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Original Article

Mood and anxiety spectrum as a means to identify clinically relevant subtypes of bipolar I disorder

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Objectives: Latent class analysis of demographic and clinical variables can help identify subtypes of patients with bipolar disorder type I (BD I). Classification of patients into clinically relevant and homogeneous subtypes may have implications for further research. We examine the structure of mood and anxiety spectrum features in patients with BD I to identify subtypes with similar profiles.

Methods: Adult patients diagnosed with BD I, who were also participants in the Bipolar Disorder Center for Pennsylvanians (BDCP) Study, were followed for a median time of 448 days. Data from self-report instruments of BD I patients were used to derive dichotomous indicators of four spectrum conditions. Latent class analysis was applied to these indicators. Demographic and clinical variables were used as external validators of the classes.

Results: A 3-class solution provided a satisfactory data fit and outlined three classes of subjects. Members of the three groups differed in terms of demographic and clinical variables, such as gender, age of onset, mean Clinical Global Impression (CGI) depressive ratings and overall CGI ratings at entry, weighted mean CGI ratings for the period between the first and last evaluation in the BDCP Study and mean Global Assessment of Functioning scores at entry and during the BDCP Study.

Conclusions: We found substantial clinical heterogeneity among individuals with BD I and found that the levels of lifetime depressive, manic, panic-agoraphobic, and obsessive-compulsive spectrum symptoms identify three distinct subtypes characterized by differences in demographic and clinical variables. These results may have implications for research on the neurobiology, genetics, and treatment of BD I.

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Converging evidence indicates that bipolar I disorder (BD I) is highly comorbid with anxiety disorders (1). Results from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Study indicate that 52.8% of patients experience at least one anxiety disorder in their lifetime and 34.2% have a current comorbidity with anxiety disorders (2). Comorbid anxiety disorders have a detrimental effect on the course of bipolar disorders because they are associated with fewer days well, a lower likelihood of timely recovery from depression, risk of earlier relapse, lower quality of life, diminished role function, and increased rates of suicide and substance abuse (3–5). Therefore, identifying and parsing out

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comorbid anxiety in BD offers an opportunity to refine nosological, prognostic and treatment models.

For the past several years, our research group has been working to define the spectrum of clinical features that accompany DSM-IV mood and anxiety disorders (6–10), and to evaluate the influence of these conditions on course of illness and treatment outcome (11–13). By spectrum conditions we refer to the broad array of manifestations of a disorder, including its core and most severe symptoms, as well as a range of more subtle features related to the core condition (14). We have recently operationalized many of these spectrum conditions by developing interviews and self-report instruments that assess lifetime mood (MOODS-SR), panic-agoraphobic (PAS-SR), and obsessive-compulsive (OBS-SR) features. The spectrum instruments include, in addition to the DSM-IV criteria for a disorder, the associated features, atypical symptoms and behavioral traits that constitute the halo of a disorder. For this reason, we hypothesize that the differences in mood and anxiety spectrum features among patients with BD may contribute to the identification of clinically relevant phenotypes. The aims of this paper are: (i) to use the lifetime spectrum assessments to identify distinct subtypes of patients with BD; (ii) to analyze the relationship of these subtypes with demographic and clinical variables collected at baseline; and (iii) to determine whether these subtypes are useful to predict severity of illness, functioning and quality of life during treatment.

Methods

Data for the present report were drawn from the Bipolar Disorder Center for Pennsylvanians (BDCP) Study, a multicenter, randomized controlled study involving subjects aged 12 years and older with BD I, BD II, BD not otherwise specified (NOS), or schizoaffective bipolar subtype (15). The BDCP Study compares the clinical outcomes of subjects who receive adjunctive enhanced clinical intervention (ECI) with the clinical outcomes of subjects who do not receive adjunctive ECI, on a background of standardized drug regimens. Exclusion criteria for the BDCP Study are pregnancy or medical contraindication to treatment with psychotropic medications, organic mental disorder, mental retardation (IQ $\leq$ 70), and current substance or alcohol dependence. Substance dependence in early remission was not an exclusion criterion. The BDCP Study started in November 2003, completed enrollment in September 2005 and will end in February 2007.

The Institutional Review Board at the University of Pittsburgh reviewed and approved all of the procedures described in this protocol, and all subjects gave written informed consent prior to participating in the study.

