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ORIGINAL ARTICLE

Changes in energy and motor activity: core symptoms of bipolar mania and depression?

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Objective: To evaluate how well symptom rating scales differentiate bipolar disorder (BD) episode types.
Methods: One hundred and six patients with BD were followed for 13 years. At each visit, the following clinical scales were administered: Young Mania Rating Scale (YMRS), Hamilton Depression Scale (HAM-D) and Clinical Global Impressions scale for use in bipolar illness (CGI-BP). To perform a comparison between the affective states of BP, three time points in each patient's follow-up period were chosen for evaluation: the most severe manic episode, the most severe depressive episode, and the euthymic period with least symptoms. Canonical discriminant analyses (CDA) were performed to identify which symptoms best discriminated episodes.
Results: CDA revealed HAM-D was worse than YMRS and CGI-BP to discriminate mood states. The items evaluating increased motor activity in YMRS (2, increased motor activity/energy) and HAM-D (9, agitation) were the best to distinguish mania, depression, and euthymia. In contrast, HAM-D item 8 (retardation) and the HAM-D and YMRS items related to mood symptoms were less important and precise.
Conclusion: Higher levels of energy or activity should be considered a core symptom of mania. However, our results do not confirm the association between a decrease in energy or activity and depression. HAM-D probably does not assess motor activity adequately.

Keywords: Bipolar disorder; discriminant analysis; motor activity; energy

Introduction

In the fourth edition of his textbook, Kraepelin[1] proposed a unitary concept of melancholia: an illness characterized by retardation of movements and thoughts. Coherently with that view, several modern authors[2,3] have considered psychomotor retardation as a central feature of depression. These claims have been supported by studies using actigraphy, which showed a decrease in motor activity in depressed patients when compared to normal controls. Longitudinally, over the course of successful treatment with antidepressants, this motor retardation was reversed.[4]

In contrast, an increase in energy or motor activity has been associated with mania in bipolar disorder (BD). Several studies have analyzed the latent structure of manic symptoms, and found that the factor related to hyperactivity showed the highest correlation with total Mania Rating Scale scores.[5-7] Moreover, actigraphic studies have reported higher levels of motor activity in manic patients than in patients with schizophrenia or healthy subjects.[8-10]

According to that new perspective, DSM-5[11] incorporated changes in criterion A for diagnosis of mania or hypomania. Classification now requires not only mood disturbance, but also increased activity or energy. To the same extent as DSM-IV-TR,[12] the DSM-5 includes psychomotor disturbance as a diagnostic criterion for major depressive episode. However, this symptom is not mandatory, and, besides motor retardation, agitation is also possible.

A previous study evaluated the symptomatology of 117 hospitalized manic patients. A factor analysis revealed that the Schedule for Affective Disorders and Schizophrenia – Change Version (SADS-C)[13] item "increased energy" exhibited the highest factor loadings, which was confirmed by item response theory analysis. Additionally, analysis of the item information function found that increased energy was associated with more severe symptoms when compared with other symptoms of mania. Therefore, the authors concluded that increased energy is more important than mood change for the diagnosis of mania, and, consequently, represents the core feature of this syndrome.[14]

The objective of the present study was to evaluate how well symptom rating scales differentiate BD episode types. In contrast to the aforementioned study, we worked with outpatient individuals and investigated depressive episodes and euthymic periods in addition to manic episodes. Because we included two other states of the same patient, a different study design and statistical approach were needed. Our hypothesis was that rating scales for patients with BD would show higher scores on the items

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related to elevated energy and agitation during mania and higher scores on the items related to decreased energy and motor retardation during depression.

Methods

Sample

The present study was conducted in an outpatient research center at the Instituto de Psiquiatria (IPUB), Universidade Federal do Rio de Janeiro (UFRJ), Brazil, from November 2002 to November 2015. Not all patients took part in the study at the same time, and they were not necessarily followed up for the entire 13-year study period.

The inclusion criteria were: diagnosis of BD, type 1 or 2; age 18 years or older; written informed consent; and occurrence of at least one manic episode, one depressive episode, and one period of euthymia during the course of the study. This project was approved by the local ethics committee.

