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Research paper

An approach to revealing clinically relevant subgroups across the mood spectrum

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ABSTRACT

Background: Individuals diagnosed with bipolar 1 disorder (BP1), bipolar 2 disorder (BP2), or major depressive disorder (MDD) experience varying levels of depressive and (hypo)manic symptoms. Clarifying symptom heterogeneity is meaningful, as even subthreshold symptoms may impact quality of life and treatment outcome. The MOODS Lifetime self-report instrument was designed to capture the full range of depressive and (hypo)manic characteristics.

Methods: This study applied clustering methods to 347 currently depressed adults with MDD, BP2, or BP1 to reveal naturally occurring MOODS subgroups. Subgroups were then compared on baseline clinical and demographic characteristics and as well as depressive and (hypo)manic symptoms over twenty weeks of treatment.

Results: Four subgroups were identified: (1) high depressive and (hypo)manic symptoms (N=77, 22%), (2) moderate depressive and (hypo)manic symptoms (N=115, 33%), (3) low depressive and moderate (hypo)manic symptoms (N=82, 24%), and (4) low depressive and (hypo)manic symptoms (N=73, 21%). Individuals in the low depressive/moderate (hypo)manic subgroup had poorer quality of life and greater depressive symptoms over the course of treatment. Individuals in the high and moderate severity subgroups had greater substance use, longer duration of illness, and greater (hypo)manic symptoms throughout treatment. Treatment outcomes were primarily driven by individuals diagnosed with MDD.

Limitations: The sample was drawn from three randomized clinical trials. Validation is required for this exploratory study.

Conclusions: After validation, these subgroups may inform classification and personalized treatment beyond categorical diagnosis.

1. Introduction

Major depressive disorder (MDD), bipolar 2 (BP2), and bipolar 1 (BP1) disorder diagnoses are currently based on categorical conceptualizations of the number and duration of symptoms and their severity. That is, individuals are required to meet clinically-defined threshold levels of (hypo)manic and/or depressive symptoms in order to receive one of these diagnoses. However, evidence of heterogeneity in symptom severity within unipolar and bipolar disorder diagnoses has been accumulating (e.g., see Cassano et al., 2004; Fagiolini et al., 2007), particularly regarding sub-clinical levels of symptoms. Cassano et al., (1999a) emphasize the importance of considering the "full range of characteristics of subthreshold mania", as even incomplete manifestations of (hypo)mania can have clinical relevance. For example, individuals with MDD may experience (hypo)manic symptoms that do not present in such a way as to meet the clinical threshold for bipolar 1 or 2 disorder (Cassano et al., 2004), and individuals who do meet the criteria for BP1 and BP2 may have varying levels of depression and (hypo)mania (Fagiolini et al., 2007). To treat MDD, BP1 and BP2 most effectively, it is important to consider the full continuum of depressive and (hypo)manic symptoms, rather than rely only on whether these symptoms meet a *syn*dromal threshold.

With the recognition of heterogeneity in symptom severity *within* MDD, BP2 and BP1 diagnoses, the potential for some individuals to have similar symptom profiles *across* these diagnoses should also be considered. To this end, nosologists have posed the question of whether MDD, BP2, and BP1 diagnoses are separated

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by natural boundaries, or whether psychopathology may be better characterized by a continuum of depressive, hypomanic, and manic symptoms. For example, Angst and Cassano (2005) suggest a schema for describing the "mood spectrum", that is, a gradient of depressive, hypomanic, and manic symptoms across a horizontal plane and symptom severity (normal, sub-threshold, threshold non-psychotic, and threshold psychotic) on a vertical plane. Beyond theoretical discussion, ample empirical evidence is available to challenge the classic unipolar-bipolar distinction, including the frequent misdiagnosis of bipolar disorder as unipolar disorder (Altamura et al., 2015; Ghaemi et al., 1999, 2001) and genetic similarities across MDD, BP2, and BP1 (Dell'Osso et al., 2014; Duffy et al., 2000; Lin et al., 2011; McGuffin and Katz, 1989).

This study searches for natural subgroups across the mood spectrum (MDD, BP2, BP1) based on the full continuum of lifetime mood severity symptoms, including those that are subthreshold. To accomplish this, we considered 347 depressed adults diagnosed with MDD, BP2, or BP1, and used clustering methods to reveal subgroups of individuals with similar symptom profiles based on the MOODS Lifetime instrument (Cassano et al., 2002; Fagiolini et al., 1999). The MOODS Lifetime instrument was created specifically to capture a continuum of self-reported depressive and (hypo)manic symptoms that may be reported across the mood spectrum over an individual's lifetime, with a particular emphasis on the subthreshold manifestations that are likely to contribute to much of the heterogeneity observed within our existing diagnoses. If novel subgroups could be identified based on the MOODS instrument, we aimed to determine whether they were related to demographic and clinical information, comorbidities, quality of life, and treatment outcome. After validation, these findings could suggest ways to improve current classification, inform existing treatment approaches, and develop new personalized treatments for each subgroup (Jablensky, 2016; Philips, 2016).

2. Methods

2.1. Participants

The sample used in the present study includes 347 depressed

Table 1.
Study comparison based on clinical and demographic characteristics. Abbreviations: BDCP = Bipolar Disorder Center for Pennsylvanians; BP2= Bipolar 2 Study, DP =Depression Phenotypes Study; QLESQ = Quality of Life Enjoyment and Satisfaction Questionnaire; PAS=Panic-Agoraphobic Spectrum; SCID = Structured Clinical Interview for DSM-IV. FE in place of statistic indicates that the Fisher's Exact test was used because of small sample sizes within each cell.

