Conceptualising the later stage of bipolar disorder: Descriptive analyses from the ORBIT trial

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Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abstract

Objectives: This study aimed to investigate the features of later stage BD and specifically, factors underlying later stage BD and potential subgroups within this stage, to understand more about the later stage group and contribute to the measurement of stage.

Methods: An exploratory factor analysis was conducted using variables relating to current phenomenological aspects of illness, followed by cluster analyses based on the identified factors. Finally, the resultant clusters were compared based on course of illness variables.

Results: Fourteen extracted factors explained 57 percent of the variance. Latent structures aligned with current depressive symptoms, energy and interest, independence, occupational functioning, symptoms of anxiety, pain, elevated symptoms, interpersonal functioning, anger, perceptions of social connections, perceptions of current medication effectiveness, cognitive issues, sleep issues, and sense of isolation. Two clusters were identified which differed significantly on each of these factors, and on a range of course of illness features including lifetime number of episodes, duration of illness and number of depressive hospitalisations.

Conclusions: Latent phenomenological features relevant to individuals in the later stage of BD were identified. Two clusters of individuals in later stage BD differ based on these features as well as course of illness, suggesting that there are distinct subgroups of individuals in the later stage of BD, distinguishable based on current phenomenology and illness history. However, findings are exploratory and therefore require confirmation before they can be applied clinically.

Key words

Bipolar

Bipolar Disorder/classification*

Bipolar Disorder/psychology

Models, Psychological*

Prognosis

Disease Progression

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Manuscript

Growing evidence indicates that for many, bipolar disorder (BD) is a progressive illness. The field of BD research is in the midst of attempts to conceptualise progression in BD, with staging models proposed to describe key features and correlates of BD as this progresses. No model of clinical staging in BD has yet been validated with systematic empirical testing, however a number of studies recently have focused on the advancement of staging in BD (e.g.¹⁻³). In line with this, the current study aims to advance the understanding of stage of illness in BD, via an exploration of latent structures underpinning phenomenological experiences, and of clinically meaningful subgroups within the ‘later stage’ of BD.

The dominant BD specific staging models were developed by Berk and colleagues^{4,5} and Kapczinski and colleagues⁶. Both models describe the features and correlates of BD as it progresses, broadly agreeing on an at-risk stage, which is followed by subthreshold symptoms, then progression to threshold illness, then recurrence and finally chronic, unremitting illness, with loss of functioning and autonomy^{7,8}. A summary of these models and their proposed features can be found in Supplementary materials.

While there is sufficient empirical evidence to indicate that a delineation exists between a broad earlier and later stage of established BD⁹, no model of staging in BD to date has presented a comprehensive picture of ‘later stage’ BD, validated by data from those classified within this stage. Within the proposed BD specific staging models, there is a lack of agreement on the borders between broad stages, and the probable sub-stages within these¹⁰. A clearer picture of later stage of BD is required to develop appropriate interventions for this ‘treatment resistant’ cohort⁸. As summarized by Salagre, et al.¹¹ improved understanding of the heterogeneity within illness stages via integration of multiple levels of information is the next step towards precision psychiatry, so called ‘staging 2.0’, potentially

identifying specifiers or subgroups of clinical importance. Additionally, as noted by Post^{10,12}, a more nuanced understanding of each stage of illness will provide a common language for researchers and allow delineation of the complex relationships between the correlates associated with progression, such as accumulating episodes and functional decline. For example, a direct comparison of the dominant BD staging models in classifying individuals resulted in the significant majority of participants classified within the later stages, prompting authors to suggest that further subclassification within the existing definitions of stages would result in greater utility¹.

Therefore, a more detailed investigation into the potential underlying characteristics of ‘later stage’ BD is warranted. Additionally, an exploration of subgroups within this broad stage will advance the understanding of the phenomenon of staging within BD, and its specific applicability to stage-tailored interventions. For example, in this vein, a recent systematic review suggested that stage of illness, operationalised by proxies, has a role in the effectiveness of psychosocial interventions for improving functioning¹³.

The current study. This study aims to investigate the features of later stage BD. This analysis will examine factors underlying later stage BD and potential subgroups within this stage, to understand more about the later stage group and contribute to the advancement of staging towards precision psychiatry. While this study is exploratory, it is hoped that two research questions will be addressed with these analyses.

1. What are the underlying dimensions of late stage BD?
2. Are there clinically meaningful subgroups within this stage, based on these features?

