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Original Article

Outcome following a first manic episode: cross-national US and Taiwan comparison

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Objectives: Bipolar disorder (BD) is recognized as a significant psychiatric condition worldwide, yet little is known about cross-national differences in the course of illness. This information might clarify features of the disorder that are illness versus culturally specific. Therefore, the aim of this study was to identify differential and shared outcome predictors in first-episode manic bipolar patients in Cincinnati, OH, USA and Taipei, Taiwan.

Methods: DSM-IV bipolar patients were identified at the time of their first manic or mixed episode and were prospectively followed in a naturalistic, longitudinal study for one year. Patients were recruited from a first psychiatric hospitalization at university-affiliated, urban hospitals in Taipei and Cincinnati. The primary outcome measures were remission, recovery, recurrence and percent of follow-up spent with affective symptoms and syndromes. Treatment adherence was also assessed, as were a number of possible mediator variables.

Results: The two patient groups showed a number of significant differences in index clinical presentation on characteristics previously associated with outcome in other studies (e.g., substance abuse). The patients in Taipei showed significantly better outcome on virtually all measures. Some of these findings reflected differences in index (mediator) variables, whereas others persisted after controlling for potential baseline confounds.

Conclusions: The early course of BD varies between Chinese and American patients. Some of this variance results from demographic and clinical cross-national differences in premorbid variables. Other sources of variance remain to be identified.

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Bipolar disorder (BD) is a common and often severe psychiatric condition that is the sixth leading cause of disability worldwide (1). Although the prevalence of BD may vary in different countries or regions, this variability is relatively modest compared to other affective disorders (2). Nonetheless, this variability suggests that cultural or national factors might influence the presentation and perhaps course of illness in different populations (2–6). However, very little is known about differences in presentation and course across different national and cultural groups, as there have been few cross-national comparisons of these variables in BD. Moreover, those comparisons that have been reported typically involved similar groups living in nearby countries [i.e., between different European nations (4, 5)], or used different methods at different sites (2). Cross-national

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comparisons of BD, particularly among clearly distinct national and ethnic groups, have the potential to identify differences and similarities in the course of illness across populations that might clarify features of the illness that are inherent to the condition versus those that occur only in the context of certain cultural variables (7, 8). In particular, studying early-onset patients provides the opportunity to identify these factors prior to extensive illness progression and the influence of chronic medications (9).

With these considerations in mind, we established a mirror study in Taipei, Taiwan to an ongoing prospective, longitudinal outcome study of first-episode bipolar mania in Cincinnati, OH, USA (10). One-year symptom outcome variables were contrasted between the Chinese and American sites, with a specific aim to identify differential and shared outcome predictors across the two samples. We hypothesized that differences in course variables would be related to differences in baseline mediator variables (e.g., rates of premorbid substance abuse). Specifically, we predicted that lower rates of substance use disorders in Taiwan would be associated with better outcome (7, 10).

Methods

The University of Cincinnati First-Episode Mania (UCFEM) Study was initiated 1 June 1996 and continued through 1 October 2003 (10–12). An exact mirror study was initiated at the Taipei Medical University Hospital and Taipei City Psychiatric Center on 1 December 1999 and continued through 1 April 2004. The principal investigator in Taipei (SYT) spent three months in Cincinnati to establish diagnostic and symptom rating reliability prior to initiating the study in Taipei. Both sites used identical methodology. Detailed descriptions of the UCFEM Study have been previously published (10–12), so a relatively brief description will be provided here.

