Baseline Characteristics and Outcomes in Patients With First Episode or Multiple Episodes of Acute Mania

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Objective: Previous studies have reported differential responses to therapeutic interventions depending on the patient's history with bipolar disorder, which highlights the importance of understanding the longitudinal nature of the disorder. The goal of the present analyses was to describe and compare the baseline characteristics, response to treatment, and medication patterns in adult patients experiencing a first episode versus multiple episodes of mania.

Method: The European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study was a 2-year prospective, observational study to evaluate outcomes in patients experiencing a *DSM-IV*– or *ICD-10*–diagnosed manic or mixed episode. The study was conducted from December 2002 to June 2004.

Results: Among 3,115 patients, 256 (8.2%) enrolled with a first manic or mixed episode. Relative to multiple-episode patients, first-episode patients were younger and had a lower body mass index (BMI), a higher incidence of past or current cannabis abuse, significantly higher baseline Young Mania Rating Scale total and Clinical Global Impressions-Bipolar Disorder (CGI-BP) mania scores, and lower CGI-BP depression and Hamilton Depression Rating Scale (5-item version) total scores. At the 12-week endpoint, rates of recovery and remission were greater for first-episode patients, and times to recovery and remission were shorter.

Conclusions: Limitations of the study were that entry of patients into this study with an acute manic or mixed episode was determined by clinical interview but not confirmed with a structured diagnostic interview. That information on the course of illness prior to entry into the study was obtained retrospectively. First-episode patients presented with different baseline illness characteristics and achieved recovery and remission more rapidly than multiple-episode patients.

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Longitudinal studies of patients with bipolar disorder experiencing their first manic or mixed episode have suggested that their outcomes are better compared to those of multiple-episode patients. In a study conducted by Tohen et al,[1] syndromal, symptomatic, and functional recovery, as well as relapse and recurrence, were characterized in first- and multiple-episode patients using operational criteria for evaluating outcomes. The total sample size of that study, however, was relatively small (N = 75), and only one third of patients were experiencing their first manic episode. More recent first-episode studies have further explored predictors of outcome and medication use.[2–5] Findings from naturalistic, observational studies provide insights into the evolution of bipolar disorder from its initial stages by identifying factors contributing to differential outcomes and by characterizing the relative efficacy of existing clinical practices. These findings also generate a number of critical questions regarding changes in the course of illness with repeated episodes and responsiveness to subsequent therapeutic interventions. Furthermore, new medications and treatment combinations have become available over the past several years, but it is yet unclear how the use of these new therapeutic tools has impacted clinical outcomes for the heterogeneous population of patients with bipolar disorder. The continued investigation of these questions may be helpful for developing therapeutic strategies that are effective in patients at different stages in the longitudinal course of this disorder.

The European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) represents one of the largest observational studies conducted in patients suffering from bipolar mania. The primary goal of EMBLEM was to assess the clinical and functional outcomes of patients who experienced a manic/mixed episode and started a new oral treatment with antipsychotics, anticonvulsants, or lithium as monotherapy or as part of combination treatment. This large-scale study offers a unique opportunity to examine and compare outcomes in both first-episode and multiple-episode patient cohorts within the same sample base population. The aims of the current manuscript were (1) to identify differences between first- and multiple-episode patients in baseline demographic and illness characteristics, (2) to examine differences in clinical and functional outcomes

between these groups, and (3) to assess treatment patterns with respect to types and numbers of medications used.

METHOD

Study Design

EMBLEM is a prospective, multicenter, observational study of outcomes of patients with bipolar disorder receiving pharmacologic treatment for an acute episode of mania. The design of this study has been described in detail in previous reports.[6–8] The study was conducted at 530 sites in 13 European countries (Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Portugal, Spain, and Switzerland) and the United Kingdom from December 2002 to June 2004. Findings from the 12-week acute phase of this study are reported herein. Patients were assessed at 1, 2, 3, 6, and 12 weeks after baseline. Additional observations from a 24-month maintenance phase are reported elsewhere.[9] All sites applied the same core set of measures at each data collection point to assess a broad range of clinical and functional outcomes, as well as information regarding treatment patterns for bipolar disorder.

