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Research report

Towards a clinical staging for bipolar disorder: Defining patient subtypes based on functional outcome

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ABSTRACT

Background: The functional outcome of Bipolar Disorder (BD) is highly variable. This variability has been attributed to multiple demographic, clinical and cognitive factors. The critical next step is to identify combinations of predictors that can be used to specify prognostic subtypes, thus providing a basis for a staging classification in BD.

Methods: Latent Class Analysis was applied to multiple predictors of functional outcome in a sample of 106 remitted adults with BD.

Results: We identified two subtypes of patients presenting "good" ($n=50$; 47.6%) and "poor" ($n=56$; 52.4%) outcome. Episode density, level of residual depressive symptoms, estimated verbal intelligence and inhibitory control emerged as the most significant predictors of subtype membership at the $p<0.05$ level. Their odds ratio (OR) and confidence interval (CI) with reference to the "good" outcome group were: episode density ($OR=4.622$, CI 1.592–13.418), level of residual depressive symptoms ($OR=1.543$, CI 1.210–1.969), estimated verbal intelligence ($OR=0.969$; CI 0.945–0.995), and inhibitory control ($OR=0.771$, CI 0.656–0.907). Age, age of onset and duration of illness were comparable between prognostic groups.

Limitations: The longitudinal stability or evolution of the subtypes was not tested.

Conclusions: Our findings provide the first empirically derived staging classification of BD based on two underlying dimensions, one for illness severity and another for cognitive function. This approach can be further developed by expanding the dimensions included and testing the reproducibility and prospective prognostic value of the emerging classes. Developing a disease staging system for BD will allow individualised treatment planning for patients and selection of more homogeneous patient groups for research purposes.

1. Introduction

Bipolar disorder (BD) is a complex and chronic mental disorder characterised by recurrent episodes of depression and mania (American Psychiatric Association (APA), 1994). Disease outcome is highly variable regardless of how endpoints are determined (Tohen et al., 2009). Clinical endpoints focus on syndromal or symptomatic remission while functional endpoints focus on psychosocial, residential, and occupational function (Tohen et al., 2009). Since the ultimate goal of treatment is to restore patients' quality of life, the current emphasis is on functional endpoints as they matter most to patients and should therefore be the focus of care planning.

The evidence for BD being associated with significant psychosocial disability is incontrovertible (López and Murray, 1998). However, there is significant heterogeneity in outcome that is independent of illness duration. For example, longitudinal follow-up of patients participating in the McLean–Harvard First Episode project showed that two years after their first hospitalisation 43% were considered recovered while 57% described variable functional deficits (Tohen et al., 2003). Similarly, 62% of multi-episode BD patients enrolled in a longitudinal study by the Stanley Foundation Bipolar Network (SFBN) reported moderate to severe functional impairment (Suppes et al., 2001).

Significant variability in outcome is not unique to BD but has been observed in all major human diseases (Krumholz, 2008). It is generally acknowledged that this variability derives from a wide range of factors and that knowledge of these determinants of

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outcome is critical for disease staging and optimisation of individualised treatment. Disease staging is a classification system that uses clinical and laboratory information to produce clusters of patients that have similar prognosis. Clinical staging is used widely throughout medicine to tailor treatment; it is also a valuable tool for planning services according to clinical need including the analysis and allocation of resources and outcomes. Additionally, clustering of patients in more homogeneous groups based on severity can inform research into disease mechanisms and new treatment evaluation.

A host of prognostic factors in BD has indeed been identified (details of relevant studies are summarised in Supplementary Table 1). The best supported clinical determinants of functional outcome are episode density, persistent subsyndromal symptoms, history of psychosis, number of hospitalisations, and psychiatric comorbidity (Supplementary Table 1; reviews by Huxley and Baldessarini, 2007; Sánchez-Moreno et al., 2009). Amongst these, residual depressive symptoms appear most robustly associated with poor outcome (Supplementary Table 1; reviews by Huxley and Baldessarini, 2007; Sánchez-Moreno et al., 2009). However, clinical variables account for up to 60% of the variance in outcome (Gyulai et al., 2008) since neither symptomatic nor syndromal remission necessarily lead to functional improvement (Tohen et al., 2009). Cognition is considered another important determinant of outcome as attention, verbal and working memory, response inhibition and processing speed appear to have significant prognostic value in BD (Supplementary Table 1; reviews by Sánchez-Moreno et al., 2009; Wingo et al., 2009).