Subjects

Bipolar patients were recruited as part of the University of Cincinnati (n = 96) and the Taipei Medical University (n = 46) First-Episode Mania Studies (10–12). Because of its later start, the number of subjects recruited in Taipei was smaller than in Cincinnati. Inclusion criteria at both sites were: (i) met DSM-IV criteria for BD, manic or mixed at index evaluation (i.e., all patients are BD type I by definition); (ii) Young Mania Rating Scale (YMRS) score ≥20 at index evaluation; (iii) age 16–45 years; (iv) no prior psychiatric hospitalizations; (v) less than one month of prior psychotropic medication exposure; and (vi) able to return for follow-up visits. Subjects were excluded: (i) if psychiatric symptoms were due entirely to acute medical illness or acute drug or alcohol withdrawal (10); or (ii) if patients had identified mental retardation (IQ < 70). Written informed consent was obtained from all adult patients and from a parent or guardian of adolescent patients (with the adolescent's assent) after the procedures, risks and benefits of the study were explained in full. The institutional review boards at the University of Cincinnati College of Medicine, the Cincinnati Children's Hospital Medical Center, and Taipei Medical University Hospital approved this protocol.

Index clinical assessment

The diagnosis of DSM-IV BD, manic or mixed, was established using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient version (SCID-I/P) (13). Affective symptoms were assessed with the YMRS (14), and the 17-item Hamilton Depression Rating Scale (HAMD) (15). The presence of psychosis was determined using the SCID-I/P in conjunction with the Scale for the Assessment of Positive Symptoms (SAPS) (16). Mixed-states were diagnosed according to DSM-IV criteria. Substance use disorders were assessed with the SCID-I/P in conjunction with the Addiction Severity Index (ASI) (17). Patients' index symptoms were rated for the worst period during the current episode. The investigators have established good inter-rater reliability for all of these measures (10).

Demographic variables

Demographic information was obtained from direct patient interviews and review of medical records. This information included age, sex, years of education, marital status (ever married or never married), living status (independent or under family supervision) and job status (student, full-time employment, or unemployed/underemployed). These variables were chosen as potential mediators since they have been previously associated with BD outcome (9, 18–20).

Follow-up assessments

Following hospital discharge, patients were re-evaluated at one month, four months, and then every four months for up to eight years at the Cincinnati site and for one year in Taipei. Consequently, we restricted the current analysis to one

Table 1. Demographic and clinical variables in bipolar patients with a first manic episode in Cincinnati, OH, USA and Taipei, Taiwan

Characteristic	Cincinnati subjects (n = 96)	Taipei subjects (n = 46)	p
Age, years	25 (7)	26 (6)	<0.5
Sex, n (%) women	40 (42)	26 (57)	<0.1
Education, years	12 (3)	13 (4)	<0.3
Ever married, n (%)	25 (26)	13 (28)	<0.8
Baseline job status, n (%)			<0.0001
Student	24 (25)	12 (26)	
Employed	17 (18)	28 (61)	
Under-/unemployed	55 (57)	6 (13)	
Baseline living status, n (%)			0.01
Independent	32 (33)	6 (13)	
With family supervision	64 (67)	40 (87)	
Age of bipolar onset, years	22 (8)	24 (7)	<0.3
Duration of current episode, weeks	8 (9)	4 (3)	<0.001
Length of hospitalization, days	9 (5)	39 (24)	<0.0001
Mean YMRS, baseline	35 (8)	37 (7)	<0.2
Mean HAMD, baseline	15 (8)	3 (4)	<0.0001
Psychosis at baseline, n (%)	80 (83)	39 (85)	<0.9
Mixed state at baseline, n (%)	32 (33)	2 (4)	0.0002
Alcohol use disorder, n (%)	39 (41)	5 (4)	0.0003
Drug use disorder, n (%)	47 (49)	1 (2)	<0.0001
Weeks of follow-up	45 (13)	51 (3)	<0.002

Values are mean (SD) unless otherwise noted.
YMRS = Young Mania Rating Scale; HAMD = Hamilton Depression Rating Scale.
The p-values were calculated using *t*-tests (continuous variables) or chi-square tests (categorical variables).

year of follow-up for both sites in order to maintain comparability. To be included in this analysis, subjects had at least four months of follow-up; mean weeks of follow-up are listed in Table 1. At the Cincinnati site, 73 patients (76%) completed the entire year, and in Taipei 44 (96%) completed the entire year ($\chi^2 = 8.2$, df = 1, p = 0.004).