Patients

Eligible and consenting adult patients were enrolled at the discretion of the treating psychiatrist if they initiated/changed oral medication for treatment of acute mania in bipolar disorder (antipsychotics, anticonvulsants, and/or lithium but not antidepressants or benzodiazepines) in the standard course of care. Psychiatric diagnosis of a manic/mixed episode was made by the lead investigator at each site using clinical judgment and/or standard diagnostic criteria (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [*DSM-IV*], or the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* [*ICD-10*]). First-episode was defined as the first occurrence of a manic or mixed episode. Multiple-episode was defined as the occurrence of at least 2 manic or mixed episodes including the current one. Therefore, patients with a previous depressive episode who were experiencing their first manic or mixed episode were considered first-episode patients.

Patients with comorbidity, substance abuse, or suicidality, or those taking other medications (including antidepressants and sedatives) were not excluded from study entry. All patient data were collected and evaluated anonymously using a unique patient identification number. Ethical board approval of the study and written patient informed consent were obtained prior to enrolling patients and prior to patients' receiving any study therapy or undergoing any study procedure, as required by local legal requirements.

Medications

All decisions with respect to the initiation or change of medication(s) were made at the discretion of the treating psychiatrist and independent from the study design. After the decision to initiate or change oral medication as treatment for mania was made, investigators could enroll the patient in the study. Investigators were asked to enroll patients such that 50% had started olanzapine treatment and 50% had started any other antimanic treatment, in order to meet the primary objective of the study. Medication given as antimanic monotherapy or in combination with any other antipsychotic, anticonvulsant, and/or lithium was recorded. Cotherapy with antidepressants and sedatives, as well as any other medications required in standard care, was allowed. Patients were not required to remain on the medication initiated. Changes in prescribed medication and doses could be made according to clinical need as determined by the treating psychiatrist.

Assessments

Sociodemographic variables recorded at baseline included sex, age, country of origin, body mass index (BMI), educational status, and history of substance abuse (alcohol, cannabis, or other illegal substances). Primary efficacy measures included (1) the Clinical Global Impressions-Bipolar Disorder (CGI-BP) overall, CGI-BP mania, CGI-BP depression, and CGI hallucinations/delusions (all rated for severity, with the score range of 1–7)[10]; (2) the Young Mania Rating Scale (YMRS)[11]; and (3) the 5-item version of the Hamilton Depression Rating Scale (HDRS-5) defined by principal component analysis[12] to find the core symptoms of depression during mania (depressive mood, suicidal ideation, guilt, obsessions, and psychic anxiety). Additional efficacy measures included recovery (defined a priori as a CGI-BP overall score ≤ 2 for 2 consecutive visits that remained ≤ 2 until last follow-up), response (defined as $\geq 50\%$ decrease from baseline to endpoint in YMRS total score), and remission (defined as endpoint YMRS total scores $\leq 12, \leq 8$, and ≤ 5, respectively). Multiple stringency levels were used to define remission in order to assess the varying degrees to which symptom severity was reduced. Response and remission criteria were defined a posteriori, but are consistent with criteria used in previous observational studies and clinical trials in bipolar mania.[13,14] Four modified items from the SLICE of LIFE[15] were applied to measure patient functional outcomes in terms of life satisfaction, work, dependent housing, and living alone.

Patterns of medication prescribed for the treatment of bipolar mania, including monotherapy or combination therapy (typical or atypical antipsychotics, lithium, anticonvulsants, antidepressants, benzodiazepines, hypnotics, and anticholinergics), were recorded at baseline and throughout the 12-week acute phase. At each visit during the acute phase, tolerability of bipolar medication was assessed by interviewers using a tolerability checklist. Symptom severity was rated as "not present," "present but not significantly interfering with patient's functioning," or "present and significantly interfering with patient's functioning."

