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Similarities and Differences between Unipolar and Bipolar Depression in Clinical Features, Adverse Childhood Experiences, and Biomarkers

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Abstract

This study examined individuals with Bipolar Depression (BDD), Major Depressive Disorder (MDD), and Controls (CONs) in order to find similarities and differences in clinical features, adverse childhood experiences, treatment adherence, functional impairment, and biomarkers. Individuals with BDD (n=86), MDD (n=47) and CONs (n=81) were assessed through a psychiatric interview to fill in a questionnaire, some scales about severity of depression and anxiety symptoms, childhood trauma, functional disability, treatment adherence, and also to measure some biomarkers. Individuals with BDD and MDD had significantly fewer education years, higher rates of functional impairment, experienced more childhood physical and emotional abuses, and more severity in depressive and anxious symptoms than CONs. Individuals with BDD presented significantly higher unemployment rates, higher levels of leptin and experienced more childhood sexual abuse compared to MDD and CONs. BDD had significantly more disability payments than CONs. BDD took significantly more lithium, other mood stabilizers, atypical antipsychotic medicines, and also presented worse treatment adherence compared to MDD. The MDD group had significantly more smokers than other groups. Our study highlighted the similarities and differences between BDD and MDD. Both groups presented similar results concerning severity of symptoms, childhood physical and emotional abuses, and functional impairment. However, BDD patients had differences in childhood sexual abuse, unemployment, poor treatment adherence, and higher levels of leptin. For clinical practice, the assessment of adverse childhood experiences, therapeutic alliance, and functional impairment may provide clues to understand the differences and similarities between MDD and BDD.

Keywords: Bipolar Depression; Major Depressive Disorder; Childhood Maltreatment; Treatment Adherence; Functioning; Biomarkers

Abbreviations

BDD: Bipolar Depression; BD: Bipolar Disorders; BMI: Body Mass Index; CONs: Controls; CTQ: Childhood; Trauma Questionnaire; $HDRS_{17}$: 17-item Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; MDD: Major Depressive Disorder; SDS: Sheehan Disability Scale; Mars: Medication Adherence Rating Scale. Compliance; hs-CRP: High-Sensitivity C-Reactive Protein; sTNF-R1: soluble Tumour Necrosis Factor α Receptor 1; sTNF-R2: soluble Tumour Necrosis Factor α Receptor 2

Introduction

Major Depressive Disorder (MDD) and Bipolar Disorders (BD) are serious chronic conditions leading to high recurrence and disability rates [1,2] Both MDD and BD are frequently misdiagnosed and BD patients are frequently diagnosed as having MDD, even after experiencing years of full-blown episodes of hypomania. The boundary is unclear and major mood disorders are better conceptualized as a continuum or as a set of overlapping pathological processes [3]. The similarity in depressive symptoms observed in individuals diagnosed with MDD or BD during the depressive phase is the main reason for such misdiagnoses [4]. Most patients who initially appear to have MDD will prove, in time, to have BD instead [5].

Patients with BD were associated with obesity and impairment in cognitive function [6]. The increased levels of inflammatory biomarkers might be associated with cognitive dysfunction in BD [7]. Increased leptin levels are risk for development mood disorders (either BD or MDD), these associations were observed when occurred comorbidity between mood disorders and obesity/overweight [8-10]. The findings of association between MDD and BD with low grade inflammation have been described in different studies [11-15]. Individuals with BD have significantly higher soluble Tumor Necrosis Factor Receptor type 1(sTNF-R1) and C-Reactive Protein (CRP) concentrations than MDD nd healthy individuals [16].

Childhood trauma subtypes, such as sexual, physical and emotional abuses, and emotional and physical neglects, have been related to depression in adults [17-20]. All types of childhood trauma lead to persistent alterations of inflammatory biomarkers [21].

