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首次發病之躁症患者的預後追蹤:跨文化之前瞻性追蹤(1/3-3/3)

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中文摘要

有鑒於東西方國家有關躁鬱症的物質濫用率調查發現有明顯的差異，台灣躁鬱症患者共存酒精/藥物濫用的盛行率低，因此以西方為主的預後追蹤調查結果，可能受物質濫用共發率高的影響，因此進行跨文化的預後研究比較，可更了解此病的病程與特徵。

方法：首先進行研究工具之中文版信度效度之測試，進而收集合乎下列條件之個案：首次躁症發病合乎ＤＳＭ-IV 診斷標準的雙極性情感疾患躁期或混合期(bipolar disorder, manic or mixed episode)、年齡介於 16～45 歲、未有急性精神住院，服用精神科藥物少於 1 個月、有溝通能力。排除因生理因素引起之躁狀態或因物質濫用相關問題引起之躁狀態，結構性會談量表 SCID-P、楊氏躁症量表、Halmiton 憂鬱量表、成癮嚴重度指標（ASI）、長期追蹤量表與社會心理壓力評估 (LIFE)。於出院前進行評估，並於出院後 4 個月進行追蹤評估。

結果：本研究完成 LIFE 中文化之工作，依據收按標準，共收集 22 位女性、12 位男性個案；美方則收集 37 位女性、46 位男性個案。發病年齡台灣(23.4± 7.4 歲)、美國(22± 7 歲)兩者並無差異。然而美方個案有顯著高比率合併有情緒不一致的精神病徵(65%)、併發情緒症狀(漢氏憂鬱量表平均 15 分)、共發酒精/藥物濫用物質的的病患並完成 4 個月之後的頭一次後續追蹤，並與美方同時期收集之 21 位個案進行比較，結果發現美方之個案有達統計意義的顯著高酒精或物質濫用率，除此之外兩研究樣本之臨床特徵如發病年齡，以及人口基本學特徵並無差異。

結論：整體而言本研究顯示東西方之躁鬱症病患可能因有相同之基因控制以致發病的時間接近，由於研究進行追蹤的時間不長，以致於第一年的成果有限。但整體而言，我方之個案有極為與西方相似之社會以及個人背景，但因酒精物質濫用的比例少，雖然對於治療配合度均類似，但我方再發病之趨勢低，可見短期的預後以症狀的層次東方較好。然而本研究上無法評估社交功能，進一步之追蹤有助於釐清雙方之差異尤其是心理社會層次。Abstract

Purpose: Studying patients from different cultures may identify outcome predictors that are inherent to bipolar disorder and those which are culturally dependent.

Method: Bipolar I, manic (DSM-IV) patients were recruited at their first psychiatric hospitalization in Cincinnati, Ohio, U.S. and Taipei, Taiwan. The two sites use the same evaluative instruments for diagnosis, symptom and outcome assessments.

Results: There were 37 women and 46 men American patients and 22 women and 12 men Taiwanese patients in the study. The mean age at illness onset of Taiwanese patients (23.4 ± 7.4 years) was similar American samples (22 ± 7 years). Mood-incongruent psychotic features (65%), concurrent depressive symptoms (HAMD=15) and alcohol/drug abuse (30%) were significantly more common in the American patients than Taiwanese ones (11.8%, HAMD=3, and 2.9%, respectively).

Conclusions: Symptom differences in bipolar disorder across countries may be related to differences in co-occurring alcohol/drug.

Introduction

The Epidemiologic Catchment Area Study(ECA) (Regier et al., 1990) revealed that bipolar disorder is associated with the highest risk of any axis I disorder for coexistence with alcohol abuse. Goodwin and Jamison (1990) summarized the existing literature and estimated a 35% prevalence of alcohol abuse and alcoholism among bipolar disorder patients. Thus, the effects of alcohol or other substance abuse vary the actual prognosis of bipolar disorder (Brady and Sonne, 1995; Feinman and Dunner, 1996).

Hwu et al.(1995) suggested that the biological protective response to acetylaldehyde is a significantly aetiological factor for alcohol abuse /dependence in the Chinese population. A 56% prevalence of ALDH-2 deficiency in Chinese affective disorder patients, mostly bipolar disorder (Yang et al., 1996), is found and as high as that of Orientals, whereas most of the Caucasian or Negroid population do not show this isoenzyme abnormality (Agarwal and Goedde, 1992). The deficiency rate for ALDH-2 in the Taiwan Han Chinese population is 50% (Chen et al., 1991). With this biologically protective mechanism, we have found that the rate of comorbid alcohol use disorders among Chinese bipolar patients would not be as high as among Western bipolar patients (Tsai et al 1997; 1999; 2002) .