Statistical Analyses

Baseline characteristics, including demographic and clinical measures, were analyzed with descriptive statistics. For continuous data, differences between the first-episode and multiple-episode groups were analyzed using a 2-sample *t* test. Where assumptions of normality were not adequately met, differences between groups were tested using a Wilcoxon 2-sample test. Differences in categorical parameters between groups were tested using a χ^2 test. Longitudinal changes in outcome measures were tested using the last-observation-carried-forward method. Changes in continuous efficacy data were analyzed using an analysis of variance model with independent factors for baseline and type of episode (first or multiple). Standard estimates of treatment effects on rates of response, recovery, and remission were calculated using the Cox proportional hazard model with corresponding 95% confidence intervals (CIs). Estimates of time to response, recovery, and remission of mania were performed using the Kaplan-Meier survival curves.

A significance level of .05 was used for all comparisons. All data were analyzed using SAS version 9.1 (SAS Institute Inc; Cary, North Carolina).

RESULTS

Patient Disposition

A total of 3,684 subjects were recruited for the EMBLEM study, of whom 3,459 met the eligibility criterion of acute mania or mixed episode with a CGI-BP mania score ≥ 3 and were included in the analysis. Patients for whom it was not possible to determine episode status (n = 344) were not included in the present analyses. In the remaining sample (n = 3,115), 256 (8.2%) patients were experiencing their first manic or mixed episode, and 2,859 (91.8%) had previously experienced manic or mixed episodes. The percentages of patients who completed the 12-week acute phase did not differ significantly between the 2 groups (first-episode vs multiple-episode: 79.7% vs 84.0%; *P* = .073).

Baseline Patient Characteristics

The demographic characteristics of this sample are shown in Table 1. Relative to patients in the multiple-episode cohort, first-episode patients were significantly younger (mean age in years, [SD]: 38.7 [14.7] vs 45.1 [13.1], *P* < .001) and had lower BMI (24.6 vs 26.3 kg/m^2, *P* < .001). A greater percentage of first-episode patients had an episode lasting ≥ 8 weeks (13.8% vs 7.9%, *P* = .001) and were inpatients at study entry (54.5% vs 37.8%, *P* < .001). A greater percentage of patients in the multiple-episode cohort entered the study with a mixed episode relative to the first-episode cohort (24.6% vs 19.1%, *P* = .05). A significantly higher percentage of patients in the first-episode group relative to the multiple-episode group had previous (19.4% vs 13.1%, *P* = .006) or current (9.5% vs 4.1%, *P* < .001) cannabis abuse and current substance abuse (other than alcohol or cannabis) (6.3% vs 2.6%, *P* < .001).

A mean (SD) CGI-BP overall score of 4.7 [1.0] at baseline in the overall patient population indicated a moderate to marked level of illness severity. Patients in the first-episode group had significantly higher mean (SD) baseline scores for CGI-BP overall (4.8 [1.1] vs 4.7 [1.0], *P* = .045), CGI-BP mania (5.0 [1.0] vs 4.8 [0.9], *P* < .001), and YMRS total scores (28.5 [10.2] vs 26.3 [9.9], *P* = .001) relative to patients in the multiple-episode group. However, the mean (SD) baseline CGI-BP depression (1.7 [1.2] vs 1.9 [1.2], *P* = .006) and HDRS-5 (2.7 [3.0] vs 2.9 [2.9], *P* = .050) total scores were significantly lower for first-episode patients relative to multiple-episode patients.

According to the investigators' assessment at baseline, the percentage of patients who reported work impairment was significantly lower in the first-episode group relative to the multiple-episode group (79.3% vs 90.0%, *P* < .001), while the percentage of patients satisfied with life was significantly higher (42.2% vs 32.7%, *P* = .002).

