (all *P* values >.05), there was more antidepressant use at baseline by BD_{recur} ($\chi^2 = 4.49$, $P = .05$). The BD_{well} group had more subjects who had experienced psychotic symptoms during the first manic episode ($\chi^2 = 5.96$, $P < .05$), and BD_{recur} had a higher proportion with substance abuse/dependence ($\chi^2 = 6.97$, $P = .01$).

Cognitive Performance

Group differences. MANOVA revealed significant group differences between all groups at both baseline ($F_{2,80} = 1.87$, $P < .05$) and year 1 ($F_{2,81} = 1.86$, $P < .05$). The BD_{recur} (mean difference = −0.59; $df = 1,55$; $P < .001$) and BD_{well} (mean difference = −0.43; $df = 1,55$; $P < .05$) groups were both impaired in overall cognitive performance relative to HS at baseline, and they performed equivalent to each other (mean difference = −0.16; $df = 1,51$; $P > .5$). At follow-up, the BD_{recur} group was impaired relative to both HS (mean difference = −0.62; $df = 1,55$; $P = .001$) and BD_{well} (mean difference = −0.41; $df = 1,52$; $P = .05$), while performance in BD_{well} was similar to that in HS (mean difference = −0.21; $df = 1,56$; $P > .4$). Differences between all patient groups at follow-up remained significant ($P < .05$) when mood scores, antipsychotic treatment, and history of psychosis were added as covariates but became nonsignificant when substance abuse was included.

Table 2. Baseline and Follow-Up Cognitive Performance in Patients and Healthy Subjects

	BD_{recur} (n = 26)			BD_{well} (n = 27)			HS (n = 31)			Group Contrasts	
Measure	Baseline, Mean (SD)	Year 1, Mean (SD)	Time, *P* Value	Baseline, Mean (SD)	Year 1, Mean (SD)	Time, *P* Value	Baseline, Mean (SD)	Year 1, Mean (SD)	Time, *P* Value	Baseline	Year 1
Overall cognitive performance	−0.30 (0.68)	−0.06 (0.78)	≤ .05	−0.14 (0.50)	0.35 (0.56)	≤ .001	0.29 (0.45)	0.56 (0.52)	≤ .001	BD_{recur} < HS***	BD_{recur} < HS***
										BD_{well} < HS*	BD_{recur} < BD_{well}*
Processing speed	−0.45 (0.75)	−0.12 (0.82)	≤ .01	−0.56 (0.63)	−0.06 (0.62)	≤ .001	−0.08 (0.80)	0.09 (0.83)	≤ .01	BD_{well} < HS*	NS
Attention	−0.33 (0.80)	0.23 (1.15)	≤ .001	0.04 (0.97)	−0.55 (0.91)	≤ .001	0.17 (0.73)	0.79 (0.67)	≤ .001	NS	NS
Verbal memory	−0.50 (1.11)	−0.20 (1.13)	> .05	0.02 (0.90)	0.59 (1.1)	≤ .01	0.51 (0.84)	0.86 (0.95)	≤ .01	BD_{recur} < HS***	BD_{recur} < HS***
											BD_{recur} < BD_{well}**
Nonverbal memory	−0.10 (0.71)	−0.18 (1.14)	> .05	0.12 (0.75)	0.43 (0.68	≤ .05	0.40 (0.50)	0.52 (0.63)	> .05	BD_{recur} < HS*	BD_{recur} < HS**
											BD_{recur} < BD_{well}*
Working memory	−0.32 (1.03)	−0.12 (0.92)	> .05	−0.15 (0.82)	0.28 (0.77)	≤ .01	0.34 (0.87)	0.49 (0.74)	> .05	BD_{recur} < HS*	BD_{recur} < HS*
Executive function	−0.12 (0.89)	0.06 (0.75)	> .05	−0.17 (0.65)	0.30 (0.70)	≤ .001	0.37 (0.69)	0.62 (0.65)	≤ .05	BD_{recur} < HS*	NS
										BD_{well} < HS*	

*$P \leq .05$.
**$P \leq .01$.
***$P \leq .001$.
Abbreviations: BD_{recur} = bipolar disorder patients with at least 1 mood episode over follow-up, BD_{well} = bipolar disorder patients who remained well over follow-up, HS = healthy subjects, NS = nonsignificant ($P > .05$).