Method

Participants

Participants were from the ORBIT RCT (experiencing ‘later stage’ BD, defined as having experienced 10 or more lifetime mood episodes). Importantly, various episodic ‘cut points’ have been used to identify later stage individuals in previous studies, for example 5 and 10 episodes^{1,14,15}. The ORBIT trial from which these data were drawn employed a conservative cut point of 10 episodes to best ensure participants were within later stage. Participants in the trial were adults (18–65 years of age) who had received a diagnosis of BD from a medical practitioner, confirmed via the Mini-International Neuropsychiatric Interview

(MINI¹⁶). Additionally, participants were not in a current mood episode or experiencing current psychotic features or active suicidality, and all were under the care of a medical practitioner.

Measures

1. DSM-IV diagnosis of BD confirmed via telephone interview with the MINI¹⁶. Presence and severity of substance or alcohol use disorders was also determined with the MINI. Additionally, number of prior episodes of mania, hypomania and depression were assessed within the context of the MINI and assessor prompts, e.g., life and world events.
2. Brief Quality of life in Bipolar Disorder Scale (QoL.BD)¹⁷. A 12-item measure assessing QoL for individuals experiencing BD, based on 12 domains (physical, sleep, mood, cognition, leisure, social, spirituality, finance, household, self-esteem, independence, and identity).
3. Functioning Assessment Short Test (FAST)¹⁸. An interviewer-rated measure evaluating functional impairment across six domains (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, leisure time), validated in patients with BD. The measure has excellent test-retest reliability and internal consistency.
4. Assessment of Quality of Life-Eight Dimension (AQOL-8D)¹⁹, a self-report assessment of health-related QoL which has been validated and demonstrated high test-retest reliability.
5. Depression Anxiety Stress Scale (DASS-21)²⁰. A validated, reliable self-report measure of depression, anxiety and stress (only items from the anxiety sub-scale will be used).
6. Young Mania Rating Scale (YMRS)²¹. A gold standard, psychometrically sound interviewer-rated scale to assess manic symptoms.
7. Montgomery-Asberg Depression Rating Scale (MADRS)²². A gold standard, psychometrically sound interviewer-rated scale to assess depression symptoms.
8. Quick Inventory of Depressive Symptoms (QIDS-SR)²³. A self-report measure of depression symptoms with high internal consistency ($\alpha = 0.87$), that correlates highly with established clinician-rated scales.

Perceived effectiveness of current medication was asked as part of an unpublished Resource Use Questionnaire designed to assess differences in mental health service utilisation between groups before, during, and after the intervention. Two questions were developed, asking

participants to rate their perception of the effectiveness of current medications for elevated symptoms and depressive symptoms respectively on a five-point scale. Detail about the trial methods is available in a published protocol ²⁴.

Analytic approach

As noted, the later stage has been broadly defined, and the features within this stage require further clarity. We chose to examine phenomenology as the basis for the present analyses for several key reasons. Firstly, pragmatically, these features are a part of routine clinical assessment. Further, gaining a clearer understanding of the distribution of these features contributes to a precision psychiatry approach, potentially adding granularity and specificity to current definitions. Therefore, we opted to include variables representing current phenomenology as the basis for an exploratory factor analysis (EFA) and subsequent cluster analysis. We then assessed whether resultant clusters varied with regard to their demographics and clinical histories to further illuminate the nature of these groups.

Prior to conducting these analyses, scores on all variables to be included in the EFA and subsequent cluster analysis were recoded such that higher scores represented ‘worse’ ratings on the measure (e.g. poorer quality of life and functioning, lower perceived effectiveness of current medications, more depressive symptoms), to aid interpretation.

Exploratory Factor Analysis. An EFA was conducted using variables relating to current phenomenological aspects of illness. Variables included in the EFA were based on the literature regarding clinical staging and proposed correlates of later stage bipolar disorder. These were individual items from measures assessing current self and clinician reported depressive, elevated and anxious symptoms, quality of life, autonomy, functioning, and perceived effectiveness of current medications. The number of factors retained was determined using a combination of three methods; scree plot, Kaiser’s criterion and parallel analysis (Monte Carlo simulation). Principle Axis extraction was used given that multivariate normality could not be assumed, and this method reportedly produces the most accurate results in most situations ²⁵. Oblique rotation methods were used as it was expected that at least some factors would be correlated. Specifically, Promax rotation was selected to approximate the best and most replicable fit among oblique methods.