Bipolar patients who had experienced history of childhood maltreatment develop a worse course of disease [22,23]. Difficulties

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and early life stress in childhood are more often described in individuals with MDD than in individuals without mood disorders; moreover, the strongest risk factor to develop depressive symptoms is associated with neglect and emotional abuse [24]. The clinical relevance that childhood sexual abuse was associated with poor therapeutic alliance [25].

The main aim of this study was to explore socio-demographic and clinical features, functioning disability, childhood trauma experiences, severity of depressive and anxious symptoms, treatment adherence, and some biomarkers, as well as anthropometric measurement in Bipolar Depression (BDD) and MDD and controls without mood disorders (CONs), to better understand their similarities and differences.

Methods

Participants

Individuals with BDD (n=86) and MDD (n=47) were recruited in the Psychiatric Outpatient Ambulatory of Londrina State University (UEL), Londrina, Brazil. Control individuals (CONs) consisted of staff workers from UEL without mood disorders (n=81).

All participants were men and women in the age group 18-65. Exclusion criteria were: a) abnormal blood values in any of the following laboratory tests: hemogram, aspartate transaminase, alanine transaminase and urea creatinine) b) cognitive disorders, c) pregnancy; d) use of nonsteroidal anti-inflammatory drugs, glucocorticoids, interferon, omega-3 polyunsaturated fatty acids and/or n-acetyl cysteine at least four weeks before the study; and e) medical conditions related to peripheral inflammation and cell-mediated immune activation (e.g., HIV, hepatitis B and C, postpartum period, hemodialysis, systemic lupus erythematosus, inflammatory bowel disease, type 1 diabetes, Alzheimer's disease, Huntington, Parkinson) [11]. The study was approved by the local Ethics Committee (number CAAE 34935814.2.0000.5231) and all subjects signed the informed consent form prior to participation.

Measures

Participants answered a questionnaire containing information such as socio-demographic and clinical features, and current use of psychotropic drugs including lithium, other mood stabilizers (valproate, lamotrigine, carbamazepine), atypical antipsychotic and antidepressants.

Participants were interviewed using Structured Clinical Interview (SCD-I) for DSM-IV, which was conducted by psychiatrists trained to diagnose BDD and MDD, according to diagnostic criteria. The SCD-I version used in the present study was translated to Portuguese and validated for the Brazilian population [26]. All diagnoses were assessed through International Classification of Diseases (ICD-10) [27].

The assessment of depression severity was applied to the participants based on 17-item Hamilton Depression Rating Scale (HDRS17) [28]. The 0-7 score is within the normal range (or in clinical remission), whereas score eight, or higher, indicates non-remitted depression. The HDRS17 was translated to Portuguese and adapted to the Brazilian population [29].

Anxiety severity was assessed through Hamilton Anxiety Rating Scale (HAM-A). This scale is composed of 14 items; each one should score from 0 to 4. The total HAM-A score ranges from 0 to 56: scores higher than 17 indicate mild severity anxiety, scores from 18 to 24 evidence mild to moderate anxiety, and scores from 25 to 30 show moderate severe anxiety [30].

Childhood Trauma Questionnaire (CTQ) was a self-administered instrument used to assess childhood maltreatment history in five domains: (a) sexual abuse, (b) physical abuse, (c) emotional abuse, (d) emotional neglect, and (e) physical neglect [31]. The CTQ feature scores were based on the five-point Likert scale, depending on the frequency of childhood events. The 28 item-version of the CTQ used in the present study was translated to Portuguese and adapted to the Brazilian population [32].

The Sheehan Disability Scale (SDS) is a disability or functional impairment scale that composed of 3-item self-report inventory to design to assess impairment in work performance, social life and household maintenance/familiar life. Patients who score 6 or greater on any of the three scales, are classified as having a significant functional impairment. In the final two items patients are asked about the number of days on which their symptoms either caused them to miss school and/or work or to be underproductive at school and/or work [33,34].