Efficacy

Outcomes at the 12-week endpoint are summarized in Table 2. Patients in the first-episode group experienced significantly greater mean (SD) decreases from baseline to endpoint in CGI-BP overall (−2.4 [1.6] vs −2.0 [1.4], *P* = .003), CGI-BP mania (−3.1 [1.4] vs −2.5 [1.4], *P* < .001), CGI-BP hallucinations and delusions (−1.8 [1.9] vs −1.3 [1.6], *P* = .004), and YMRS total (−23.2 [11.4] vs −19.2 [10.7], *P* < .001) scores relative to those in the multiple-episode group. Among patients with multiple episodes, concomitant antidepressant use was associated with significantly smaller baseline to endpoint (SD) decreases in YMRS total score irrespective of manic (antidepressant vs no antidepressant: −17.0 [8.4] vs −21.1 [11.0], *P* < .0001) or mixed (−15.2 [9.3] vs −17.5 [11.3], *P* = .039) episode at study entry. No statistically significant differences in outcomes on this measure were observed for first-episode patients with either manic or mixed episodes.

A significantly greater percentage of patients in the first-episode group met criteria for recovery (CGI-BP overall score ≤ 2 for 2 consecutive visits and a score ≤ 2 at endpoint) at any time (37.9% vs 32.0%, *P* = .054) and at the 12-week endpoint (39.6% vs 33.1%, *P* = .055), and did so more rapidly (*P* = .0126, log rank test) relative to the multiple-episode group. Rates of response (> 50% decrease from baseline YMRS total score) at any time during the 12-week period did not differ significantly between the first- and multiple-episode groups (79.3% vs 80.8%, *P* = .57), but were significantly greater for the first-episode group at the 12-week endpoint (89.1% vs 83.2%, *P* = .037). There was no significant difference in time to reach response. Rates of remission at any time did not differ significantly between first- and multiple-episode patients regardless of criterion stringency (YMRS total score < 12, < 8, or < 5 at endpoints) (all *P* > .050); however, significant differences were observed at the 12-week endpoint (first- vs multiple-episode:

Table 1. Sociodemographic Data and Clinical Baseline Characteristics of Patients Experiencing First or Multiple Episodes of Mania

	First Episode			Multiple Episodes			Overall			First vs Multiple	
Variable	N	n (%)	Mean (SD)	N	n (%)	Mean (SD)	N	n (%)	Mean (SD)	Statistic, χ^2	*P* Value
Demographic characteristic											
Age, y	256		38.7 (14.7)	2853		45.1 (13.1)	3109		44.6 (13.4)	51.4	< .001
Sex (female)	250	131 (52.4)		2758	1539 (55.8)		3008	1670 (55.5)		1.1	.300
BMI (kg/m^2)	243		24.6 (4.4)	2767		26.3 (5.0)	3010		26.1 (5.0)	27.4	< .001
Duration of episode ≥ 8 wk	254	35 (13.8)		2828	223 (7.9)		3082	258 (8.4)		10.6	.001
Hospitalization status (inpatient)	255	139 (54.5)		2852	1077 (37.8)		3107	1216 (39.1)		27.6	< .001
History of suicide attempts ≥ 1	254	15 (5.9)		2819	202 (7. 2)		3073	217 (7.1)		1.3	.727
Alcohol abuse ever	250	61 (24.4)		2808	727 (25.9)		3058	788 (25.8)		0.3	.606
Cannabis abuse ever	248	48 (19.4)		2784	364 (13.1)		3032	412 (13.6)		7.6	.006
Substance abuse ever	254	27 (10.6)		2830	225 (8.0)		3084	252 (8.2)		2.2	.135
Alcohol abuse current	245	33 (13.5)		2728	291 (10.7)		2973	324 (10.9)		1.8	.178
Cannabis abuse current	242	23 (9.5)		2658	109 (4.1)		2900	132 (4.6)		14.9	< .001
Substance abuse current	253	16 (6.3)		2818	74 (2.6)		3071	90 (2.9)		11.2	< .001
Illness measures											
CGI-BP overall at baseline	247		4.8 (1.1)	2812		4.7 (1.0)	3059		4.7 (1.0)	4.0	.045
CGI-BP mania at baseline	256		5.0 (1.0)	2843		4.8 (0.9)	3099		4.8 (1.0)	11.0	< .001
CGI-BP depression at baseline	251		1.7 (1.2)	2799		1.9 (1.2)	3050		1.9 (1.2)	7.7	.006
CGI hallucination and delusion at baseline	255		3.1 (1.9)	2846		3.0 (1.8)	3101		3.0 (1.8)	1.8	.180
YMRS total at baseline	255		28.5 (10.2)	2834		26.3 (9.9)	3089		26.5 (10.0)	10.7	.001
HDRS-5 total at baseline	248		2.7 (3.0)	2738		2.9 (2.9)	2986		2.9 (2.9)	3.8	.050
Dependent housing (yes)	256	116 (45.3)		2851	1195 (41.9)		3107	1311 (42.2)		1.1	.292
Living alone (yes)	255	144 (56.5)		2855	1632 (57.2)		3110	1776 (57.1)		0.0	.831
Satisfied with life (yes)	256	108 (42.2)		2848	931 (32.7)		3104	1039 (33.5)		9.5	.002
Work impairment (yes)	241	191 (79.3)		2720	2447 (90.0)		2961	2638 (89.1)		26.1	< .001
Medication history											
No psychotropic medication before baseline	256	114 (44.5)		2859	734 (25.7)		3115	848 (27.2)		42.2	< .001
Psychotropic medication before baseline											
1 medication	256	95 (37.1)		2859	1039 (36.3)		3115	1134 (36.4)		0.1	.807
≥ 2 medications	256	46 (18.0)		2859	1078 (37.7)		3115	1124 (36.1)		39.7	< .001
Antidepressant medication before baseline	256	79 (30.9)		2859	872 (30.5)		3115	951 (30.5)		0.0	.905