As described elsewhere (10–12), the general study design is based on the NIMH multi-site Collaborative Depression Study (21) and our previously published studies (18, 19). At each follow-up visit, the investigators reviewed affective symptoms for the prior interval, week-by-week. Each review included the symptom ratings scales (YMRS, HAMD, SAPS), the Affective and Psychotic and Substance Use Disorders Modules of the SCID-I/P, the ASI, and week-by-week 6-point ratings of symptom severity based on ratings (Table 2) (10–12). From these ratings, periods of recovery and recurrence were identified and the percent of weeks in different phases of illness (e.g., remission, full syndrome, subsyndromal symptoms) were calculated (10–12).

Recovery and recurrence

Symptomatic recovery (referred to as 'recovery' in the rest of this manuscript) was defined as at least eight contiguous weeks of remission, i.e., symptom severity ratings of 1 or 2 (Table 2) (10). An affective recurrence was defined as at least one week of several new significant subsyndromal symptoms (scores > 3; Table 2), as per our previous work (10).

Treatment assessments

Since this was a naturalistic study, the investigators did not administer treatment. However, treatments that patients received during each follow-up interval were reviewed, and treatment adherence for each medication was assessed as: (i) full adherence in which the medication was taken more than 75% of the time as prescribed; (ii) total non-adherence in which the medication was taken less than 25% of the time prescribed; and (iii) partial non-adherence in which the medication was taken between these two extremes (10). This rating was obtained by reviewing week-by-week interval medication use with each patient and with family members or clinicians when necessary (i.e., if the patient's reliability was suspect). From this review,

Table 2. Definitions for week-by-week overall symptom severity ratings following a first hospitalization for mania

Rating	Definition
6	FULL SYNDROME, SEVERE: meets several DSM-IV criteria, more than the minimum required for a manic, mixed, or major depressive episode
5	FULL SYNDROME, MILD TO MODERATE: meets minimal DSM-IV criteria for a manic, mixed or major depressive episode
4	MARKED SYMPTOMS: does not meet full affective syndrome criteria, but several DSM-IV affective syndrome criteria are scored > mild on the HAMD or YMRS
3	PARTIAL REMISSION: no DSM-IV affective syndrome criteria are rated > mild on the HAMD or YMRS, but total HAMD score > 7, YMRS score > 5 or any SAPS global item score ≥ 2
2*	RESIDUAL SYMPTOMS: one or more mild symptoms, but YMRS ≤ 5 and HAMD ≤ 7 and SAPS global item scores are all <2
1*	USUAL SELF – no significant symptoms

*Scores required for remission. Eight weeks of remission define recovery.
HAMD = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; SAPS = Scale for the Assessment of Positive Symptoms.

the percent of follow-up in which patients exhibited each category of compliance was determined for each prescribed psychotropic medication and an average score across medications was used for analysis (10).

Statistical analysis

All statistical analyses were performed on the Statistical Analysis System for the PC, Windows Version, release 8.02 (SAS Institute, Cary, NC, USA). Survival analysis techniques were used to compare the groups on rates of recovery and recurrence; the log-rank χ^2 test was the statistic of comparison. Times to events (e.g., recovery, recurrence) were evaluated using Cox regression models (PROC PHREG). Analysis of variance (ANOVA) and covariance (ANCOVA) models were used to compare the groups on the percentage of weeks spent in remission (symptom severity scores of 1 or 2; Table 2), with full affective syndromes (scores of 5 or 6), and with subsyndromal symptoms (scores of 3 or 4). For these planned comparisons, significance was defined as $p < 0.05$. Other analyses were performed as necessary for completeness.