The aforementioned evidence has substantially enhanced our understanding of predictors of functional outcome in BD. However, its impact on clinical practice has been minimal for three reasons. First, there is no standardized approach to establishing the comparative importance of the different predictors (Wingo et al., 2009). Second, the definition and assessment of functional outcome is complex because of its multidimensional nature. Categorical recovery-oriented measures are difficult to operationalize while dimensional definitions based on broad ratings of functional status [e.g., Global Assessment of Functioning (American Psychiatric Association (APA), 1994)] may not fully capture the range of patients' problems. Third, all available studies have adopted a "variable" as opposed to a "person-centred" approach. Variable-centred analyses are useful in identifying mechanisms mediating disease progression but are of limited value to clinicians. This is because clinical practice is "person-centred" as decisions about treatment and advice about prognosis are based on the clinical presentation of each individual patient. Therefore, the pertinent issue is whether individual patients can be categorised into different classes based on their functional outcome. Such categorisation might provide an empirically derived outcome-based staging of BD which could inform current theoretical models (Berk et al., 2007; Kapczinski et al., 2009).

With these considerations in mind, we used a person-centered, Latent Class Analysis (LCA) (Vermunt and Magidson, 2002) to classify remitted BD patients on the basis of their functional outcome. In keeping with the multi-dimensional nature of functional outcome we incorporated scores from multiple measures covering disability, quality of life and occupational status. We elected to study a unique cohort of patients from the Barcelona Bipolar Disorders Program who have been assessed prospectively using extensive clinical and cognitive measures (Vieta, 2011). Our goals were (a) to specify the number and types of prognostic classes that best describe the range of functional outcomes in BD patients and (b) to determine whether the identified classes might be characterized further by different combinations of clinical and cognitive predictors.

2. Materials and methods

2.1. Sample

The sample derived from patients attending the Barcelona Bipolar Disorders Program (Hospital Clínic, University of Barcelona, Spain) (Vieta, 2011). In this analysis we selected patients that fulfilled the following criteria: (a) diagnosis of BD (type I or II) as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association (APA), 1994) (b) working age (18–65 years) (c) in symptomatic remission for 6 months as determined prospectively based on maintaining total scores <7 in the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and Young Mania Rating Scale (YMRS) (Young et al., 1978). None of the patients had a history of substance dependence or abuse in the year prior to enrolment. Characteristics of the sample ($n=106$) are shown in Table 1. All patients were medicated (Table 1). Treatment decisions were based on the clinical judgement of experienced psychiatrists in the Program. The study was approved by the Hospital Clinic Ethics Committee and informed consent was obtained from each participant.

2.2. Assessment

2.2.1. Clinical assessment

Diagnosis was confirmed using the Structured Clinical Interview for DSM-IV axis I and axis II Disorders (First et al., 1997, 2002). Information on patients' psychiatric history as well as on symptoms and treatment during their follow-up in the Program were collected during consultations and through medical records. The following variables were recorded: age, sex, years of education, age of onset, duration of illness, lifetime number and type of episodes, episode density (total number of episodes divided by duration of illness), number of hospitalizations, history of psychosis, Axis I, II and III comorbidity, family history of affective disorders, and total HDRS and YMRS scores.

2.2.2. Functional assessment

Patients' outcome was assessed using the World Health Organization Disability Assessment Schedule-2 (WHODAS-2) (Garin et al., 2010), the Spanish version of the Short Form-36 Health Survey (SF-36) (Alonso et al., 1995) and occupational function.

The WHODAS-2 is a 36-item self-report instrument of disability severity with a recall period of 30 day, covering the following domains: understanding and communicating; getting around; self-care; getting along with others; life activities; participation in society. Domain scores are computed by adding the relevant item responses and transforming them into a range from 0 to 100, with higher scores indicating greater disability. A global score is also calculated from all the items.

The SF-36 is a 36-item instrument of quality of life covering eight domains: physical functioning; role limitations due to physical health; bodily pain; general health; vitality; social functioning; role limitations due to emotional problems; and mental health. The first four domains, summarized in the Physical Component Score (PCS index), mainly evaluate physical health. The remaining subscales examine mental health and are summarized in the Mental Component Score (MCS index). The SF-36 score ranges from 0 to 100, with higher scores indicating better quality of life.

Assessment of occupational function was based on information from patients and independent informants and was coded on a three point scale (poor, moderate, good). Patients who were in full time employment, full time education or were full time