



Contribution of long duration of undiagnosed bipolar disorder to high frequency of relapse: A naturalistic study in China

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Abstract

Background: With attention to misdiagnosis of bipolar disorder (BP), long duration of undiagnosed bipolar disorder (DUBP) had been reported recently in years. This study aims to investigate the contributions of long DUBP to the frequency of relapse in bipolar patients, and explore affect factors of DUBP.

Method: From 26 hospitals throughout China, 3896 participants diagnosed with BP according to International Classification of Diseases 10th criteria were enrolled in this study. Socio-demographic and clinical data were collected from medical records and specific questionnaires through clinical interviews with patients and their relatives.

Results: (1) Our results showed that the mean of DUBP was 40.52 months. In total, 779 patients (19.995%) reported DUBP greater than 5 years, and 1931 patients (49.564%) reported their DUBP greater than 2 years. The number of mood episodes was averaged 5.44, and the frequency ratio of (hypo) mania to depressive episodes was 1.49 (3.27/2.19). (2) Multiple linear regression analysis revealed that DUBP was significantly contributed to the number of relapse (Beta = 0.072, $p < 0.001$) after considering the confounding including gender, age at study entry, age of onset, age of first (hypo) manic episodes, age of first depressive episodes, type of first episodes and family history of mental illness. (3) Factors including age at the study entry (Beta = 0.526, $p < 0.001$), age of onset (Beta = -1.654, $p < 0.001$), age of first (hypo) manic episode (Beta = 0.348, $p < 0.001$), age of first depressive episode (Beta = 0.983, $p < 0.001$), depression as the type of first episode (Beta = 0.058, $p < 0.001$) and family history of mental illness (Beta = 0.029, $p < 0.05$) were significantly contributed to long DUBP.

Conclusion: It was concluded that long DUBP might lead to high frequent relapse in bipolar patients. The factors correlated with long DUBP include older age, early age of onset, depression as the type of first episode and family history of mental illness. The findings of our study suggest emergency task to early reorganization of bipolar disorder, and improving clinicians' recognition of bipolar disorder from patients with depressive episodes, especially in children and adolescents.

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1. Introduction

Bipolar disorder (BP) is a severe mental disorder associated with significant social function impairment, high risk of suicide, and notable economic burden (Kemp et al., 2008). Therefore, BP is responsible for a greater loss of disability-adjusted life years (DALYs) than all forms of cancers or major neurological conditions, primarily because of its early onset and chronicity across the life span [1].

Conflict of Interest: The authors declare no conflict of interest.

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Unfortunately, BP is often misdiagnosed with major depressive disorder, schizophrenia, anxiety disorders, borderline personality disorder, or other similar mental disorder [2–4]. Hirschfeld et al. [5] reported that two thirds of BP patients were initially misdiagnosed with MDD and that these patients had consulted a mean of 4 physicians for their mood symptoms before receiving a definitive diagnosis of bipolar disorder.

Alongside misdiagnoses, actual correct diagnose of BP can take several years after onset [6]. Two recent studies found that BP went unrecognized in 28% of patients in Europe and North America [7] and nearly 20.8% in China [8]. Typically, the average time from the emergence of a patient's first psychotic episode to the diagnosis of BP [also known as the duration of undiagnosed bipolar disorder (DUBP)] was 5–10 years [5,9].

Several studies found serious consequence of long DUBP [10], including lack of effective treatments that do not include mood stabilizers, more subsyndromal affective symptoms, more severe course of BP, increased risk for suicide and treatment resistance, and larger number of unstable mood states [2,11–14]; these altered mood states also appear to have negative effects on both cognitive and psychosocial functioning [15,16]. Conversely, there are also some studies reported that DUBP was not a discriminating factor in predicting prognosis of BP [17]. The conflicting result may be due to different populations and different measure of prognosis.

Here, this study aimed to investigate the DUBP, the time from initial onset of symptoms to being diagnosed accurately in Chinese bipolar patients with large sample, explore the contribution of long DUBP to frequency of relapse, and investigate factors of long DUBP.

2. Methods

2.1. Study participants and settings

Between November 2012 and January 2013, 3906 patients [including 2027 male patients (51.9%) and 1879 female patients (48.1%)] who had been diagnosed with bipolar disorder by psychiatrist according to International Classification of Diseases 10th criteria (ICD-10) were systematically enrolled. All patients were from 26 hospitals located at in the northern, southern, eastern, western and center of China (15 major psychiatric hospitals and 11 psychiatric units of general hospitals). Inclusion criteria were as follows: diagnosis of bipolar disorder according to ICD-10, and consent to participate in the study. Socio-demographic and clinical data (such as gender, age at study entry, age of first episode, number of mood episodes, etc.) were collected not only from existing medical records, but also from specific questionnaire through clinical interviews with patients and their relatives. Prior to any procedures of the study, the basis of the study was explained to all participants, who were proved written consent. All

protocols and procedures of this study were approved by the Ethics Committee of Shanghai Mental Health Center, and abide by the terms of the Declaration of Helsinki and other relevant national and international standards.

2.2. Statistical analysis

Data were analyzed using IBM Statistical Product and Service Solutions version 19.0 (IBM SPSS 19.0). Kolmogorov–Smirnov test was used for assessing normality of the variables distributions. Descriptive statistics were used to characterize patients' socio-demographic and clinical features. Spearman correlation and multiple linear regression analysis were used to test the correlations among variables. Linear regression analysis was used to measure the effect of significant variables to the frequency of relapse and long DUBP. All significance levels were two-sided, with statistical significance set at $p < 0.05$ for all tests.

3. Results

3.1. Socio-demographic and clinical features

Of the 3906 patients participating in this study, DUBP data were not gained from 10 patients, leaving 3896 patients for inclusion in the present analysis on DUBP. Overall, the mean age at the study entry was 34.76 years old (SD 14.09 years) and with a median age of 32 years old. The mean age of onset was 26.74 years old (SD 11.08 years old) with a median age of 24 years old. In terms of age of onset, the numbers were roughly split, with 1376 patients (35.2%) reporting their first onset having occurred under the age of 20, and a further 1445 patients (36.1%) reporting onset between the ages of 21 and 30. A majority (2269; 58.1%) of patients reported Mania/hypomania as their first episodes.

Our data showed that in this Chinese population, the mean DUBP was 40.52 months, with 779 patients (20.0%) reporting DUBP greater than 5 years, and 1931 patients (49.6%) reporting DUBP greater than 2 years. A large majority of patients (3230; 82.7%) reported that they had been hospitalized because of bipolar disorder. The number of mood episodes averaged 5.44, and the number ratio of (hypo) mania to depressive episodes was 1.49 (3.27/2.19) with 200 patients (5.1%) experiencing mixed episodes. Of the sampled population, 44 patients (1.1%) currently had rapid cycling bipolar disorder, while 252 patients (6.5%) reported current suicidal ideation or suicide behavior. Table 1 displays the socio-demographic and clinical characteristics of the entire sampled population.

3.2. Contribution of long DUBP to number of relapse

A significant correlation between DUBP and the number of relapse ($r = 0.208$, $p < 0.001$), number of (hypo) manic episodes ($r = 0.207$, $p < 0.001$) and depressive episodes ($r = 0.151$, $p < 0.001$) was revealed by means of the correlation analysis. Clinical characteristics, including

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