Results

Demographic and baseline clinical group differences

Demographic and baseline clinical variables are provided in Table 1. The groups demonstrated similar ages, ages at bipolar onset, sex distribution, years of education, marital status, index mania ratings, and rates of psychosis during the index episode. The groups differed significantly in job status prior to hospitalization ($\chi^2 = 32.5$, df = 2, $p < 0.0001$), due to the much higher rates of under- and unemployment in the Cincinnati sample. The Taipei sample was significantly more likely to be living under family supervision ($\chi^2 = 6.5$, df = 1, $p = 0.01$). The Cincinnati patients were ill for a longer period of time prior to hospitalization (i.e., longer current episode length; $t = 3.3$, df = 140, $p = 0.001$), and hospitalizations in Taipei were significantly longer ($t = 12.2$, df = 140, $p < 0.0001$). The Cincinnati sample was much more likely to present in a mixed mood state ($\chi^2 = 14.3$, df = 1, $p = 0.0002$) and, consequently, exhibited significantly higher HAMD total scores at the index assessment ($t = 9.5$, df = 140, $p < 0.0001$). The Cincinnati patients also exhibited significantly higher rates of drug ($\chi^2 = 30.4$, df = 1, $p < 0.0001$) and alcohol ($\chi^2 = 12.9$, df = 1, $p = 0.0003$) use disorders. At both sites, cannabis was the predominant drug of abuse. Finally, the patients in Taipei demonstrated a significantly greater mean duration of follow-up ($t = 3.2$, df = 140, $p < 0.002$), with few subjects dropping out of the study (Fig. 1).

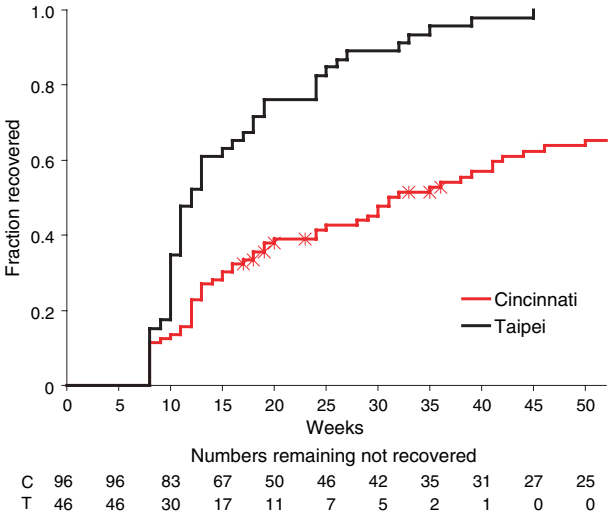

Fig. 1. Survival curves for recovery from a first manic episode in bipolar patients from Cincinnati, OH, USA (C) (n = 96) and Taipei, Taiwan (T) (n = 46). Censored data (subjects dropping out of the study prior to recovery) are indicated by asterisks (*). The curves are significantly different ($p < 0.0001$).

Group differences in survival measures

Survival curves for time to recovery are illustrated in Fig. 1. The recovery curves significantly differed between groups (log-rank $\chi^2 = 38.7$, df = 1, $p < 0.0001$); specifically, all of the patients in Taipei achieved symptomatic recovery during the one-year follow up, compared to 65% of the Cincinnati sample. Cox regression demonstrated significant group differences in time to recovery ($\chi^2 = 32.6$, df = 1, $p < 0.0001$); this difference persisted (adjusted $\chi^2 = 7.5$, df = 1, $p = 0.006$) even after controlling for potential mediator variables that significantly differed between the groups (i.e., job status, duration of the current episode, length of hospitalization, baseline HAMD score, living status, the presence of an alcohol or drug use disorder, and weeks in follow-up). Of these variables, only job status was significantly associated with recovery in this model (employed associated with greater likelihood of recovery than unemployed or students; $\chi^2 = 10.4$, df = 1, $p = 0.001$). Despite these differences in rates of recovery, in those patients who recovered, rates of recurrence were virtually identical in the two samples (log-rank $\chi^2 = 0.4$, df = 1, $p < 0.6$; Fig. 2). Similarly, Cox regression indicated no significant group