Clinical evaluation

Diagnoses of BD and affective episodes were established according to DSM-IV-TR criteria,[12] using the Structured Clinical Interview for DSM (SCID).[15] At each visit, the following clinical scales were administered: Young Mania Rating Scale (YMRS),[16] Hamilton Depression Scale (HAM-D),[17] and Clinical Global Impressions scale for use in bipolar illness (CGI-BP).[18]

For comparison between the affective states of BP, three time points along each patient's follow-up were chosen: the most severe manic episode, the most severe depressive episode, and the euthymic period with least symptoms. We adopted the CGI-BP score as the criterion of severity. In case of a draw, total YMRS or HAM-D scores were considered for mania and depression, respectively, and both scales were considered for euthymia.

Statistical analysis

Descriptive statistics (mean and standard deviation [SD]) were used to characterize age and clinical information. Episodes were described using mean and SD for HAM-D and YMRS scores. To compare total scores in each instrument between episodes, three groups were created: mania (most severe manic episode), depression (most severe depressive episode), and euthymia (period with least symptoms); a one-way ANOVA was performed to test the null hypothesis; Cohen's f, lambda (λ), and statistical power were also used for effect-size measurement. The least significant difference (LSD) method was chosen for post-hoc analyses.

To understand which instruments and symptoms best discriminate episodes, canonical discriminant analyses (CDAs) were conducted. These statistical procedures find patterns of canonical correlation between features that separate scores and items according to a dependent variable. In other words, CDA is a type of regression that allows identification of which items or instruments are better than others to separate groups. Three indexes are used to interpret CDA: chi-square, Wilk's lambda, and the standardized canonical coefficient (SCC). The chi-square statistic reveals whether the variable is able to discriminate groups in a significant manner ($p < 0.05$). Wilk's lambda tests the extent to which a variable contributes to discrimination: the closer to 0 the index, the higher the extent to which the variable contributes to separate groups. Finally, the SCC ranks the importance of variables to separate groups; i.e., the higher the coefficient, the more important the variable. SCC and Wilk's lambda are different because, on one hand, SCC accounts for the variable that separates most symptoms in terms of polarity; on the other, Wilk's lambda reveals the extent of separation related to the amount of individuals in the sample, thus not necessarily associated to polarity. In the present study, three CDAs were performed to discriminate the three groups: 1) total score of instruments, which are all expected to be discriminative; 2) item scores of YMRS; and 3) item scores of HAM-D.

Results

A total of 243 patients with BP were evaluated during the period of the study, but only 106 experienced all of the events of interest (mania, depression, and euthymia). The mean age of the participants on the last day of data collection was 51.55 years (SD = 11.66). The sample comprised 74 women (69.8%) and 32 men (30.2%). Table 1 lists mean (SD) age at each of the events of interest, as well as CGI-BP, HAM-D, and YMSR scores divided by episode.

Table 1 Mean (SD) age and CGI-BP, YMRS, and HAM-D total scores

Variable	Mean (SD)
Age at episode	
Euthymia	44.39 (12.10)
Depression	45.92 (12.01)
Mania	45.83 (12.36)
CGI-BP	
Euthymia	
CGI-BP-mania	1.03 (0.19)
CGI-BP-depression	1.05 (0.23)
CGI-BP-global	1.08 (0.28)
Depression	
CGI-BP-mania	1.07 (0.27)
CGI-BP-depression	4.45 (0.95)
CGI-BP-global	4.47 (0.96)
Mania	
CGI-BP-mania	4.32 (1.14)
CGI-BP-depression	1.19 (0.40)
CGI-BP-global	4.30 (1.17)
YMRS	
Euthymia	2.29 (2.84)
Depression	3.97 (4.12)
Mania	20.79 (8.44)
HAM-D	
Euthymia	3.69 (3.07)
Depression	16.61 (6.53)
Mania	6.94 (4.56)

CGI-BP = Clinical Global Impressions Bipolar; HAM-D = Hamilton Rating Scale for Depression; SD = standard deviation; YMRS = Young Mania Rating Scale.

Regarding YMRS, comparisons of total scores using one-way ANOVA showed significant differences between groups for $F_{2,297}$ = 327.65; $p < 0.01$, and effect size of Cohen's f = 0.83; λ = 205.04; power = 0.99, which shows good differentiation between groups. Regarding depression symptoms (HAM-D), statistical differences were also revealed by $F_{2,297}$ =187.85; $p < 0.01$, with an effect size of Cohen's f = 0.74; λ = 166.31; and power = 0.99. We conclude that both YMRS and HAM-D total scores were significantly different and had good effect sizes.