Medication Adherence Rating Scale (MARS) is a scale about treatment adherence of ten items [35]. The patient answered the statements in the questionnaire by circling the answer which best described their behavior or attitude towards their medication during the past week. The MARS has been validated for the Portuguese language [36]. This scale was assessed after 12 weeks of follow-up.

Anthropometric Measurements

The Body Mass Index (BMI) was calculated by dividing weight in Kilograms (Kg) by height in meters (m) squared.

The waist circumference was measured during expiration, in a standing and relaxed position, at the midline between the lower costal margins and the iliac crest parallel to the floor.

Lifetime cigarette consumption

Lifetime cigarette consumption or Smoking load (Pack-years) was calculated according to the definition: the number of cigarettes smoked per day divided by 20 and multiplied by number of years smoked (1 pack has 20 cigarettes).

Biomarkers

To evaluate biomarkers of leptin, serum levels of soluble tumor necrosis factor receptor 1 and 2 (sTNF-R1 and sTNFR-2), Luminex MAGPIX® system assay was used. The results are expressed as picograms (pg) of biomarker per ml of serum.

We measured the serum concentration of high-sensitivity C-reactive protein (hs-CRP) levels by an immunonephelometry system on a BNII analyzer (Siemens® System BNTM II, Deerfield, IL, USA).

Statistical analyses

Statistical analyses were performed in order to examine the link between socio-demographic, clinical and scales among groups. We used ANOVA followed by Tukey test to compare differences between

Table 1: Socio-Demographic and clinical characteristics, childhood trauma in Bipolar Depression (BDD) Major Depressive Disorder (MDD), and Controls (CONs).

Variables	Controls - CONs (n=81)	Bipolar Disorder - BDD (n=86)	Major Depressive Disorder - MDD (n=47)	p-value*
Age (years); mean (SD)	42.63 (12.24) ab**	41.00 (11.92) a	47.09 (10.59) b	0.01
Gender; n(%)				0.03
Female	52 (64.2%)	68 (79.1%)	39 (83.0%)	
Male	29 (35.8%)	18 (20.9%)	8 (17.0%)	
Education (years); mean (SD)	12.63 (5.71) a	10.39 (4.46) b	9.09 (5.15) b	< 0.01
Marital status; n(%)				0.34
Single	23 (28.4%)	17 (19.8%)	11 (23.4%)	
Stable relationship	46 (56.8%0	49 (57.0%)	24 (51.1%)	
Unstable relationship	11 (13.6%)	19 (22.1%)	9 (19.1%)	
Widow	1 (1.2%)	1 (1.2%)	3 (6.4%)	
Work; n(%)				< 0.01
Employed	65 (80.0%) a	30 (35.3%) b	29 (60.9%) a	
Unemployment	8 (10.0%) a	34 (38.8%) b	6 (13.0%) a	
Disability -payments	0 (0.0%) a	8 (9.4%) b	3 (6.5%) ab	
Unemployment insurance	1 (1.25) a	0 (0.0%) a	0 (0.0%) a	
Retired	2 (2.5%) a	7 (8.2%) a	4 (8.7%) a	
Other	5 (6.2%) a	7 (8.2%) a	5 (10.9%) a	
Ethinicity; n(%)				0.07
White	52 (64.2%)	67 (77.9%)	29 (61.7%)	
Black	7 (8.6%)	2 (2.3%)	6 (12.8%)	
Yellow	4 (4.9%)	0 (0.0%)	2 (4.3%)	
Mix	2 (2.5%)	4 (4.7%)	3 (6.4%)	
Other	16 (19.8%)	13 (15.1%)	7 (14.9%)	
BMI; mean (SD)	26.70 (4.82)	28.16 (5.72)	25.95 (4.74)	0.07
Smokers; n (%)	43 (53.1%) a	47 (54.1%) a	40 (85.1%) b	< 0.01
Pack-years; mean (SD)	35.98 (25.43)	32.89 (28.11)	35.63 (24.57)	0.52
CTQ				
Sexual Abuse; mean (SD)	5.32 (1.56) a	8.37 (5.24) b	6.02 (3.00) a	< 0.01
Physical abuse; mean (SD)	6.81 (3.29) a	9.96 (4.67) b	8.98 (4.55) b	< 0.01
Emotional abuse; mean (SD)	7.35 (3.45) a	12.93 (5.64) b	11.33 (6.03) b	< 0.01
Emotional neglect; mean (SD)	10.86 (6.45) a	14.59 (6.31) b	12.13 (6.19) ab	< 0.01
Physical neglect; mean(SD)	8.26 (3.88) a	10.39 (4.44) b	9.38 (4.27) ab	< 0.01