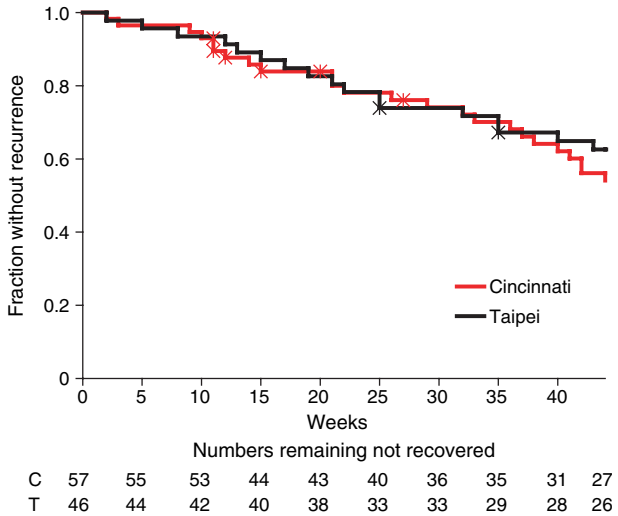

Fig. 2. Survival curves for symptomatic recurrence for bipolar patients after recovery from a first manic episode in Cincinnati, OH, USA (C) (n = 57) and Taipei, Taiwan (T) (n = 46). Censored data (subjects dropping out of the study prior to recurrence) are indicated by asterisks (*). The curves are not different (p < 0.6).

differences in time to recovery ($\chi^2 = 0.4$, df = 1, p < 0.6).

Group differences in percent of follow-up in different phases of illness

The percent of follow-up spent in full affective episodes, with subsyndromal symptoms, and in remission are listed in Table 3. Consistent with survival data, the patients in Taipei spent significantly less time in a full affective episode [$F(1,140) = 20.9$, p < 0.0001], including manic [$F(1,140) = 6.4$, p < 0.02], depressed [$F(1,140) = 4.8$, p = 0.03] and mixed [$F(1,140) = 5.6$, p = 0.02] states. They also spent significantly less time with subsyndromal affective symptoms [$F(1,140) = 15.8$, p = 0.0001] and more time in remission [$F(1,140) = 52.8$, p < 0.0001]. These initial analyses were performed without controlling for covariates.

We then performed analyses controlling for potential mediator variables in order to determine whether these variables might explain some of the group differences that were observed in these outcome measures. In fact, many of these group differences did not persist when adjusted for potential mediators (i.e., job status, living status, HAMD total scores, rates of alcohol or drug use disorders, length of hospitalization, and duration of the index episode; Table 3). After adjusting for these covariates, percent of time with a full affective episode was no longer significantly associated with group [$F(1,133) = 0.0$, p < 0.9], although it was significantly associated with HAMD scores [$F(1,133) = 4.1$, p < 0.05], duration of the index affective episode [$F(1,133) = 8.1$, p = 0.005] and a drug use disorder [$F(1,133) = 5.6$, p < 0.02]. Similarly, group differences did not persist after adjusting for these variables in percent time in manic [$F(1,133) = 1.0$, p < 0.4], depressed [$F(1,133) = 0.8$, p < 0.4] and mixed [$F(1,133) = 0.0$, p < 1.0] affective episodes. Time spent manic and mixed were both associated with the duration of the index episode [$F(1,133) = 5.0$, p < 0.03 and $F(1,133) = 4.7$, p = 0.03, respectively], whereas time spent depressed was associated with the index HAMD total score [$F(1,133) = 7.4$, p < 0.008]. The difference between groups in the percent of time spent with subsyndromal affective symptoms remained significant after adjusting for the previously noted mediator variables [$F(1,133) = 15.1$, p = 0.0002]; job status [$F(1,133) = 6.5$, p = 0.01] and index HAMD score [$F(1,133) = 4.4$, p < 0.04] were also associated with this measure. Similarly, time spent in remission remained significantly different between groups after adjusting for these mediator variables [$F(1,133) = 13.3$, p = 0.0004] and was also associated with job status [$F(1,134) = 13.2$, p = 0.0004].