At baseline (Table 2), group differences were seen for processing speed ($F = 3.28$, $P < .05$), verbal memory ($F = 7.90$, $P = .001$), nonverbal memory ($F = 4.34$, $P < .05$), working memory ($F = 4.21$, $P < .05$), and executive function ($F = 4.81$, $P < .05$). Post hoc analysis indicated that, while BD_{recur} performed worse than HS on all domains except attention and processing speed ($P < .05$), the BD_{well} group was impaired only in executive function. There were no differences between patient groups.

At 1 year (Table 2), group differences were seen for verbal memory ($F = 7.57$, $P = .001$), nonverbal memory ($F = 5.65$, $P < .01$), working memory (4.03, $P < .05$), and executive function ($F = 4.66$, $P < .05$). There were no significant differences for attention ($F = 2.63$, $P = .08$) or processing speed ($F = 0.14$, $P = .56$). Post hoc analysis revealed that, while performance in BD_{well} was similar to that in HS on all domains (all *P* values > .1), BD_{recur} showed deficits in verbal memory, nonverbal memory, and working memory (all *P* values < .05). Furthermore, BD_{recur} had worse performance than BD_{well} in verbal and nonverbal memory ($P < .05$). Addition of mood scores, antipsychotic treatment, psychosis, or substance abuse/dependence as covariates did not change results.

Longitudinal Change

All groups showed significant improvements in overall cognitive performance (all *P* values < .05; Table 2). The HS group showed practice effects in processing speed, attention, verbal memory, and executive function (all *P* values ≤ .05) but not nonverbal memory or working memory ($P > .2$). While BD_{well} showed improvements in all domains (all *P* values < .05), BD_{recur} had gains in only processing speed and attention (all *P* values < .01).

Group Differences in Longitudinal Change

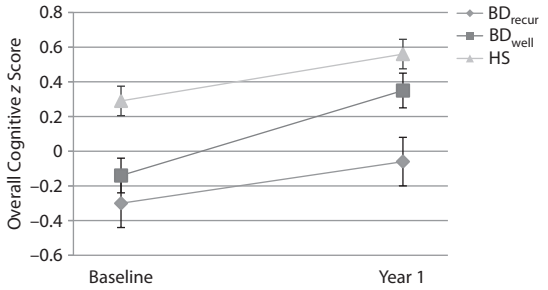
There was a significant group × time interaction ($F_{2,81} = 3.26$, $P < .05$) for overall cognitive performance (Figure 1) but not within any individual domain (all *P* values > .05). The BD_{well} group showed larger improvements than both HS ($F_{1,57} = 6.11$, $P < .05$) and BD_{recur} ($F_{1,52} = 4.48$, $P < .05$), with change seen in BD_{recur} similar to that in HS ($F_{1,56} = 0.06$, $P = .8$). Differences between patient groups remained significant after introducing mood scores or comorbidities to the model, although effects were reduced when history of psychosis ($F_{1,52} = 3.53$, $P = .07$), change in antipsychotic dose ($F_{1,52} = 3.25$, $P = .08$), and substance abuse/dependence ($F_{1,52} = 3.23$, $P = .08$) were included as covariates.

Association Between Cognitive Change and Clinical/Treatment Variables

In order to investigate potential factors underlying change in cognitive performance in each of the patient groups, exploratory correlations were conducted between change in overall and individual cognitive domain scores and changes in symptoms (YMRS, HDRS, PANSS), functioning (GAF), medications (antipsychotic dose), as well as clinical outcome (number/duration/polarity of recurrences). Additional comparisons between patients receiving different treatments (lithium vs valproate) or with different baseline characteristics (psychosis during first manic episode, comorbidities) were also conducted.