Cluster analysis. A k-means cluster analysis based on the resultant standardized factor scores was conducted to identify potentially clinically meaningful subgroups. Based on previous research, a two-cluster solution was expected, but this assumption was tested

statistically in the data with a two-step cluster analysis conducted prior to the k-means analysis. Two-step cluster analyses involve automatic identification of the ideal number of clusters to be retained (via a combination of Akaike information criterion [AIC], Bayesian information criterion [BIC] and ratio of change methods) with excellent accuracy, while also enabling forced selection of cluster numbers for the comparison and validation.. Subsequent comparison of assignment of cluster membership by k-means assessed stability of the solution ²⁶.

Cluster-based comparisons of demographic and clinical course variables. The identified clusters were compared based on relevant demographics and course of illness characteristics using independent samples t-tests, Mann-Whitney tests or chi-square tests of independence, as appropriate based on distribution and/or data characteristics.

Results

Sample characteristics

Table 1 describes the demographic characteristics of the sample. The ORBIT CONSORT diagram has been presented in Supplementary materials.

[Table 1 about here]

EFA Results

The means, standard deviations, ranges (actual and potential) and Cronbach's alpha for measures included in the EFA are shown in Table 2.

[Table 2 about here]

Suitability for Factor Analysis. The factorability of the selected variables was tested by conducting an initial Pearson's correlational analysis. As per Francis' ²⁷ recommendations, all items demonstrated correlations of greater than .30 with at least one other item, without exceeding .80. Bartlett's test of sphericity was significant ($\chi^2(2278) = 12262.363, p < .001$), verifying the significance of the correlations between items²⁷. The Kaiser-Meyer-Olkin measure of sampling adequacy was .90 indicating that the strength of the relationships amongst variables was 'marvellous' and confirming the appropriateness of the data for factor analysis ²⁷. Communalities were mostly above .40 and crossloading items were eliminated according to the .40/.30/.20 rule, which recommends that satisfactory variables (a) load onto their primary factor above 0.40, (b) load onto alternative factors below 0.30, and (c) demonstrate a difference of 0.20 between their primary and alternative factor loadings ²⁵.

Factor Solution. Fourteen extracted factors comprised 68 items and explained 57 percent of the variance in the sample. The large number of items (over one third) removed iteratively during the EFA reflects the similarity of many items across scales (multicollinearity), as well as items appearing to reflect overlapping latent structures (crossloading; for example, an item assessing social isolation loading on depression as well as independence), while other items did not significantly contribute to the factor structure.

The final model had 14 factors as informed by the scree plot, Kaiser and parallel analysis. These were Depressive Symptomatology (accounting for 27.7 % variance), Independence (5.0%), Energy and Interest (4.4% variance), Occupational Functioning (3.7 %), Anxiety (3.2%), Physical Pain (2.4 %), Elevated Symptomatology (2.1%), Interpersonal Functioning (1.8%), Anger (1.5%), Social Connectedness (1.4%) Perceived Effectiveness of Medication (1.3%), Cognitive functioning (1.1%), Sleep (1.0%) and Isolation (.9%). Most factors had at least 3 items loading on them, with the exception of the Social Connectedness, Perceived Effectiveness of Medication, Sleep, and Isolation factors; retained due to support in prior research and as, according to Yong and Pearce ²⁸, a factor with 2 variables can be considered reliable when items are highly correlated with each other but fairly uncorrelated with other variables. In addition, in some cases only two conceptually similar items were included in the analyses (e.g. only two medication-related items were entered). We retained one item, *How enthusiastic do you feel*, which crossloaded on factors 1 and 3 with a difference in loadings of .18 (while meeting the other conditions of the .40/.30/.20 rule).

Factor 1 (Depressive Symptomatology) comprised items reflecting current depressive symptomatology including sadness, anhedonia, despair, and self-perception. Factor 2 (Independence) comprised items relating to autonomy, activities of daily living (self-care, home duties, shopping) and ability to solve basic problems. Factor 3 (Energy and Interest/Activation) comprised items tapping interest, enjoyment and energy. Factor 4 (Occupational Functioning) reflected performance at work. Factor 5 (Anxiety) comprised items reflecting current anxiety symptoms; panic, fear and physical symptoms. Factor 6 (Pain) reflects the experience and impacts of physical pain. Factor 7 (Elevated Symptoms) reflects experiences common within mania or hypomania, elevated mood and activity levels, pressured speech and thought disorder. Factor 8 (Interpersonal functioning) reflects functioning in relationships with friends and family. Factor 9 (Anger) reflects irritability and aggressive behaviour. Factor 10 (Social Connectedness) reflects current levels of social activity and interaction. Factor 11 (Medication Effectiveness) contains items tapping

perceived effectiveness of current medications taken for BD symptoms. Factor 12 (Cognitive Impairment) largely reflects difficulty concentrating. Factor 13 (Sleep) contains items reflecting difficulty sleeping. Finally, factor 14 (Isolation) contains items reflecting perception of difficulties feeling accepted and navigating outside one's home. Table 3 provides representative items per factors, and their loadings, while the full list of items can be found in Supplementary materials.