Table 3. Outcome variables from patients with first-episode bipolar mania in Cincinnati, OH, USA and Taipei, Taiwan

Characteristic	Cincinnati subjects (n = 96)	Taipei subjects (n = 46)	Unadjusted p	Adjusted p[a]
Percent of weeks with an affective episode	27 (31)	7 (7)	<0.0001	<0.9
With mania	11 (21)	3 (5)	<0.02	<0.4
With depression	10 (21)	3 (6)	0.03	<0.4
With mixed state	6 (16)	1 (2)	0.02	<1.0
Percent of weeks with subsyndromal affective symptoms	34 (35)	14 (14)	0.0001	0.0002
Percent of weeks in remission	39 (37)	79 (18)	<0.0001	0.0004
Percent of follow-up with full treatment adherence	59 (50)	79 (26)	0.001	<1.0

Values are mean (SD).
[a]Analyses adjusted by job status, Hamilton Depression Rating Scale total scores, rates of alcohol or drug use disorders, length of hospitalization, and duration of the index episode (Table 1).

Group differences in treatment adherence

Treatment adherence can serve as either an outcome or mediator variable. As an outcome variable, patients from Taipei exhibited a significantly greater percentage of follow-up with full treatment adherence than patients from Cincinnati [$F(1,140) = 6.6$, $p = 0.01$; Table 3]. When adjusted for the previously noted variables (Table 3), this finding no longer persisted [$F(1,133) = 0.0$, $p < 1.0$]; instead, in this model only the presence of a drug use disorder was significantly associated with adherence [$F(1,133) = 8.8$, $p < 0.004$]. As a mediator variable, adherence did not alter associations between outcome variables and site (i.e., Taipei versus Cincinnati).

Discussion

In this cross-national comparison of Chinese and American bipolar patients early in their course of illness, we observed significant differences in both the initial presentations and outcomes. Although the two groups exhibited similar mania and psychosis ratings, patients in Cincinnati demonstrated significantly higher rates of alcohol and drug use disorders. Previous reports suggested that substance use disorders are less common in Taiwan than the USA in general and in bipolar patients from these respective countries specifically (7, 8, 22). Moreover, the rates of alcohol and drug use disorders in this Cincinnati sample were similar to those reported from other US bipolar samples (18, 23, 24). Therefore, group differences in rates of substance use disorders observed in this study likely reflect the population differences in substance abuse between the two countries. The patients in Cincinnati also demonstrated more concurrent depressive symptoms, and, consequently, a higher rate of mixed states, than the subjects from Taipei. A previous cross-national epidemiological study found very low rates of depression in Taiwan relative to other, particularly Western, countries (2). Consequently, the site differences in depressive symptoms observed during this first manic episode may reflect these cross-national differences more generally as well. Alternatively, since mixed states have been associated with substance abuse, disparities in rates of substance abuse may have contributed to the differences in rates of mixed states (25, 26).

The two sites also exhibited disparities that might reflect cross-national differences in health care seeking and delivery. The patients in Cincinnati exhibited longer manic episodes prior to treatment than those in Taipei. This observation might reflect cultural differences in how long manic behavior is tolerated before help is sought. Alternatively, this finding might reflect differences in mental health care access. There have been few cross-national comparisons of mental health delivery in the US and Taiwan to inform these considerations. In the US, health care delivery is tightly linked to multiple second-party payers, which influence the type and duration of treatment provided, and which are unevenly distributed across socioeconomic groups. In contrast, Taiwan has a national health care system that provides similar care to more than 95% of the people in that country, independent of a patient's personal resources. These differences in health care systems appear to have been reflected in the lengths of hospitalization permitted at each site as well and may have also contributed to how patients sought mental health care, thereby contributing to the duration of untreated symptoms. Moreover, patients in Taipei were less likely to drop out of follow-up, perhaps again reflecting differences in the perceived quality or availability of care. Additionally, the patients in Taipei were relatively more socioeconomically advantaged, in that they demonstrated higher rates of premorbid employment, and were more likely to be living with family, which might also have influenced treatment access and the ability to remain in the hospital for extended care. Differences in employment may also reflect differences in substance abuse rates, since substance abuse negatively impacts employment levels (27).