A high comorbidity (18% to 31%) of alcoholism in bipolar disorder has been found from Western studies on individuals seeking treatment for bipolar disorder (Brady and Sonne, 1995). However, based on the results of chart reviews, we found only 8.2% of Chinese bipolar patients had had alcohol problems during 15-or-more years of illness (Tsai et al 1997). Furthermore, results of interviews showed that the lifetime prevalence of alcohol abuse/dependence among help-seeking bipolar patients was 9.9%, including alcohol abuse 6.9% and alcohol dependence 3.0%. In previous work at the University of Cincinnati, Strakowski et al (1996; 1998) found that poor outcome is associated with poor treatment compliance which, in turn, is negatively influenced by substance abuse.

By studying patient groups from different cultures, it may be possible to identify which clinical factors are inherent to the course of bipolar disorder and which are culturally or environmentally dependent. With these considerations in mind, we are proposing to develop an international two-site long term outcome study of bipolar patients following their first manic episode. The aims of this study will be (1) the comparison of comorbid substance/alcohol use disorders in the Western and Eastern bipolar patients (2) the cross-cultural difference and similarity in clinical characteristics of bipolar disorders.

Method

Subjects

Patients were recruited from consecutive admissions to Taipei City Psychiatric Center, Taipei, Taiwan and to the University of Cincinnati Hospital, Cincinnati, Ohio, inpatient psychiatric units. All new psychiatric admissions were reviewed daily. Patients were included if they (1) were aged 15 to 45 years; (2) met D5M-III-R criteria for bipolar manic or mixed episode; (3) had no previous psychiatric hospitalizations, less than 3 months of previous antipsychotic or mood stabilizer treatment, and less than 6 months of previous antidepressant treatment (verified by interviews with the patient and family members and review of medical records); (4) could communicate; and (6) could fully understand the study procedures and provide written informed consent. Patients were excluded if psychotic symptoms (1) resulted entirely from

acute intoxication or withdrawal from drugs or alcohol as determined by symptom resolution within the expected period of acute intoxication and withdrawal as described previously; or (2) resulted entirely from a medical illness as determined by medical evaluation.

DEMOGRAPHIC VARIABLES

Age, sex, race, educational achievement, and SES (the highest employment level before the onset of symptoms) were recorded. The SES was scored as follows: 0, student; 1,skilled/professional worker; 2, semiskilled manual laborer; and 3, unskilled laborer or unemployed.

DIAGNOSTIC ASSESSMENTS

Axis I psychiatric diagnoses were assessed at the index hospitalization by means of the Structured Clinical Interview for DSM-III-R, Patient Version, performed by psychiatrists (S.M.S. and T.S.T.), with good interacter reliability for principal (β=0.94) and comorbid (β >0.90) diagnoses. In addition, the youngest age that a full affective syndrome could be identified was defined the age at onset of the affective illness (intraclass correlation coefficient [ICC] >0.90).

To complete the SCID-P, information was obtained from the patient, medical records, clinicians, and family members. Mood-incongruent psychosis was identified by means of DSM-III-R criteria during the SCID-P. Delusions and hallucinations were considered mood-incongruent if they did not involve manic or depressive themes, eg, non-grandiose persecutory delusions. If both mood-congruent and mood-incongruent psychotic symptoms were present, the interviewer made a final diagnosis based on the relative severity of each.

SYMPTOM ASSESSMENT

Symptoms were rated within 3 days of admission by psychiatrists using the Young Mania Rating Scale (YMRS), 17-item Hamilton Depression Rating Scale (HAMD), Scale for the Assessment of Positive Symptoms (SAPS), Scale for the Assessment of Negative Symptoms (SANS), and Global Assessment Scale (GAS). Raters had established interrater reliability from joint ratings of more than 100 patients as follows: HAMD total, ICC=0.94; YMRS total, ICC=0.71; SAPS global scores, ICC=0.72 to 0.93; SANS global scores, ICC=0.55 to 0.73; and GAS, ICC=0.73.