[Table 3 about here]

Cluster solution

Two-step cluster analysis resulted in a two-cluster solution which had 'fair' cohesion and separation. The number of clusters to retain was decided based on a range of criteria (the elbow method and AIC criteria to determine the best separation and cohesion as well a comparison of different numbers of clusters found in similar prior analyses²⁹⁻³². Subsequent k-means clustering assigned 88 % of participants to the same cluster as within the two-step solution, indicating adequate stability²⁶. K-means cluster analysis demonstrated that a two-cluster solution clearly distinguished between groups based on each of factor scores, as shown in Figure 1.

[Figure 1 about here]

ANOVA confirmed that the clusters differed significantly on each of the factor scores, and all were higher in Cluster 2. Specifically, given that variables were recoded such that higher scores reflected 'worse' outcomes across all domains, Cluster 2 represents individuals experiencing higher levels of current depression, reduced independence, poorer occupational and social functioning, poorer social connection, more severe anxiety, anger and elevated symptoms, poorer concentration, lower perceptions of effectiveness of medications as well as more pain and sleep issues.

Relationship of clusters to demographics and clinical course. Finally, the two clusters were compared on a range of demographic and clinical course of illness variables, via independent samples t-tests, Mann-Whitney tests or chi-square tests of independence. Results are presented in Table 4. Participants in cluster 2 had experienced significantly more total NoE as well as depressed and mixed episodes, longer duration since first symptoms, more hospitalisations for depression, and had spent a greater proportion of their life depressed or elevated (and inversely, less time well). Additionally, they were more likely to have attempted suicide and to experience rapid cycling. The clusters did not differ significantly on

any of the substance-related issues assessed, nor on age, gender identity or BD diagnosis distribution.

[Table 4 about here]

Discussion

This study aimed to further illuminate the later stage of BD, by interrogating a convenience sample of individuals with established BD and a history of ten or more mood episodes, which we classified as within ‘later stage’ BD. Exploratory factor analyses explained 57 percent of the variance in this sample and revealed a 14 factor solution. Latent structures aligned with current depressive symptoms, energy and interest, independence, occupational functioning, symptoms of anxiety, pain, elevated symptoms, interpersonal functioning, anger, perceptions of social connections, perceptions of current medication effectiveness, cognitive issues, sleep issues, and sense of isolation. Two subgroups were identified which differed on these factors, and on a range of course of illness features.

Phenomenology of later stage BD. Several of the emergent factors reflect the salient features of later stage illness described in clinical staging models. Specifically, interepisode symptoms in our sample of participants linked with Factors 1, 2 and 7, are a hallmark of both Berk’s⁵ and Kapeczinski’s later stages³³. Factor 1, subthreshold depressive symptomatology, was responsible for the largest proportion of variance in the factor model (and was among the determinants of the cluster structure). This suggests that residual depressive symptoms are prominent within the phenomenology of later stage BD. Indeed, multiple previous studies have pointed to the importance of residual depressive symptoms in BD, linked to impairments in functioning^{34,35} cognition³⁶, quality of life³⁷ and increased likelihood of suicidality³⁸.

Reduced autonomy is another central feature of later stage illness, which is common between staging models and aligns with Factor 3 in the current analyses⁶. Functioning is the basis for Kapeczinski’s staging model, and several of the factors revealed latent structures aligned with functional domains; Independence (Factor 2) describes individuals’ ability to manage their daily needs, Occupational Functioning (Factor 4) comprises items relating to performance at work, while Interpersonal Functioning (Factor 8) and Social Connectedness (Factor 10) encapsulate functioning within relationships, social activity and interaction. Treatment resistance is a defining feature of late stage within Berk’s model^{4,39}, while a related factor emerging from the current analysis was the perceived effectiveness of current

medications (Factor 11). Cognitive impairment is associated with progression in BD and captured in the dominant staging models, reflected in Factor 12. Another feature of Kapczinski's model is the emergence of comorbidities as the illness progresses; the Anxiety factor may lend some support to a role for comorbidity in the later stage of BD (Factor 5). These features differ from those described within proposals of the earlier illness stages, where cognition and functioning are intact, comorbidities less frequent and impactful, and symptoms remit between episodes (see, for example^{9,11,40} and Supplementary materials).