Abbreviations: BMI = body mass index; CGI-BP = Clinical Global Impressions-Bipolar Disorder scale; HDRS-5 = 5-item Hamilton Depression Rating Scale; N = number of patients (denominator); n = number of patients (numerator); YMRS = Young Mania Rating Scale.

Table 2. Changes From Baseline to Endpoint (12 Weeks) in Outcome Measures for Patients With First or Multiple Episodes of Mania

Outcome Measure	First Episode, Change From Baseline to 12-Week Endpoint, mean (SD)	Multiple Episodes, Change From Baseline to 12-Week Endpoint, mean (SD)	First vs Multiple	
			Statistic	*P* Value
CGI-BP overall	−2.4 (1.6)	−2.0 (1.4)	9.0	.003
CGI-BP mania	−3.1 (1.4)	−2.5 (1.4)	30.3	< .001
CGI-BP depression	0.0 (1.5)	−0.2 (1.4)	2.5	.111
CGI hallucination and delusion	−1.8 (1.9)	−1.3 (1.6)	8.1	.004
HDRS-5 total	−0.7 (3.5)	−0.9 (3.3)	0.6	.441
YMRS total	−23.2 (11.4)	−19.2 (10.7)	20.2	< .001
	n (%)	n (%)		
Improvement in impairment at work, yes	25 (15.0)	328 (15.7)	0.1	.812
Improvement in satisfaction with life, yes	73 (39.2)	978 (42.9)	0.9	.338
Improvement in housing condition, yes	15 (8.0)	136 (6.0)	1.3	.259
Improvement in relationship status, yes	1 (0.5)	55 (2.4)	0.1	.123

Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Disorder; HDRS-5 = 5-item Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.