Table 2 depicts pairwise post-hoc comparisons using LSD analyses. All groups and the total scores of both instruments showed significant differences. This means there are differences in severity of manic symptoms even between depressive and euthymic patients, as well as differences in severity of depression symptoms between euthymic and manic patients.

CDA excludes all variables that do not contribute significantly to discrimination as revealed by the chi-square statistics. Table 3 described the three CDAs conducted in the present study. The first (CDA 1) included all total scores of the instruments in the regression model. Therefore, all scores contributed, to some extent, to separating participants among groups. The highest SCC (1.18) was found for the CGI-BP-Mania subscale, which suggest that this instrument is the best choice to discriminate participants according to episodes. The lowest Wilk's lambda was found for the CGI-BP-Global scale (λ = 0.12), which means this instrument had the largest number of correct discriminations among the whole sample of participants, thus contributing to the highest extension of discrimination in the sample. HAM-D had an SCC = 0.61 and Wilk's lambda = 0.33, which was the worst set of indexes in CDA 1.

Regarding YMRS, the second CDA (CDA 2) showed item 2 (increased motor activity/energy), followed by item 6 (speech rate and amount), as the most important group discriminants, with SCCs of 0.70 and 0.49, respectively. Wilk's lambda shows that item 2 is also the best item to indicate which type of episode a patient is in, followed by a second-place draw of items 1 (elevated mood), 3 (sexual interest), and 4 (sleep). However, among the YMRS's whole set of 11 items, seven were included in the regression and four were excluded because they did not show significant contributions to the model using a null-hypothesis test (i.e., item 7, language-thought disorder; item 8, content; item 9, disruptive/aggressive behavior; item 10, appearance).

The third CDA (CDA 3) comprised HAM-D items. Among the seven items included in the discriminant analysis, item 9 (agitation) was the most important (SCC = 0.82) and precise (Wilk's lambda = 0.13). Considering importance for discrimination, item 1 (depressed mood) ranked second,

Table 2 Post-hoc analysis results

Post-hoc	LSD
YMRS	
Euthymia < depression	$p < 0.05$; low = -3.26; high = -0.10
Depression < manic	$p < 0.01$; low = -18.39; high = -15.25
Euthymia < manic	$p < 0.01$; low = -20.08; high = -16.93
HAM-D	
Euthymia < depression	$p < 0.01$; low = -14.29; high = -11.56
Euthymia < manic	$p < 0.01$; low = -4.61; high = -1.88
Manic < depression	$p < 0.01$; low = -11.04; high = -8.31

HAM-D = Hamilton Rating Scale for Depression; LSD = least significant difference; YMRS = Young Mania Rating Scale.

Table 3 Results of the CDA

Included variable	SCC	Wilk's lambda	χ^2	p-value
CDA 1: Total scores				
CGI-BP-Mania	**1.18**	**0.13**	**774.65**	**< 0.001**
CGI-BP-Depression	0.83	0.17	987.51	< 0.001
CGI-BP-Global	*0.85*	*0.12*	*540.63*	*< 0.001*
YMRS (total score)	0.75	0.31	327.65	< 0.001
HAM-D (total score)	0.61	0.33	262.17	< 0.001
CDA 2: YMRS items				
1. Elevated mood	0.22	0.24	51.42	< 0.001
2. Increased motor activity-energy	***0.70***	***0.21***	***207.78***	***< 0.001***
3. Sexual interest	0.26	0.24	71.25	< 0.001
4. Sleep	0.18	0.24	59.36	< 0.001
5. Irritability	0.48	0.29	87.75	< 0.001
6. Speech	0.49	0.27	108.21	< 0.001
11. Insight	0.21	0.31	45.26	< 0.001
CDA 3: HAM-D items				
1. Depressed mood	0.47	0.23	110.88	< 0.001
4. Insomnia: early in the night	0.39	0.21	50.68	< 0.001
7. Work and activities	0.42	0.20	202.79	< 0.001
8. Retardation	0.23	0.23	57.76	< 0.001
9. Agitation	***0.82***	***0.13***	***94.03***	***< 0.001***
13. General somatic symptoms	0.44	0.20	79.95	< 0.001
17. Insight	0.22	0.25	67.17	< 0.001