Implications of latent phenomenological structures. It should be noted that we intentionally included variables reflecting current phenomenology with previously reported relationships to progression, and specifically the later stage of BD, so these parallels are perhaps unsurprising. Nonetheless, our results add support for the relevance of and relationship between these constructs for those classified within the later stage of BD. Increasing the understanding of the experiences of those within later stage is a step towards precision psychiatry. A benefit of this approach to adding granularity to staging over reliance on clinical history is avoiding validity and reliability concerns resulting from the recall and measurement-related issues assessment of distal and often distressing events inherently involves⁴¹. Indeed, data about current symptoms, functioning, quality of life, and medication effectiveness are routinely collected as part of clinical assessment.

In terms of measurement, most factors included a combination of items from distinct measures. For example, Factor 1 contained items from the QIDS, QoL.BD and AQOL8D scales and Factor 3 contained items from the FAST, QIDS and QOL.BD, which have distinct foundations and applications. Other factors contained subsets of items from individual scales, such as the Anxiety subscale of the DASS (Factor 5), yet other items from these source scales were discarded as they did not contribute meaningfully to the variance within this sample. This may indicate that adequately encapsulating the phenomenological experiences of later stage BD (i.e. for the purpose of treatment decision-making) is likely to require a combination of existing measures or the development of a new measure. The development of such a measure could begin with the domains identified in the current study, should these be confirmed through subsequent investigations.

Meaningful subgroups in later stage BD. Our results indicate that latent phenomenological features, denoted by factor scores, reliably distinguish between two subgroups of individuals within the later stage of BD. Cluster 2 represented greater illness

severity and impacts based on current phenomenology, with significantly higher scores across all latent domains. Concordantly, several previous cluster analyses have distinguished between groups of individuals with BD based on features present in the current model. For example, an analysis conducted by Grande, et al.³¹ with the aim of contributing to staging models aligns with our findings: Two clusters were distinguishable based functioning (FAST) scores. Another cluster analysis based on FAST scores distinguished between three groups, representing low, intermediate and good functioning⁴². Further, these clusters differed significantly in residual depressive and elevated symptomatology, as within the current study. Similarly, another study clustered participants based on changes to FAST scores across five years, with a two-cluster solution reflecting progressive and a non-progressive cluster which also differed in cognitive functioning²⁹. Another analysis used cognitive functioning as the determinant of clusters, and resulted in three clusters³⁰, paralleling differences on the (subjective) cognitive impairment factor between our clusters. In a further study, a broader range of ‘profilers’ were used, reflecting severity across several domains (including FAST scores, quality of life and cognitive impairment), and five clusters significantly differed on these³². These parallels support the existence of multiple subgroups of individuals experiencing BD, with phenomenological differences in domains of functioning, cognitive functioning, residual symptoms and quality of life.

Implications of the identified subgroups. These clusters may reflect substages or distinct phenotypes within later stage BD, with potential implications for the treatment of BD. For example, Deckersbach, et al.⁴³ found that membership within clusters formed based on severity and course of illness predicted response to treatment in the STEP-BD psychotherapy sample. Similarly, a recent systematic review explored differences in response to psychosocial treatments in subgroups formed based on stage-related characteristics (NoE, cognitive functioning, general functioning, comorbidities), and found that these subgroups exhibited differences in improvements to general or social functioning¹³.

Our findings also indicate that the cohort classified as ‘later stage’ (≥ 10 mood episodes) in this study included individuals with experiences ranging from minimal functional or cognitive impairments and intact ability to work and live independently to significantly impaired across these domains. Indeed, these findings suggest that even those individuals who might be classified within the same stage according to current models may in fact comprise multiple subgroups, which has significant clinical implications. Identifying models that group patients according to quantitative cutoffs of clinical variables is a further step toward designing personalised treatments, which move beyond current nosology and

even discrete clinical stages, to better account for individual experiences and needs¹¹. Next steps may include developing tailored treatments for subgroups, which is a primary aspiration for a staging model in BDs.