Table 3. Patterns of Antimanic Combination Therapy at Baseline

Medications as Part of Combination Therapy	First Episode, n (%)	Multiple Episodes, n (%)	Statistic	*P* Value
Typical antipsychotic	55 (21.5)	658 (23.0)	0.3	.577
Atypical antipsychotic	98 (38.3)	1,606 (56.2)	30.4	< .001
Lithium	27 (10.5)	712 (24.9)	26.8	< .001
Anticonvulsants	79 (30.9)	1,284 (44.9)	18.9	< .001

89.1% vs 81.4%, $P = .009$; 80.4% vs 69.0%, $P = .001$; 62.0% vs 53.6%, $P = .030$, respectively). Times to reach remission were shorter for patients in the first-episode group relative to the multiple-episode group using the YMRS score < 8 ($P = .053$, log rank test) and YMRS score < 5 ($P = .010$, log rank test) criteria.

Weight Gain and BMI

Mean (SD) weight gain from baseline to endpoint in the overall sample was 1.7 (4.0) kg. Patients in the first-episode group gained significantly more weight (2.6 [4.7] kg vs 1.6 [3.9] kg, $P = .027$) and experienced an increase in BMI (0.9 [1.6] vs 0.6 [1.4], $P = .020$) relative to those in the multiple-episode group.

Suicidality

At baseline, 5.9% of first-episode and 7.2% of multiple-episode patients had previously attempted suicide on at least one occasion. Based on reported data during the 12-week period of this study, 4 (1.6%) patients in the first-episode group attempted suicide, with one attempt being completed. In the multiple-episode group, 91 (3.3%) patients attempted suicide, with 3 attempts being completed.

Patterns of Antimanic Medication Use

Prior to study entry, as expected, a significantly greater proportion of patients in the first-episode group were not using medication relative to the multiple-episode group (44.5% vs 25.7%, $P < .001$). Upon entry into the study, a significantly greater proportion of patients in the first-episode group were taking antimanic monotherapy relative to the multiple-episode group (50.8% vs 32.4%, $P < .001$). Table 3 shows the types and percentages of medications used as part of combination treatment.

By the end of the 12-week acute phase, 42.6% of patients in the first-episode group and 52.6% of those in the multiple-episode group who started monotherapy were still taking it, but the difference was not statistically significant ($P = .110$). Of the patients who started combination therapy, a significantly greater proportion of first-episode patients switched to monotherapy (27.2%) or stopped taking medication (21.4%) relative to the multiple-episode group (19.6% and 13.8%, respectively; $P = .007$).

DISCUSSION

The present study is unique considering its large sample size (n = 3,115), which allowed comparison between first- and multiple-episode patients within the same sample population. Most prior observational studies have focused on either first- or multiple-episode patients separately. Differences between first- and multiple episode patients in the same cohort have previously been reported,[2,3] but the sample sizes have been relatively small. The large sample size in the present study allowed comparisons that, in previous studies, were limited due to the small statistical power.

In this study, first-episode patients differed from multiple-episode patients in a number of baseline measures of illness severity, degree of symptom improvement, comorbid substance use, and degree of functional impairment. These findings highlight important distinctions in illness characteristics, outcome, and possibly treatment response between patients at different points in the longitudinal course of bipolar disorder. Baseline illness severity,

as reflected in YMRS total score, CGI-BP mania score, incidence of hospitalization at study entry, and proportion of patients with an episode lasting ≥ 8 weeks, was significantly greater in the first-episode relative to the multiple-episode cohort. Nevertheless, self-reported ratings of functional impairment (work impairment, satisfaction with life) were significantly lower in the multiple-episode cohort. Also of note, multiple-episode patients had a higher baseline level of depressive symptom severity as documented by the CGI-BP depression and the HDRS-5 scores. These findings suggest that the level of functional impairment may not be directly related to the symptomatic severity of the index manic episode but, rather, reflect the extent of prior illness course. Indeed, other studies have suggested that the degree of cognitive and functional impairment associated with bipolar disorder increases with the number of previous episodes and a longer illness duration.[16,17] The greater severity of depressive symptoms in the multiple-episode cohort may represent residual symptoms from previous episodes and/or a reflection of illness chronicity and functional impairment. Differences in symptomatic and functional outcomes have been reported previously in both first- and multiple-episode patients,[1,18] and, while treatment may lead to a rapid resolution of symptoms, functional impairment is more persistent and does not completely resolve. Furthermore, it is possible that differences in the duration of manic episode at study entry and other factors, such as concurrent drug use, have an impact on the time course of manic episode resolution. Taken together, these findings lend support to the staging model, which incorporates the longitudinal dimension of bipolar disorder in the determination of prognosis and treatment strategies.[19]