Participants

The present study sample includes 261 adult (aged >18 years) subjects (104 male, 157 female, mean age $=$ 44.6 years) with BD I consecutively recruited at the Pittsburgh and Dubois sites of the BDCP Study between November 2003 and September 2005, and treated in the period between November 2003 and February 2006 for a median time of 448 days (range 26–830 days). As part of the BDCP Study, patients were seen and evaluated at least every two months when in remission and at least every two weeks when experiencing depressive or manic symptoms. Because patients had different numbers of assessments depending on their clinical status, weighted means were calculated.

Of the 261 participants, 127 were euthymic at study entry. The remaining 134 were in a depressive (n = 94), manic (n = 19), mixed (n = 16), hypomanic (n = 4), or unspecified (n = 1) state. Current comorbidity with obsessive-compulsive disorder (OCD) and panic disorder (with or without agoraphobia) was found in 7 and 30 subjects, respectively, and lifetime comorbidity in 12 and 64 subjects. Obsessive-compulsive spectrum traits and panic-agoraphobic spectrum traits were found in 128 (49%) and 150 (57.5%) of subjects, respectively.

Assessment

Diagnostic assessment was conducted using the Structured Clinical Interview (SCID) for DSM-IV, Patient Version (16) by experienced evaluators who were certified in the administration of the SCID.

At the baseline assessment, participants completed three self-report instruments intended to assess their lifetime experience of mood (MOODS-SR) (7), panic-agoraphobic (PAS-SR) (10), and obsessive-compulsive (OBS-SR) (8) spectrum features. Each instrument consists of over 100 dichotomous (Yes/No) items. A copy of the instruments is available at http://www.spectrum-project.org. The total score on each instrument is obtained by counting the number of items answered with 'Yes'.

In a previous study conducted on separate samples unrelated to the subject population of the present report, we used receiver operating characteristic (ROC) analysis to determine a threshold for clinically significant levels of panic-agoraphobic spectrum (10). We then validated this

threshold in two clinical samples of patients with recurrent unipolar and bipolar disorder (11, 12).

We subsequently reanalyzed data from the large samples originally used to validate the mood and obsessive-compulsive spectrum instruments (for details see 6–8) using ROC analyses to establish similar thresholds for scores on those instruments. For the present report, the total score on each of the spectrum measures was dichotomized at this threshold. Scores on the manic and depressive components of the mood spectrum questionnaire were dichotomized separately. Those individuals who scored above the threshold on any instrument were considered to have the relevant spectrum condition. According to our conceptualization of the spectrum conditions, it is possible, albeit not very common, to endorse a sufficient number of items to cross the threshold for the presence of a spectrum condition (i.e., the mood spectrum) even in the absence of the corresponding DSM-IV diagnosis (i.e., a manic episode). This occurs, for instance, in patients who endorse a large number of non-criterion symptoms. It is also possible that patients meeting the criteria for a DSM-IV disorder do not cross the threshold for the corresponding spectrum condition. This occurs in patients who endorse a sufficient number of DSM-IV criterion symptoms to meet criteria for the disorder but endorse very few other items on the mood spectrum questionnaire.

External validators of the latent classes included gender, age, baseline assessments of severity of illness [Clinical Global Impression-Bipolar version (CGI-BP) (17)], quality of life [Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (18)], and Global Assessment of Functioning (GAF) (19) scores, age at onset of BD, and duration of illness. The choice of these variables as validators of the latent classes reflects hypothesized relationships for which there is some evidence in the literature, but which are limited to comorbid anxiety disorders, that need to be confirmed or disproved for the spectrum measures.

Data analysis

Latent class analysis (LCA) was used to examine the latent structure of spectrum comorbidity. The goal of LCA is to identify the minimum number of classes that describe the association between the spectrum variables, starting from a 1-class model. If no sub-groups exist, the 1-class model is the best-fit model. If there are sub-groups within the dataset, multiple-class models will better fit the data. The variables we used for this analysis were dichotomous indicators denoting the presence or absence of four spectrum conditions: manic/hypomanic spectrum, depressive spectrum, panic-agoraphobic spectrum, and obsessive-compulsive spectrum.