CDA = canonical discriminant analyses; CGI-BP = Clinical Global Impressions Bipolar; HAM-D = Hamilton Rating Scale for Depression; SCC = standardized canonical coefficient; YMRS = Young Mania Rating Scale.
Bold: highest ranked variable to discriminate groups according to SCC; Italic: variable that contributed the most to differentiating participants in their original groups, according to Wilk's lambda.

with SCC = 0.47, followed by items 13 (somatic symptoms general) and 7 (work and activities) (SCC = 0.44 and 0.42, respectively). Considering discriminant accuracy, items 13 and 7 tied for second (Wilk's lambda = 0.20 and 0.20, respectively), whereas item 1 ranked fifth (Wilk's lambda = 0.23). Among the whole set of 17 HAM-D items, 10 were excluded from the CDA because they did not contribute significantly to discrimination: items 2 (feelings of guilt), 3 (suicide), 5 (insomnia middle), 6 (insomnia late), 10 (anxiety – psychosocial), 11 (anxiety – somatic), 12 (somatic symptoms – gastrointestinal), 14 (genital symptoms), 15 (hypochondriasis), and 16 (loss of weight).

Discussion

In this study, we used clinical rating scales to investigate the relationship between level of energy or motor activity and clinical status in an outpatient sample of subjects with BD. YMRS, HAM-D, and CGI-BP were used to assess affective symptoms and syndromes. Each of the 106 subjects was evaluated three times: during a manic episode, a depressive episode, and a period of euthymia.

As expected, overall CGI-BP scores were lower in euthymia than in mania and in depression, CGI-BP depression scores were higher in depression than in mania and in euthymia, and CGI-BP mania scores were higher in mania than in depression and in euthymia. In addition, mean YMRS total scores were significantly higher in mania, and mean HAM-D total scores were significantly higher in depression. Pairwise post-hoc analyses revealed that both YMRS and HAM-D total scores could distinguish BP episode types. On comparison of clinical scales, CDA revealed HAM-D was worse than YMRS and CGI-BP as a discriminant of mood states according to both SCC and Wilk's lambda.

Item 2 of the YMRS specifically evaluates energy and activity. CDA revealed that this item was the most discriminative, according to the SCC and Wilk's lambda statistics. However, the YMRS items related to mood (5 – irritability and 1 – elevated mood) ranked only third and fifth most important, respectively, according to SCC. Considering Wilk's lambda, item 1 ranked second position, tied with items 3 (sexual interest) and 4 (sleep).

In the HAM-D, energy and activity are not associated with only one item. Razavi et al.[19] mention two items directly linked to motor behavior, 8 (retardation) and 9 (agitation), and one item indirectly so linked, 7 (work and activities). If we also consider energy, item 13 (general somatic symptoms) is likewise significant because the expression "loss of energy and fatigability" can be found as an anchor for this item. In our study, item 9 was the most discriminative, according to both coefficients. In relation to SCC, item 1 (depressed mood) came second in discriminant ability, but was only the fifth most discriminative item if we consider Wilk's lambda. (Items 7 and 13 ranked second according to Wilk's lambda.)

In short, the items that evaluate increased motor activity in the YMRS (item 2) and HAM-D (item 9) were better able to indicate which type of episode each patient was experiencing, distinguishing mania, depression, and euthymia. On the other hand, the items related to mood presented less significant results on both clinical scales.

Surprisingly, HAM-D item 8 (retardation) was not among those most discriminative, although it was among the items that contributed significantly to discrimination. A possible explanation could be the fact that decreased motor activity is also evaluated, at least in part, through items 7 and 13, which were among the three most discriminative according to Wilk's lambda. Another explanation would be a floor effect: the item was not discriminative because all participants presented similar levels of this symptom within groups. However, it contributed because it helped explain variance between groups.

Three actigraphy studies carried out by the same group revealed increased motor activity in mania.[8-10] In a novel exploratory paradigm, the authors used an ambulatory monitoring device, the human Behavioral Pattern Monitor (hBPM), in patients and healthy controls. In all three studies, manic patients exhibited higher activity than controls. Minassian et al.[8] observed that manic patients exhibited greater ambulation than patients with schizophrenia, whereas Perry et al.[10] did not find differences in object interactions or perseverative and socially disinhibited behaviors between groups.