The prevalence of alcohol and cannabis abuse observed in this study was somewhat lower than those reported in previous studies.[2,20–22] This may be due to differences in base populations, which in this study included patients recruited from European sites, whereas previous studies have mostly recruited patients from North American sites. An unexpected finding was the higher prevalence of cannabis use among first-episode patients compared to multiple-episode patients. Previous reports have shown higher prevalence of cannabis use in multiple-episode patients[3,23] compared to first-episode patients.[18,24] However, most of the previous studies have been conducted in the United States, and the epidemiology of the use of cannabis in bipolar patients may be a reflection of its use in the general population. The higher incidence of cannabis use among first-episode patients may also be an age-related effect. Rates of cannabis abuse have increased in Europe, and use of cannabis is more frequent in younger populations.

Statistically significantly smaller decreases in YMRS total scores were observed for patients with multiple episodes who received concomitant antidepressant treatment regardless of episode type. This finding was not observed in first-episode patients. It is possible that multiple-episode patients with current antidepressant use may have had a past history of interepisode depressive symptoms, which has been associated with poorer outcome.[25] Unfortunately, a detailed history of past episodes and antidepressant use was not available, and it is not possible to determine a causal relationship between antidepressant use and poor outcomes in the present study. As in any observational study, the relationship between treatment and outcome is difficult to discern, as it is possible that outcome determines treatment rather than treatment determining outcome.

No differences were observed with respect to suicidality between first- and multiple-episode patients. Nevertheless, a total of 95 patients attempted suicide in 12 weeks of treatment, and 4 patients died by suicide. These results reconfirm the high morbidity and mortality of bipolar disorder.[26,27]

It is interesting to note that a greater proportion of first-episode patients were prescribed monotherapy at the beginning of this study relative to multiple-episode patients. In light of the observation that first-episode patients had higher baseline illness severity scores than multiple-episode patients, this finding suggests that the choice of medication strategies by treating clinicians is influenced more by the previous course of illness and history of poor response to treatment rather than symptom severity.

Consistent with previous reports,[18] the vast majority of first-episode patients in this study achieved symptomatic recovery and significantly greater baseline-to-endpoint decreases in CGI-BP overall, CGI-BP mania, and YMRS scores, and a significantly greater proportion achieved recovery relative to multiple-episode patients. Furthermore, a significantly greater proportion of first-episode patients achieved remission at all criterion stringency levels at the 12-week endpoint, which suggests that a greater degree of symptom resolution is achieved during the normal course of treatment in these patients. This finding reinforces the notion that patients with repeated episodes and a longer course of illness become progressively less responsive to treatment.[28–30] It should also be noted that a sizeable proportion of patients in both groups (46% first-episode, 49% multiple-episode) did not reach this stringent criterion, which suggests that subsyndromal symptoms persisted. Previous studies have shown that the presence of subsyndromal symptoms impairs functional outcomes and increases the probability of a subsequent relapse.[18,31]

Several limitations should be taken into account when considering the findings of this study. First, diagnosis was determined by clinical interview instead of a structured diagnostic interview in order to limit the extent of intervention in this naturalistic study. Second, information on the course of illness prior to entry into the study was obtained retrospectively. Third, patients with hypomania were not included in the study. It is possible that the pattern of functional outcomes for first-episode patients with hypomania may be better than that observed in first-episode patients with mania.

In summary, this report confirms and expands findings from previous studies of patients with bipolar disorder experiencing their first manic or mixed episode compared with patients with a history of multiple episodes. The findings highlight the longitudinal nature of bipolar disorder and identify differences in patient and illness characteristics and treatment outcomes at various points along its course.

Drug names: lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa).

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