Subgroup differences in features and clinical histories. Further, course of illness variables differed significantly between clusters, including NoE, duration of illness, number of hospitalizations, likelihood of having attempted suicide and rapid cycling, and these have been linked to progression and clinical staging. This suggests that the identified subgroups differ not only in their current phenomenological experiences, but also in their history and course of illness. Compatible findings have been reported previously. For example, Grande, et al.³¹ found that their two clusters were distinguishable based on lifetime NoE and duration of illness. Likewise, the two progression-based clusters found by López-Villarreal, et al.²⁹ could be distinguished by duration of illness. In summary, parallels between findings of the current study and those in prior analyses include differences between clusters in course of illness; specifically, NoE and duration of illness. Notably, our clusters did not differ in age, gender or diagnosis.

Implications. Taken together, these findings suggest that there may be distinct profiles within later stage BD, and that individuals differentiated based on current phenomenology, reflecting the severity and impacts of current functional impairments and symptoms, also differ with regards to their clinical histories, but not the assessed demographic variables. Potential implications of this finding include adding granularity to existing staging proposals. For example, adding data about individuals' scores on well-validated measures assessing current phenomenology to information about their diagnosis and course of illness ('stage') may prove to be informative for selecting appropriate treatments (for example, adjunctive psychosocial treatments with differing intensities or foci), in line with a stepped care ideology^{44,45}. To achieve this aspiration, confirmation of phenomenology based subgroups in other samples is required. An important next step before such efforts have clinical utility is examining whether subgroups, based on this more granular approach, respond differently to treatments, and one such study is currently underway in our group to provide this data.

Limitations. The present investigation had several key limitations. Specifically, our sample was a treatment seeking sample of individuals not currently experiencing a mood episode, not necessarily representative of the population⁴⁶. Extrapolating from clinical trial samples may lead to distorted conclusions, and epidemiological data are required to confirm

the current findings. Further, the analyses were exploratory, and no validation methods were employed; as such the factor structure requires confirmation. The model would also benefit from replication within ‘later stage’ samples categorized using other methods (not dependent on NoE), and within broader groups of individuals with BD as it is not possible to infer from our findings whether the identified factor structure is unique to the population sampled. While we utilized a number of gold standard measures, we relied on self-report for most measures: most notably, NoE, an inclusion criterion for the RCT from which these data were drawn. NoE as a construct suffers from issues with conceptualization and measurement and there are no established episodic boundaries aligned with stage of illness⁴¹. Likewise, our measure of medication effectiveness has not been published or validated, calling into question the validity and reliability of the resultant factor, which also had a small eigenvalue. We retained this due to theoretical relevance and face validity as well as meeting our threshold for retention. Another key limitation is that staging models are underpinned by the assumption of neuroprogression, involving progressive changes to the structure and function of brain, yet the current study included no measure of brain function outside subjective self-assessment cognitive impairment. This limits the explanatory potential of the resultant models and should be a focus of future research, given the absence of biomarkers of stage to date.

Conclusion. This study sought to further illuminate the features pertinent to, as well as subgroups within, the broadly defined later stage of BD. Results of the factor analysis revealed phenomenological features relevant to individuals in the more advanced, “later” stage of BD, in particular residual symptoms during euthymia, energy and interest, and current level of independence and functioning (occupational, interpersonal and cognitive). Two clusters differed on each of these features as well as course of illness, suggesting that there are distinct subgroups of individuals in the later stage of BD, distinguishable based on current phenomenology. These findings may contribute to the conceptualization and advancement of stage of illness in BD towards its precision psychiatry aims, and ultimately toward the development of tailored interventions for the later stage group, for whom existing interventions are inadequate. However, findings are exploratory and therefore require confirmation before they can be applied clinically.

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Table 1
Demographics of the Sample

Variable	Percentage or Means, Standard Deviation and range (n = 302)
Age	M = 44, SD = 11.8, 20-65
Gender identity % (n)	
Male	29.1 (88)
Female	68.9 (208)

Transgender	1.3 (4)
Not identified	0.7 (2)

Diagnosis % (n)

Bipolar Disorder I	80.1 (242)
Bipolar Disorder II	17.9 (54)
Bipolar Disorder NOS	2.0 (6)

Number of Episodes

Depressive	M = 40.73, SD = 57.92, 0-600
Manic	M = 7.49, SD = 20.43, 0-210
Hypomanic	M = 19.98, SD = 48.90, 0-460
Mixed	M = 2.41, SD = 9.10, 0-96
Total	M = 93.33, SD = 163.44, 10-1860