While there was no relationship between overall cognitive performance and any symptom or treatment variable in either group, in BD_{well} working memory improvements were larger in those who showed a greater longitudinal reduction in antipsychotic dose ($r = 0.43$, $P < .05$), while greater verbal memory gains were seen in those with larger improvements in YMRS scores ($r = -0.47$, $P < .05$). Likewise, larger improvements in

Figure 1. Baseline and Follow-Up Cognitive Performance in Patients and Healthy Subjects[a]



[a]Data points represent mean and standard error.
Abbreviations: BD_{recur} = bipolar disorder patients with at least 1 mood episode over follow-up, BD_{well} = bipolar disorder patients who remained well over follow-up, HS = healthy subjects.

executive function were seen with greater reductions in PANSS scores ($r = -0.39$, $P < .05$). In BD_{recur}, more manic or hypomanic episodes over follow-up was associated with declines both in overall cognitive performance ($r = -0.40$, $P < .05$) and working memory ($r = 0.42$, $P < .05$). Within BD_{recur}, patients who experienced psychosis during their first manic episode showed less improvement in verbal memory than those who did not ($t_{52} = 2.03$, $P = .05$), and substance abuse/dependence negatively affected executive function change ($t_{52} = 2.33$, $P < .05$). Those with other Axis I comorbidities did show larger improvements in verbal memory than those without ($t_{52} = 3.21$, $P < .01$).

In both groups, patients who stayed on valproate at both time points had larger improvements in working memory than those who stayed on lithium ($t_{34} = 4.00$, $P < .001$); this was a result of impairments in the valproate group at baseline ($t_{34} = 3.80$, $P < .001$) normalizing by follow-up ($t_{34} = 0.35$, $P < .001$).

While changes in GAF were unrelated to changes in cognition (all P values > .15), improvements in functioning were associated with reductions in HDRS ($r = -0.36$, $P < .01$), YMRS ($r = -0.37$, $P < .01$), and PANSS ($r = -0.39$, $P < .01$) scores.

DISCUSSION

This study demonstrates that patients with bipolar I disorder who maintain syndromal remission in the year following a first manic episode show noticeable recovery in cognitive functions. These results are consistent with hypotheses on the longitudinal course of cognition in bipolar I disorder, which suggest deficits are exacerbated during acute mood episodes and partially recover with continued symptomatic improvement.[26] This may not be a direct consequence of changes in mood, however. In the current study, variability in manic and psychotic symptoms was only modestly correlated with cognitive changes and depressive symptoms did not show any association, results that are consistent with other longitudinal studies. For instance, during 3-month follow-up of a heterogeneous sample of initially symptomatic patients, Chaves et al[10] found minimal association between changes in mood ratings and cognitive variability. Likewise, Hill et al[5] found performance did not improve alongside clinical recovery during the initial 6 weeks of treatment of a first psychotic manic episode. Despite the lack of associations seen, mood symptoms are still likely to have contributed to differences found between groups, as the proportion of patients in the recurrence group who were fully euthymic was significantly lower at follow-up, with HDRS scores numerically higher at both time points. Indeed, prior meta-analysis does indicate that patients who are symptomatic have more severe impairments than those who are euthymic.[27]

While there are several reports[9,11] of correlations between the number of mood episodes and level of cognitive impairments, this is the first study comparing trajectories between those who experience a mood episode versus those who maintain recovery over longitudinal follow-up. As expected, performance gains seen in those who remained well were not found in patients who experienced a recurrence, suggesting that acute mood episodes do have a negative effect on cognitive function. Because we did not directly see performance decrease in those who experienced a recurrence when compared to healthy subjects, it could be hypothesized that the effects of a single episode are not severe enough to create noticeable decline. Cross-sectional comparisons do indicate that impairments may rather cumulate with multiple rather than a single recurrence.[12,28] Furthermore, combining patients who experienced a manic or hypomanic and depressive event may have also limited our ability to detect cognitive declines: post hoc correlations consistently report stronger associations with the number of prior manic or hypomanic versus depressive episodes,[11] with a report[29] from a subset of the STOP-EM sample also showing that depressive episodes prior to and in the year following the first manic episode are not associated with further cognitive impairments. Although we did see a relationship between the number of manic or hypomanic episodes experienced over follow-up and declines in overall cognitive performance and working memory, we were underpowered to compare patients who experienced a single depressive (n = 13) versus manic or hypomanic (n = 5) episode or multiple recurrences (n = 8). Thus, further studies are needed to confirm hypotheses on the relative negative impact of mood episodes of different polarities.