LatentGold, version 4.0.3, was used to conduct the analyses (20). One-, 2- and 3-class models were fitted to the data. The Bayesian Information Criterion (BIC) and the likelihood ratio goodness-of-fit statistics (L^2) were used to test the model fit. L^2 is a chi-square-based statistic that compares observed frequencies with those predicted by the model. The BIC statistic takes into account the parsimony of the model, imposing a penalty for increasing the number of parameters in the model. When comparing models, the lower the BIC value, the more parsimonious is the model. Bootstrap test (21) was performed to compare nested models. An individual's posterior class membership probabilities were computed from the estimated model parameters and the observed scores. Subjects were assigned to the class with highest posterior probability.

Chi-square, F-tests and Median test were used to compare members of the three classes derived from the latent class analysis. For post-hoc comparisons between classes, the alpha level was set to $p = 0.016$ ($p = 0.05/3$) to reduce the risk of type I error. SPSS, version 12.0, was used for these comparisons.

Results

Latent class analysis using four groups of dichotomous variables was performed. While the 1-class and 2-class solutions did not fit the data well (1-class: BIC = 1063.8, $L^2 = 181.5378$, $p < 0.0001$, classification error = 0; 2-class: BIC = 943.2, $L^2 = 33.1540$, $p < 0.001$, classification error = 0.0534), the 3-class solution provided a satisfactory data fit (BIC = 938.8, $L^2 = 0.9499$, $p = 0.51$, classification error = 0.1170). The improvement with respect to the 2-class model was significant (−2 log-likelihood difference = 32.2, bootstrap test p-value < 0.001).

The three classes included respectively 126 (48%), 105 (40%), and 30 (12%) of the subjects.

The profile plot in Fig. 1 shows the probability of exceeding the threshold for the spectrum condition in the three classes. Each of the four spectrum conditions is listed on the abscissa. The four probabilities are connected with a line to indicate the three class profiles.

Members of class 1 had high probabilities of exceeding the threshold for depressive, manic, panic-agoraphobic and obsessive-compulsive spectrums. Members of class 2 had probabilities close to unity of exceeding the threshold for depressive and manic spectrum, a 0.3 probability of having

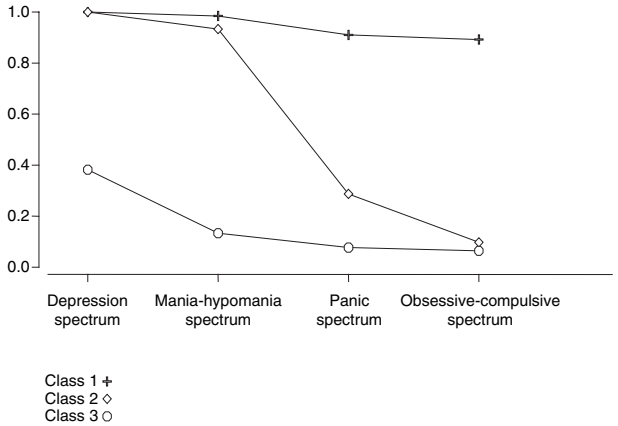

Fig. 1. Profile plot showing the conditional probability of exceeding the threshold for lifetime depressive spectrum, manic-hypomanic spectrum, panic-agoraphobic spectrum and obsessive-compulsive spectrum in three latent classes of individuals with bipolar disorder.

panic-agoraphobic spectrum and virtually no obsessive-compulsive spectrum. Class 3 included subjects with a 0.4 probability of crossing the threshold for depressive spectrum and very low probability of having the other three spectrum conditions.

Fifteen subjects in class 3 did not cross either the depressive or the manic thresholds of the mood spectrum. Symptoms endorsed by these subjects included at least the DSM-IV symptom criteria for mania. The other 15 subjects of the class exceeded the manic or the depressive threshold.

Demographic and clinical variables associated with the three classes are summarized in Table 1. Members of class 1 were more likely to be female, to have an early onset of BD, a lower level of functioning, and concomitant higher severity of BD, both at study entry and during the study, as shown by CGI scores. Compared to class 1 members, those of class 2 displayed lower severity and a higher quality of life and satisfaction. Members of class 3 were more likely to be male, with a later age at onset of the disorder than the rest of the sample and better functioning, better quality of life and less severe CGI scores than class 1 members, both at intake and during the study.

Discussion

It is well known that the presence of psychiatric comorbidity in patients with BD is associated with a more severe course, poorer treatment compliance, and worse outcomes related to suicide and other complications (22). However, the impact of comorbid psychiatric symptoms and partially endorsed syndromes, and the extent to which they can influence the course of BD, is yet to be completely understood.