Statistical analysis

For the univariate statistics, chi-square, *t*-test, analysis of variance (ANOVA), and linear correlation were used.

To examine the effects of substance abuse on new-onset mania, cross-correlations using Kendall τ-b were used to compare the weekly time series of severity of affective symptom/syndrome ratings with cannabis and alcohol symptom/syndrome ratings for each patient.

Results

A total of 254 potential study subjects were identified, of whom 117 (46.1%) met inclusion and exclusion criteria in US. In Taiwan, there were 36 potential study subjects patients meeting inclusion and exclusion criteria, and 34 (95%) of them provided written informed consent. On the other hand, 109 (93.2%) American patients provided written informed consent and are the subjects of this report. Eight patients refused to participate in this study or were discharged too rapidly to be recruited. These patients did not significantly differ from the remaining subjects on any demographic variable. Table 1 shows the comparison in socio- and clinical

characteristics between Taiwanes and American patients

Table 1. Demographic and Clinical Characteristics of Taiwanese and American Patients at Their First Hospitalization for Bipolar Disorder

	Taiwan (n=34)	USA (n=83)	*t or* x^2	p
Age, y	26.1±7.0	25±6		NS
Age at onset, y	23.4± 7.4	22±7		NS
Male	12(35.3)	46(55.4)	3.88	0.06
Socioeconomic status			30.51	<0.0001
Student	7(20.6)	19(23)		
Skilled/ professional	23(67.6)	15(18)		
Semiskilled	0	9(11)		
Unskilled/ unemployed	4(11.8)	40(48)		
Mood-incongruent psychosis	4(11.8)	62(75)	38.85	<0.0001
Scores				
YMRS	35.1+ 8.1	25.3 ± 11.2	4.93	<0.05
HAMD	2.7 + 3.8	15.5 ± 8.7	8.7	<0.05
SAPS	4.9 + 3.1	9.1 ± 4.6	5.45	<0.05
Comorbid substance/alcohol use disorders	1 (2.9)	19 (22.9)	6.77	<0.01 (fisher's)

Age at onset findings:

There is no significant difference in the age of onset between Taiwanese and American patients. But further analysis of American patients found show differences in age at onset of substance use and bipolar disorder. Specifically for that analysis, we defined "antecedent" drug or alcohol abuse as either abuse or dependence beginning at least one year prior to the first affective episode. The mean age at onset of antecedent alcohol use disorders was 17 (± 3) years, compared to a mean age at onset of 22 (± 6) years for the bipolar illness. Patients with antecedent alcohol use disorders had a significantly older onset of bipolar disorder than patients without [27 (± 4) vs. 21 (± 6) years, p=.001]. In the American patients with histories of drug abuse or dependence , the drug use disorder was antecedent in 86% of substance abusers. Cannabis was the primary drug abused. In contrast to alcohol abuse, the age at onset of bipolar disorder in patients with drug abuse or dependence was not significantly different than that of patients without drug use disorders [24 (± 5) vs 21 (± 6) years]. Thus, alcohol abuse may contribute differently to the age of onset of bipolar disorder than abuse of other drugs. In Taiwanese sample, there is only one patients abuse alcohol and amphetamie which was antecedent the age of bipolar disorder.

The socioeconomic status showed Taiwanese patients have higher socioeconomic classes than the American patients. Data are given as mean ±SD and number (percentage) of patients. YMRS indicates Young Mania Rating Scale; HAMD, Hamilton Depression Scale; SAPS, Scale for the Assessment of Positive Symptoms; AD, antidepressant; MS, mood stabilizer; AP, antipsyhotics. The Taiwanese patients present significantly more manic syndrome than American patients with more mixed mania and depressive

syndrome. Furthermore, American patients more frequently experiences mood-incongruent psychotic features.

There is significantly higher comorbidity of substance or alcohol use disorders in the American patients than Taiwanese ones (22.9% vs 3.0%).