	Full sample (N=347)	**BDCP (N=91; 78% BP1, 22% BP2)**	**BP2 (N=66; 100% BP2)**	**DP (N=190; 100% MDD)**	**F or Chi-square Statistic (*p*-value)**	**Pairwise Comparisons (|d| > 0.2)**
Lifetime MOODS, *mean (SD)*						
Mood-Manic	19.19 (4.76)	20.66 (4.37)	20.5 (4.01)	18.04 (4.88)	13.31 (< 0.001)	(1, 2) > 3
Mood-Depressive	13.54 (6.83)	17.88 (5.39)	18.38 (5.21)	9.78 (5.54)	100.65(< 0.001)	(1, 2) > 3
Energy-Manic	6.54 (2.48)	7.35 (1.92)	7.48 (2.02)	5.83 (2.64)	19.39 (< 0.001)	(1, 2) > 3
Energy-Depressive	6.16 (3.66)	8.88 (2.52)	8.61 (2.68)	4.02 (2.96)	124.19(< 0.001)	(1, 2) > 3
Cognition-Manic	15.17 (5.07)	18.05 (3.86)	16.76 (5.19)	13.24 (4.69)	38.62(< 0.001)	1 > 2 > 3
Cognition-Depressive	9.02 (5.24)	12.33 (4.48)	12 (4.36)	6.39 (4.34)	75.37(< 0.001)	(1, 2) > 3
Rhythm	16.91 (5.01)	19.42 (4.43)	19.13 (4.83)	14.94 (4.47)	39.93(< 0.001)	(1, 2) > 3
Clinical characteristics, *mean(SD) or %(N)*						
Age of First Depressive Episode (N=333)	21.17 (10.91)	18.39 (7.8)	16.22 (5.68)	24.13 (12.44)	17.87 (< 0.001)	3 > 1 > 2
Age of First Manic or Hypomanic Episode (N=144)	20.94 (7.83)	21.83 (7.88)	19.81 (7.68)	NA	2.37 (0.126)	
First Episode ≤ Age 15 (N=338)	34.91 (118)	44.83 (39)	50.77 (33)	24.73 (46)	19.44 (< 0.001)	(1, 2) > 3
Years since First Depressive Episode (N=333)	17.37 (12.74)	22.13 (11.98)	17.12 (11.08)	15.36 (13.11)	8.41 (< 0.001)	1 > 2 > 3
Years Since First (hypo)manic Episode (N=144)	16.7 (10.95)	19.01 (10.98)	13.73 (10.25)	NA	8.7 (0.004)	1 > 2
Family History of MDD, BP1, BP2, Anxiety, or Schizophrenia (N=248)	96.37 (239)	94.32 (83)	100 (57)	96.12 (99)	FE (0.208)	
Quality of Life (QLESQ; N=324)	38.95 (8.11)	40.43 (9.84)	37.81 (7.91)	38.71 (7.33)	1.94 (0.145)	
Life Satisfaction (QLESQ; N=338)	2.55 (0.84)	2.68 (1.06)	2.56 (0.82)	2.49 (0.72)	1.59 (0.206)	
Panic-Agoraphobic Symptoms (PAS; N=345)	33.29 (20.11)	41.11 (20.63)	41.63 (19.78)	26.73 (17.51)	25.71 (< 0.001)	(1, 2) > 3
SCID diagnoses (Lifetime)						
Any Anxiety Disorder	62.25 (216)	54.95 (50)	69.7 (46)	63.16 (120)	3.69 (0.158)	
Obsessive Compulsive Disorder	6.05 (21)	5.49 (5)	4.55 (3)	6.84 (13)	FE (0.867)	
Substance Use Disorder	35.16 (122)	58.24 (53)	34.85 (23)	24.21 (46)	31.26 (< 0.001)	1 > 2 > 3
Eating Disorder	12.1 (42)	17.58 (16)	15.15 (10)	8.42 (16)	5.57 (0.062)	
Posttraumatic Stress Disorder	12.39 (43)	15.38 (14)	15.15 (10)	10 (19)	2.21 (0.33)	
SCID diagnoses (Past Month)						
Any Anxiety Disorder	50.43 (175)	37.36 (34)	63.64 (42)	51.11 (99)	11.03 (0.004)	2 > 1
Obsessive Compulsive Disorder	2.59 (9)	1.1 (1)	3.03 (2)	3.16 (6)	FE (0.652)	
Substance Use Disorder	2.31 (8)	4.4 (4)	3.03 (2)	1.05 (2)	FE (0.151)	
Eating Disorder	2.59 (9)	4.4 (4)	4.55 (3)	1.05 (2)	FE (0.073)	
Posttraumatic Stress Disorder	4.03 (14)	4.4 (4)	6.06 (4)	3.16 (6)	FE (0.503)	
Demographics						
Female (vs. Male)	63.11 (219)	68.13 (62)	65.15 (43)	60 (114)	1.89 (0.388)	
White (vs. Non-white)	82.42 (286)	82.42 (75)	74.24 (49)	85.26 (162)	4.11 (0.128)	
Age	38.37 (12.17)	40.87 (11.6)	32.96 (10.79)	39.05 (12.38)	9.14 (< 0.001)	(1, 3) > 2
Current mood symptom Scores						
Depressive Symptoms	12.76 (3.48)	6.20 (4.06)	13.79 (2.64))	13.43 (2.39)	94.89 (< 0.001)	2 > 3 > 1
Square Root of (Hypo)anic Symptoms	1.02 (0.86)	0.80 (1.08)	1.79 (0.73)	0.72 (0.64)	50.06 (< 0.001)	2 > 3 > 1