Main Occupation % (n)

Employed	53.6 (162)
Unemployed	11.6 (35)
Student	6.0 (18)
Volunteer	4.3 (13)
Retired	5.0 (15)
Home duties	6.3 (19)
Pension	13.2 (40)

Marital Status % (n)

Single	37.1 (112)
Married	41.4 (125)
Divorced	11.9 (36)
Separated	2.3 (7)
Defacto	5.3 (16)
Widowed	2.0 (6)

Difficulty with everyday activities % (n)

No	53.6 (162)
Yes, no support	32.5 (98)
Yes, support required	13.9 (42)

Table 2

Means, Standard Deviations and Reliability of Study Measures

	M (SD)	Range (potential range)	Cronbach's alpha
QIDS-SR	8.3 (4.8)	0-21 (0-27)	0.90
MADRS	8.2 (7.2)	0-40 (0-60)	0.86
YMRS	2.9 (3.7)	0-29 (0-60)	0.77
DASS-Anx	4.1 (3.6)	0-17 (0-21)	0.76
FAST	15.6 (11.02)	0-58 (0-72)	0.88
QoL.BD	39.74 (8.58)	13-47 (12-60)	0.87
AQOL8D	85.66 (19.92)	45-149 (35-176)	0.95

QIDS-SR = Quick Inventory of Depressive Symptoms, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale, DASS-Anx = Depression Anxiety Stress Scale 21 item, Anxiety subscale, FAST = Functioning Assessment Short Test, QoL.BD = Brief Quality of life in Bipolar Disorder Scale, AQOL8D = Assessment of Quality of Life-Eight Dimension

Table 3
Description and Representative Items of Extracted Factors

Factor	Representative items (source measure)	Loading
Depressive Symptomatology	<ul style="list-style-type: none"> How often do you feel worthless? (AQOL8D) How content are you with your life?? (AQOL8D) How often do you feel happy?? (AQOL8D) 	.91 .76 .64
Independence	<ul style="list-style-type: none"> Difficulty doing the shopping independently (FAST) Difficulty living on your own (FAST) Difficulty solving daily problems (FAST) 	.77 .72 .62
Energy and Interest	<ul style="list-style-type: none"> Over the past 7 days, I have... - Enjoyed things as much as I usually do (QoL.BD) Energy Level (past 7 days) (QIDS-SR) Ability to enjoy hobbies (FAST) 	.79 .69 .69
Occupational Functioning	<ul style="list-style-type: none"> Are you paid according to the position you occupy? (FAST) Difficulty holding down a paid job (FAST) Difficulty working in the field in which you were educated (FAST-Occ) 	.94 .87 .83
Anxiety	<ul style="list-style-type: none"> I felt scared without any good reason (DASS-Anx) I felt I was close to panic (DASS-Anx) I was worried about situations in which I might panic and make a fool of myself (DASS-Anx) 	.78 .78 .58
Physical Pain	<ul style="list-style-type: none"> How much pain or discomfort do you experience? (AQOL8D) 	.91 .85

	• How often does pain interfere with your usual activities? (AQOL8D)	.79
	• How often do you experience serious pain? (AQOL8D)	
Elevated Symptomatology	• This past week, have you been much more talkative than usual? (YMRS)	.79
	• Over the past 7 days, have you had more energy than usual to do things? (YMRS)	.76
	• Have there been times in the past week when you felt unusually good, cheerful, or happy? (YMRS)	.70
Interpersonal Functioning	• How much do you enjoy your close relationships (family and friends)? (AQOL8D)	.73
	• How satisfying are your close relationships (family and friends)? (AQOL8D)	.65
	• How satisfying are your close and intimate relationships (including any sexual relationships)? (AQOL8D)	.53
Anger	• In the past week, have you had difficulties cooperating or getting along with other people? (YMRS)	.87
	• Have you been feeling irritable or angry this past week? (YMRS)	.78
	• How often do you feel angry? (AQOL8D)	.38
Social Connectedness	• Over the past 15 days, to what extent did you experience difficulty participating in social activities? (FAST)	.76
	• Over the past 15 days, to what extent did you experience difficulty maintaining friendships? (FAST)	.65
Effectiveness of Medication	• Current effectiveness of medications for depression (RUQ)	.76
	• Current effectiveness of medications for mania (RUQ)	.57
Cognitive functioning	• To what extent did you experience difficulty concentrating over the past 15 days? (FAST)	.88
	• To what extent has Concentration/Decision Making changed over the past 7 days (QIDS-SR)	.53
	• Over the past 7 days, I have had good concentration (QoL.BD)	.52
Sleep	• Falling Asleep (past 7 days) (QIDS-SR)	.65
	• How often do you have trouble sleeping? (AQoL8D)	.60
Isolation	• Over the past 7 days, I have felt accepted by others (QoL.BD)	.49