Importantly, essentially all of the baseline characteristics that significantly differed between the two groups have been associated with the course of BD (9, 18–20). Moreover, from these previous studies, the directions of these differences would predict better outcomes in the patients from Taipei, and, indeed, the patients in Taipei exhibited better outcomes on virtually every measure. Several of these differences appeared to be related to mediator variables, however. Specifically, the percent of time spent in full affective episodes, when controlled for potential mediating variables, no longer differed between groups. Instead, time spent in manic and mixed states was associated with the duration of the index episode prior to treatment, whereas time spent in depression was related to the severity of index depressive symptoms. These observations suggest that more rapid treatment seeking or modifying factors that might contribute to mixed-state presentations (e.g., substance abuse) might lead to improved outcomes. Moreover, differences in rates of drug use disorders appeared to explain differences in treatment adherence, consistent with previous findings (18, 19).

In contrast, rates of and time to recovery, as well as percent of follow-up spent in remission, differed between groups even after controlling for all of the possible mediators assessed. This observation suggests that other cultural or clinical factors that were not measured might better explain these differences. However, given the number of clinical differences observed, all of which might contribute toward outcome, it is possible that subtle features of these differences, that cannot be identified or controlled by statistical methods, may, nonetheless, contribute to cross-national disparities in early-course bipolar outcome. Importantly, once patients recovered, the rate of recurrence was virtually identical at both sites, suggesting that, over the longer term, the courses of illness may become more similar than different.

Several limitations must be considered when interpreting these results. Neither of the sites recruited an epidemiological sample from their respective countries. Consequently, these results have limited generalizability to larger, cross-national comparisons. However, the results from both sites are consistent with other studies from the respective countries, supporting the validity of the findings (7, 8, 18, 19). Moreover, both sites recruited patients from consecutive hospital admissions, so that the samples are representative of the centers involved in this study. Additionally, the outcome period was relatively brief at the Taipei site, and it is possible that some of the differences observed may have diminished over time, as reflected in the similar recurrence rates. Other possible comorbid syndromes (e.g., personality disorders) were not assessed and if they differed across sites, might have contributed to the findings. Both groups exhibited high rates of psychosis. Although these rates are similar to other studies of inpatients with acute mania (18, 19), the high rates of psychosis may limit generalizability to other bipolar samples. Finally, although the instruments used were translated back and forth between Chinese and English, it is possible that subtle language effects contributed to measurement errors despite an identical study design at the two sites. However, it is unlikely that these errors, if present, would have contributed any more than a minor portion of the variance between sites, given the consistent pattern of differences across multiple measures.

In summary, a cross-national comparison between first-episode manic bipolar patients in Cincinnati, OH, USA and Taipei, Taiwan found much better outcomes in the latter sample. Patients in Taipei were much more likely to recover and spent more time in remission than the patients in Cincinnati. Although some of these findings appeared to reflect disparities in baseline characteristics, particularly in rates of substance use disorders, other observations appeared to reflect differences in cultural and clinical variables that were not assessed. Nonetheless, despite these differences, once patients had recovered, they exhibited similar recurrences rates, suggesting the longer-term courses of illness may be similar. Additional cross-national studies would further clarify predictors of outcome in the full spectrum of bipolar patients, leading to culturally linked interventions to improve outcome worldwide.

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