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Original article

Early clinical predictors and correlates of long-term morbidity in bipolar disorder

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ABSTRACT

Objectives: Identifying factors predictive of long-term morbidity should improve clinical planning limiting disability and mortality associated with bipolar disorder (BD).
Methods: We analyzed factors associated with total, depressive and mania-related long-term morbidity and their ratio D/M, as %-time ill between a first-lifetime major affective episode and last follow-up of 207 BD subjects. Bivariate comparisons were followed by multivariable linear regression modeling.
Results: Total % of months ill during follow-up was greater in 96 BD-II (40.2%) than 111 BD-I subjects (28.4%; $P = 0.001$). Time in depression averaged 26.1% in BD-II and 14.3% in BD-I, whereas mania-related morbidity was similar in both, averaging 13.9%. Their ratio D/M was 3.7-fold greater in BD-II than BD-I (5.74 vs. 1.96; $P < 0.0001$). Predictive factors independently associated with total %-time ill were: [a] BD-II diagnosis, [b] longer prodrome from antecedents to first affective episode, and [c] any psychiatric comorbidity. Associated with %-time depressed were: [a] BD-II diagnosis, [b] any antecedent psychiatric syndrome, [c] psychiatric comorbidity, and [d] agitated/psychotic depressive first affective episode. Associated with %-time in mania-like illness were: [a] fewer years ill and [b] (hypo)manic first affective episode. The long-term D/M morbidity ratio was associated with: [a] anxious temperament, [b] depressive first episode, and [c] BD-II diagnosis.
Conclusions: Long-term depressive greatly exceeded mania-like morbidity in BD patients. BD-II subjects spent 42% more time ill overall, with a 3.7-times greater D/M morbidity ratio, than BD-I. More time depressed was predicted by agitated/psychotic initial depressive episodes, psychiatric comorbidity, and BD-II diagnosis. Longer prodrome and any antecedent psychiatric syndrome were respectively associated with total and depressive morbidity.

1. Introduction

Major mood disorders are leading contributors to disease-burden due to their high prevalence and risks of recurrences, sustained morbidity, and mortality from suicide and comorbid medical illnesses [1]. Factors reported to be associated with morbidity and disability in mood disorders include symptomatic severity in acute episodes, more recurrences and hospitalizations, financial and legal problems, co-occurring anxiety disorders, and delay of or nonadherence to treatment [2–5]. Findings from a recent meta-analysis involving 25 studies indicated similarly high levels of long-term morbidity (44.4% [CI: 39.6–49.2] of months ill/time at risk, overall) in clinically treated bipolar disorder (BD-I, BD-II) and major depressive disorder (MDD) patients [1]. Notably, in BD subjects, 70%–80% of this unresolved morbidity was depressive (31% in BD-I, 36% in BD-II), whereas mania-like morbidity, averaged much less among BD-I (10%) and BD-II (6%) subjects [1].

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Given these high morbidity levels despite ongoing treatment, and especially depressive morbidity, the need to identify factors that can inform prognosis and predict future levels and types of morbidity is of great clinical importance. Encouraging findings arise from the strong predictive power of the type of initial affective episode in BD, notably for the predominant long-term polarity (excess of depressive or mania-like recurrences per year at risk). That is, depressive polarity was in large excess among patients presenting with an initial depressive, mixed (DSM-IV), or anxious episode, whereas an excess of mania-like recurrences was more likely to follow an initial manic, hypomanic, or psychotic episode both in type I and II BD subjects [6,7]. Other factors have been reported to be related to an initial depressive episode and to a later prevalent depressive polarity, and to predict a less favorable, long-term course. These include a predominant Depression-Mania-euthymic Interval (DMI) illness-course (contrasted to a Mania-Depression-Interval [MDI] course), a tendency toward a rapid cycling or continuous circular course, more use of antidepressants, more suicidal thoughts and actions, more mixed features, and a co-occurring personality disorder diagnosis [6,8].

Little has been reported about juvenile clinical features as predictors of the types and severity of future adult morbidity in BD, although it is recognized that adult mood disorders with a juvenile onset, generally are more severe and more recurrent than similar illnesses starting in adult years [9–13]. In particular, onset of BD in childhood or adolescence was associated with a greater number of future episodes, higher percent-time ill, higher risk of rapid cycling, more severe manic and depressive episodes [10,14], and greater rates of comorbid psychiatric disorders, especially anxiety and substance use disorders, as well as greater likelihood of suicide attempts and violent behavior [14].