These studies also investigated the correlation between hBPM results and YMRS in mania. Minassian et al.[8] did not find a significant correlation between total YMRS scores and mean motor activity quantified by actigraphy. They observed only a modest correlation between item 1 (elevated mood scores) and motor activity. Perry et al.[10] detected positive correlations between YMRS items and hBPM variables: item 1 correlated with total object interactions, time spent with objects, and object-proximal sector entries; item 2 (motor activity) correlated with percent object perseveration, time spent walking, and object-proximal sector entries; item 5 (irritability) did not present any correlation. Finally, Perry et al.[9] did not observe a correlation between item 2 scores and mean motor activity according to hBPM. Additionally, they created two criteria for increased energy: item 2 score $\geqslant 3$ in YMRS; and acceleration or number of object interactions > 2 SD above the mean of normal controls in hBPM. The authors concluded that the YMRS criterion was more specific in relation to the diagnosis of mania, whereas the actigraphic criterion was more sensitive.

A recent systematic review and meta-analysis of 19 papers addressed actigraphy in depressed patients. It concluded that a decrease in daytime activity is associated to depression.[4] Furthermore, motor retardation measured by actigraphic methods tends to remit when patients respond to treatment. Raoux et al.[20] evaluated the 24-hour motor activity pattern of 26 inpatients with major depression at treatment onset and after 4 weeks of antidepressant therapy, and observed that activity level was significantly increased on discharge. Volkers et al.[21] investigated the effects of antidepressants on 24-h motor activity in 52 depressed inpatients. In this study, patients treated with imipramine, but not fluvoxamine, exhibited higher motor activity levels during the waking period in comparison to the medication-free period. Finally, Todder et al.[22] investigated the daytime, nighttime, intensity, and quantity of circadian motor activity during a 4-week course of treatment among 27 patients with depression. Actigraphy revealed that measures of the

daytime level of movement captured the clinical improvement of depression.

Few studies have approached the relationship between actigraphic measures and the evaluation of depression with clinical scales. Finazzi et al.[23] investigated the association between motor activity and severity of depression in six depressed adolescent outpatients and found a correlation between lower levels of activity and higher scores on the Children's Depression Rating Scale Revised. Razavi at al.[19] studied the correlation between the HAM-D and actigraphy in 76 medicated inpatients with major depression. Motor activity correlated with item 7 (work and activities), but not with items 8 (retardation) or 9 (agitation), nor with overall HAM-D score. In our study, the fact that several HAM-D items are related to energy and activity may have presented a similar challenge in correlation analyses.

The most significant aspects of our study include comparison of each patient with himself or herself and the crossover design. However, some factors limit the generalizability of our results. First, it took approximately 13 years of longitudinal research to gather a representative sample size. Additionally, we had to exclude those patients who did not experience all three clinical statuses of interest, which consisted of the majority of our initial sample. Another limitation was the decision to evaluate only the most severe episodes of mania and of depression, because these episodes are not necessarily the most representative ones of each syndrome. Moreover, our patients were undergoing treatment at a university hospital, a setting in which cases are generally more severe cases than in the community. Another limitation was use of the HAM-D to evaluate depressive symptoms, because this clinical scale does not contain a single specific item combining evaluation of both energy and activity. Finally, CDA is a method used to separate variables according to groups, which does not necessarily provide for repeated measures such as the data we had. This implies that further analyses are still needed to determine the accuracy of our results.

Our results indicate that items related to increased energy or activity in clinical scales have greater discriminant ability than items related to mood to inform whether a patient with BD is manic, depressed, or euthymic. Therefore, higher levels of energy or activity should be considered a core symptom of mania. However, regarding depression, our findings were insufficient to confirm our hypothesis. In HAM-D, the absence of a single item that concentrates assessment of energy and activity may have posed an obstacle to the present study. Actigraphic studies assessing the same patients in different clinical statuses could supplement our investigation by addressing the relationship of energy or motor activity with mania and depression from an alternative standpoint.

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Disclosure

The authors report no conflicts of interest.

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