In the American patients, the fraction of time with noncompliance were associated with either interval cannabis or alcohol ratings (at $p < .2$) and so were entered as potential confounds in the regression model. In this model, the fraction of time with alcohol abuse symptoms/syndromes was significantly associated with the fraction of time with any affective syndrome (adjusted partial $R = .37$, $p = .01$) after controlling for the fraction of time with cannabis abuse symptoms/syndromes and the confounds. (All subsequent R values reported in this section are likewise partial scores adjusted for con-founds and the other substance use disorder.) Most of this association was due to correlations between the fraction of time with alcohol symptoms/syndromes and the fraction of time spent in depression ($R = .33$, $p = .025$) rather than mania ($R = .17, p > .2$) or mixed slates ($R = .11, p > .4$). In contrast, the fraction of time with cannabis abuse symptoms/syndromes was not significantly associated with the fraction of time in depression ($R = .21$, $p > .1$) nor in mixed states ($R < .02$, $p > .9$), but was significantly associated with the fraction of time with mania ($R = .42$, $p = .004$). The fraction of time with alcohol abuse symptoms/syndromes was significantly correlated with the time with cannabis abuse symptoms/syndromes ($R = .49$, $p = .0005$). Thus, the interaction between substance abuse and clinical manifestation , the results show the substance related to the mixed syndrome.

Discussion

Our results demonstrate that the prevalence of alcohol problems among Chinese bipolar patients is quite similar to that of the Chinese population in Taiwan and remarkably lower than that reported for Western bipolar patients (Regier et al., 1990; Feinman and Dunner, 1996). This finding may be additional evidence demonstrating the effect of deficiency in ALDH-2 activity against development of alcoholism. Less than 10% comorbidity of alcohol/drug use disorders among Chinese bipolar patients in Taiwan has been repeatedly reported (Tsai et al., 1996, 1997; Lin et al., 1998).

One of the major finding is that the age of onset in the Western patients is quite comparable to the Eastern patient despite of significant difference in symptomatology. However, the Western patients divided into two groups based on the prior history of substance abuse. One explanation is the effects of substance abuse on the onset of affective disorder may be related to the type of substance. By studying patients at the time of the first manic episode, potentially confounding factors such as prior treatment and illness chronicity are controlled. Other potentially important factors, particularly temporal relationships such as age of onset, can be more clearly defined. Finally, as suggested by Post and Weiss (1989), the effects of substance abuse may be more robust early in the course of the bipolar illness than after multiple affective episodes. Some effects of substance dependence on the course of bipolar illness may not be apparent until after repeated affective episodes, which cannot be determined at index assessment in first-episode patients. By following these patients longitudinally, however, this limitation is minimized.

The effects of substance on symptomatology also be illustrated in this study. The cannabis abuses have more common mixed episode during the illness. Significantly more American patient experiencing

in-congruent psychotic features, depressive symptoms, and psychotic symptoms than Taiwanese patients support that the racial difference in symptomatology of new-onset mania (Strakowski et al 1996). More than a half of American patients were African-Americans who may be vulnerable to mood-incongruent psychotic features. The other possibility is that the substance/ alcohol use disorders have direct or indirect influence on the affective onset. In terms of mood-congruent psychotic feature, the mood-congruent psychotic feature may differentiate the patients with various suicide risk and psychosocial outcome (Tsai et al 2002). As the substance abuse is related to psychotic feature, the higher comorbidity of substance abuse in American patients indirectly increase the possibility of bipolar patients with psychotic feature. As the substance antecedent the bipolar disorder, substance abuser may worsen premorbid psychosocial function and explain the lower socioeconomic class in the American patients.

There are significant differences in severity of manic and depressive symptoms in first hospitalization between American and Taiwanese patients. The phenomenon can be explained by that alcohol and substance was associated with mixed state as Himmelhoch (1976). However, it still can not be excluded the cross-culture difference in patients' affective expression despite the inter-rater reliability is satisfied.

To conclude, this investigation indicates a lower prevalence of alcohol problems among Taiwanese bipolar disorder patients. With such a low comorbidity of substance and alcohol use disorders, the mean age of bipolar disorder in Chinese patients is comparable to that of the American patients. The phenomena may indicate the substance abuse does not precipitate the illness onset. The symptomatic manifestations of the American patients show more mixed mood state in the first affective episode than Taiwanese patients. It is suggested the prevalence of substance and racial difference directly or indirectly influence the symptomatology. As drug and alcohol abuse may contribute to the development of mixed states or rapid cycling and certain cultural and ethnic groups may be more prone to developing psychosis. Furthermore, as the difference in symptomatology in bipolar disorder may be related to the substance abuse, the effects of substance abuse on outcome may be necessary to be examined by prospective follow-up in this cross-ethnical study.

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