Consistent and concordant findings have linked early onset of mood disorder to less favorable long-term outcomes, but details of relationships between early onset or longer delay of diagnosis and appropriate treatment, and particular aspects of future morbidity remain uncertain or inconsistent in BD. For example, whether longer delay of diagnosis and treatment yields a less favorable long-term outcome is debated. Such a relationship is clinically plausible [15], but the specific question of whether early history exerts a dominant influence on future response to treatment seems increasingly unlikely in both BD [16–20] and MDD [21].

Given the limited information about early factors associated with long-term morbidity in adult BD, the present study aimed to identify demographic, family history, and antecedent juvenile or early adult clinical features associated with time in overall and polarity-specific morbidity in a sample of adult BD subjects observed prospectively and systematically over several years.

2. Methods

Historical and prospective data obtained during clinical assessment and treatment were extracted from detailed, semi-structured clinical records of adult outpatients diagnosed with BD, evaluated and treated for many years by the same mood disorder expert, the late Athanasios Koukopoulos, M.D., at the Lucio Bini Mood Disorder Center which he had founded in Rome. At clinic intake, participants provided written, informed consent for potential research analysis and anonymous reporting of clinical findings in aggregate form, in accord with Italian ethical requirements. Two investigators (GS and LDC) selected patients' records in random order among those of subjects with a final DSM-IV-TR diagnosis of BD (type I or II). Study subjects were drawn at alphabetically from a total of approximately 1000 bipolar patients evaluated and followed by Dr. Koukopoulos for at least one year. Records had to include details of family history, past history, features of current and previous illness including comorbid syndromes (anxiety, eating, or substance abuse disorders) based on at least one year of repeated, systematic assessments and observation at the study center. Only records with required information were selected (leading to the exclusion of 5.0% of records with missing required information).

Dr. Athanasios Koukopoulos systematically followed and treated all study subjects for several years before this study was designed. His diagnoses following DSM-IV-TR criteria were later confirmed for this study by direct examination (the majority were confirmed based on live clinical reassessments and some from chart reviews) by one other senior research psychiatrist at the study center (Dr. Gabriele Sani or Prof. Paolo Girardi) using the Structured Clinical Interview for DSM-IV-TR-Patient Edition (SCID-I/P).

If diagnoses were not consistent, more data were gathered and diagnostic assessment was continued until final consensus was reached or the potential participant was excluded. To maximize reliability, each chart was reviewed independently by two investigators (LDC and AEK) and required data were extracted from clinical records and summarized in structured research forms by the two investigators, working to consensus with a third investigator (GS).

2.1. Subject assessment

Historical and prospective information was collected in semi-structured assessments used at Lucio Bini Mood Disorder Center since 1974 with mood disorder patients at first evaluations and during long-term follow-up. Assessments are based on DSM criteria and on detailed clinical evaluation (not on simple yes/no answers to structured questions). Wording of questions posed could be changed to improve understanding, and evaluations were routinely supplemented with information from family members or close friends during at least one visit, as well as by all available medical documentation. Data collected about education, employment, past, social and family history were entered into preprinted medical record forms. Affective temperaments were evaluated clinically, following criteria described by Akiskal & Mallya [22].

Current and historical assessments included retrospective evaluation of juvenile psychiatric symptoms, syndromes, or behavioral abnormalities, with approximate ages at their appearance, as well as estimates of their intensity and approximate duration. In addition, details of the history of BD prior to entering the study center were recorded routinely, including the type of first episode, number and types of subsequent affective episodes, treatments, hospitalizations, levels of impairment, and information about suicidal behaviors.

2.2. Long-term follow-up

During follow-up at the study center, participants were assessed at 1–12 week intervals, as required clinically, with semi-structured interviews routinely supplemented with standardized ratings of for depressive (21-item Hamilton Depression Rating Scale [HDRS-21]) [23] and (hypo)manic features (Young Mania Rating Scale [YMRS]) [24]. During follow-up the number, type (polarity and subtype), duration and severity of major affective episodes were recorded in life-charts used at the center since 1980 [25], as well as information about treatments, psychiatric hospitalizations, and the occurrence, timing, methods and circumstances of lifetime suicidal or self-injurious behaviors. Mania-related morbidity included manic, hypomania and mixed episodes (DSM-IV-TR) with and without psychosis whereas depressive morbidity included simple depression as well as

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