The primary limitation of the current study is that the sample size does increase the likelihood of type II error. Specifically, while we did find differences in change in overall cognitive functioning, none of the effects for any individual domain reached significance. Likewise, the sample size may have also limited our ability to detect a relationship between changes in mood symptoms and cognition. Furthermore, the confounding effects of substance abuse/dependence does limit our ability to establish causality between cognitive change and episode recurrence or sustained recovery, although inclusion of patients with this comorbidity does enhance the generalizability of results to clinical settings. Nearly half of patients in the STOP-EM sample reported misuse of illegal substances (67% cannabis), with those who

experienced a recurrence having significantly higher rates compared to those who remained well. Along with increasing the risk for recurrence,[30] substance use has also previously been suggested to influence cognitive performance[31] and in the current sample was associated with more extensive executive function deficits. Similarly, a history of psychosis may have also confounded findings, both directly as well as through choice of treatment strategy. Determination of pharmacologic treatments was based on clinical judgment and patient preference, with drug and dosing changing dynamically throughout the study. In particular, many patients receiving antipsychotics at baseline were taken off these drugs by follow-up. Many previous studies[32–36] have indicated that that antipsychotic use is associated with cognitive impairments, with a previous study[14] from STOP-EM also indicating that patients who discontinue their use show larger improvements. Results from the current study also indicate that antipsychotics may have a negative effect on cognition, with dose reductions in patients who remain well being associated with larger working memory improvements.

In summary, we found that sustained recovery in the year following a first manic episode is associated with significant improvements in cognitive function when compared to patients who experienced recurrence of a mood episode. These findings support current staging models that describe bipolar I disorder as a dynamic and progressive illness, further highlighting the potential benefits of successful early intervention in reversing impairments present early in the course of illness. Future investigation into neurobiological factors underlying cognitive changes as well as clarifying the impact of manic versus depressive relapses, substance abuse/dependence, and pharmacologic treatments are also warranted.

Drug names: aripiprazole (Abilify), lithium (Lithobid and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others).

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Potential conflicts of interest: **Dr Bond** has received speaking fees or sat on advisory boards for the Canadian Network for Mood and Anxiety Treatments (CANMAT), the Canadian Psychiatric Association, Pfizer, Sunovion, Bristol-Myers Squibb, Otsuka, AstraZeneca, and Janssen-Ortho; and has received research support from the Canadian Institutes of Health Research (CIHR), the UBC Institute of Mental Health/Coast Capital Depression Research Fund, and Pfizer. **Dr Lam** has received speaking honoraria or is a member of advisory boards for AstraZeneca, Bristol-Myers Squibb, Canadian Psychiatric Association, Canadian Network for Mood and Anxiety Treatments, Eli Lilly, Litebook (unpaid), Lundbeck, Lundbeck Institute, Mochida, Pfizer, Servier, and Takeda; has received research funds through UBC from Bristol-Myers Squibb, CIHR, Canadian Psychiatric Association Foundation, Litebook, Lundbeck, Merck, Pfizer, St Jude Medical, and UBC Institute of Mental Health/Coast Capital Savings; receives book royalties from Cambridge University Press and Oxford University Press; and holds copyright on the Lam Employment Absence and Productivity Scale. **Dr Yatham** has been an advisory board member for and received honoraria and grant/research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Novartis, Pfizer, Abbott, Servier, and Wyeth; has been on an advisory board member for Forest; and has received grant/research support from the Stanley Foundation, the National Alliance for Research on Schizophrenia and Depression, CIHR, and the Canadian Psychiatric Foundation. **Dr Torres** has received funding from CIHR. **Drs Kozicky** and **Silveira** report no conflicts of interest.

Funding/support: The data for this article were generated from the Systematic Treatment Optimization Program for Early Mania (STOP-EM), which is supported by unrestricted grant funding from AstraZeneca, Canada.

Role of the sponsor: AstraZeneca was not involved in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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