- Over the past 7 days, I have travelled around freely (e.g., driving, using public transport) (QoL.BD) .42

QIDS-SR = Quick Inventory of Depressive Symptoms, YMRS = Young Mania Rating Scale, DASS-Anx = Depression Anxiety Stress Scale 21 item, Anxiety subscale, FAST = Functioning Assessment Short Test, Cognitive domain, QoL.BD = Brief Quality of life in Bipolar Disorder Scale, AQOL8D = Assessment of Quality of Life-Eight Dimension, RUQ = Resource Use Questionnaire

Table 4

Comparison of Clinical Course Variables between Clusters

Clinical course variable	Cluster 1 (n = 177)	Cluster 2 (n = 125)	Statistical test, <i>p</i>
Total number of episodes (M [SD])	46.91 (51.5)	77.17 (63.58)	$t = 3.619, <.001^{**}$
Illness duration (M [SD])	26.42 (11.50)	29.99 (12.15)	$t = 2.56, .010^{*}$
Age (M [SD])	43.11 (11.39)	45.22(11.51)	$t = 1.55, .123$
Gender identity			
Male (n [%])	54 (31%)	34 (27%)	Fisher's Exact test .87
Female (n [%])	120 (68%)	88 (70%)	
Transgender (n [%])	2 (1%)	2 (2%)	
Other (n [%])	1 (<1%)	1(<1%)	
Diagnosis			
Bipolar Disorder I (n [%])	145 (82%)	97 (78%)	Fisher's Exact test .12
Bipolar Disorder II (n [%])	31 (18%)	23 (18%)	
Bipolar Disorder NOS (n [%])	1 (<1%)	5 (4%)	
% of lifetime depressed (M [SD])	32.71 (19.58)	44.15 (18.67)	$t = 5.10, <.001^{**}$
% of lifetime elevated (M [SD])	16.80 (11.90)	21.59 (13.51)	$t = 3.26, .001^{*}$
% of lifetime well (M [SD])	50.05 (23.19)	34.26 (19.45)	$t = 6.60, <.001^{**}$
Depressive episodes (Mdn [Range])	15 (0-210)	30 (2-202)	$U = 6917, <.001^{**}$
Manic episodes (Mdn [Range])	3 (0-64)	2.5 (0-64)	$U = 7739, .322$
Mixed episodes (Mdn [Range])	0 (0-8)	0 (0-20)	$U = 7136, .011^{*}$
Hypomanic episodes (Mdn [Range])	6 (0-136)	6 (0-136)	$U = 4767, .942$
Hospitalisations, total (Mdn [Range])	1 (0 -33)	2 (0-104)	$U = 9573, .071$
Hospitalisations, mania (Mdn [Range])	0 (0-23)	0 (0-54)	$U = 9851, .089$
Hospitalisations, depression (Mdn [Range])	0 (0-20)	1 (0-50)	$U = 7534, <.001^{**}$
Psychotic features (yes %)	57%	50 %	$\chi^2 = 1.310, .252$
Rapid cycling subtype (yes %)	42%	67%	$\chi^2 = 18.11, <.001^{**}$
Lifetime suicide attempt (yes %)	51%	68%	$\chi^2 = 8.70, .003^{*}$
Alcohol Use Disorder, Mild (yes %)	1.69%	<1%	Fisher's Exact test .65
Alcohol Use Disorder, Moderate (yes %)	1.69%	<1%	Fisher's Exact test .65
Alcohol Use Disorder, Severe (yes %)	1.69%	6.40%	Fisher's Exact test .056
Substance Use Disorder, Mild (yes %)	3.39%	<1%	Fisher's Exact test .246
Substance Use Disorder, Moderate (yes %)	1.69%	2.4%	Fisher's Exact test .694
Substance Use Disorder, Severe (yes %)	3.95%	4.8%	Fisher's Exact test .778

*Significant at the .05 level; **significant at the .001 level

NB. These analyses were conducted after outliers in the episode variables were transformed. However, all comparisons remained significant when outliers were retained.

Figure 1. Mean factor scores for Clusters 1 and 2.

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