In the present study, we observed that the assessment of mood and anxiety spectrum conditions enables us to identify three subtypes of BD I. The first subtype, which was present in about half of the sample, is characterized by the presence of a high probability of crossing our pre-established thresholds for depressive, manic, panic-agoraphobic, and obsessive-compulsive spectrum symptoms. The second subtype is characterized by the endorsement of

Table 1. Latent class analysis-derived class membership in relation to demographic and clinical characteristics

	Class 1 (high spectrums)	Class 2 (depressive and manic spectrums)	Class 3 (low spectrums)	Test, p and significant post-hoc comparisons at p = 0.016
% Female	67.5	57.1	40.0	$\chi^2 = 8.3$, p = 0.016, 1 > 3
% Married	31.5	36.9	43.3	$\chi^2 = 1.8$, p = 0.41
% Employed	35.2	38.5	36.7	$\chi^2 = 0.2$, p = 0.88
Mean age, years (SD)	43.1 (13.7)	43.6 (14.0)	53.9 (16.3)	$F = 7.5$, p = 0.001, 3 > 1, 2
Mean age at onset of disorder, years (SD)	19.9 (13.2)	21.5 (14.2)	31.1 (16.6)	$F = 7.4$, p = 0.001, 3 > 1, 2
Mean duration of illness, years (SD)	23.2 (16.3)	22.1 (16.7)	22.0 (11.7)	$F = 0.14$, p = 0.86
Median number of psychotropic medications at study entry	3	3	2	Median test $\chi^2 = 6.8$, p = 0.034, 3 > 1, 2
Mean Q-LES-Q score at entry[a]	2.9 (1.1)	3.4 (1.0)	3.7 (1.0)	$F = 8.0$, p < 0.001, 1 < 2, 3
Outcome variables				
Mean CGI depression score during study[a]	2.2 (0.7)	1.9 (0.7)	1.6 (0.6)	$F = 11.2$, p < 0.001, 1 < 2, 3
Mean CGI mania score during study[a]	1.6 (0.5)	1.3 (0.4)	1.3 (0.4)	$F = 3.5$, p = 0.032
Mean CGI overall score during study[a]	2.4 (0.8)	2.0 (0.7)	1.7 (0.6)	$F = 10.7$, p < 0.001, 1 < 2, 3
Mean GAF score during study	64.1 (6.7)	66.8 (7.4)	69.2 (8.8)	$F = 7.7$, p = 0.001, 1 < 3
Mean Q-LES-Q score during study[a]	3.0 (0.7)	3.3 (0.7)	3.7 (0.6)	$F = 11.6$, p < 0.001, 1 < 2, 3

SD = standard deviation; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; CGI = Clinical Global Impression; GAF = Global Assessment of Functioning.
[a]Arithmetic average of all assessments.

depressive and manic spectrum symptoms, in the absence of many comorbid obsessive-compulsive and panic spectrum symptoms. The third subtype is characterized by the endorsement of a limited number of symptoms from both the mood and anxiety spectra. Interestingly, we found clinical and demographic differences among the subtypes. The spectrum profiles of the classes are not parallel and do not have a similar shape. This means that the three classes are not characterized by increasing levels of spectrum comorbidity but are qualitatively different. Anxiety comorbidity, for instance is very pervasive only in class 1.

This class includes predominantly females and subjects with a lower age at onset of BD, in line with other findings from the literature (23).

Our findings that the latent class membership is associated with poorer functioning, higher severity and lower quality of life during treatment highlights the utility of the spectrum measures as clinically meaningful predictors of clinical course and treatment response. In addition, the identification of clinically relevant phenotypes may help research aimed at evaluating the underlying genetics and neurobiology of BD.

We acknowledge that the set of variables we have selected has led to specific subtypes and that the use of different variables might generate different subtypes. Still, we believe that this does not diminish the potential clinical and research utility of our results. The spectrum approach has the advantage of being complementary and not alternative to the DSM classification, because it includes the DSM-IV criteria but extends the assessment to associated features of the disorder of interest. Complementing the DSM assessment with a spectrum approach to psychopathology holds clear promise for the identification of *specific* sub-groups of patients likely to respond to *specific* treatments or treatment strategies, for more targeted genetic and neuroimaging studies and, ultimately, for establishing a benchmark for durable recovery with return to satisfactory functioning.

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