BMI: Body Mass Index; CTQ: Childhood Trauma Questionnaire

*p-value obtained in the ANOVA or Kruskal-Wallis test for the quantitative variables or Chi-square test or Fisher exact test for the qualitative variables

**Equal letters for the same variable indicate that there are no differences between the means or percentages among the groups, and different letters for the same variable indicate that there is such a difference

groups, when the assumptions were attended (homogeneity of variances and residual normality), or the Kruskal-Wallis test followed by post hoc for the comparisons when the assumptions were not met. We applied the Chi-square test or the Fisher exact test, followed by z-test, to the qualitative variables in order to compare the percentages between groups. The statistical significance level was 0.05; when the p-value was lower than 0.05, the means (quantitative variables) or percentages (qualitative variables) among groups, were followed by letters. Equal letters applied to the same variable indicated no difference between means, or percentages, among groups. Different letters used for the same variable indicate difference between means, or percentage among groups. The analysis was performed in the R software [37].

Results

Socio-demographic, clinical characteristics and childhood trauma questionnaire

Results of socio-demographic and clinical characteristics are summarized in Table 1. The MDD patients were older than the ones with BDD ($p<0.01$). There were no significant differences among

Table 2: Medication, Functional Impairment and Clinical features in Bipolar Depression (BDD) Major Depressive Disorder (MDD) and Controls.

Variables	Controls - CONs (n=81)	Bipolar Disorder - BDD (n=86)	Major Depressive Disorder - MDD (n=47)	p-value*
Lithium; n(%)	0 (0.0%) a**	33 (38.6%) b	1 (2.2%) a	< 0.01
Other mood stabilizer; n(%)	0 (0.0%) a	46 (53.6%) b	4 (8.7%) c	< 0.01
Atypical Antipsychotic; n(%)	1 (1.4%) a	37 (43.5%) b	5 (11.1%) a	< 0.01
Antidepressants; n(%)	6 (6.8%) a	38 (44.7%) b	20 (42.2%) b	< 0.01
HDRS17; mean (SD)	2.74 (3.55) a	11.09 (7.95) b	8.13 (6.58) b	< 0.01
HAM-A; mean (SD)	6.79 (7.56) a	16.80 (12.50) b	15.98 (21.46) b	< 0.01
SDS				
Occupational ≤ 6; n(%)	71 (87.7%) a	41 (48.2%) b	28 (58.7%) b	< 0.01
Occupational > 6; n(%)	10 (12.3%) a	45 (51.8%) b	19 (41.3%) b	
Social Life ≤ 6; n(%)	73 (90.1%) a	36 (42.4%) b	25 (52.2%) b	< 0.01
Social Life > 6; n(%)	8 (9.9%) a	50 (57.6%) b	22 (47.8%) b	
Family Life ≤ 6; n(%)	70 (86.4%) a	47 (54.1%) b	25 (52.2%) b	< 0.01
Family Life > 6; n(%)	11 (13.6%) a	39 (45.9%) b	22 (47.8%) b	
Work absences (last 30 days); mean (SD)	0.37 (3.33) a	4.75 (9.62) b	4.11 (9.04) b	< 0.01
Underproductive days (last 30 days); mean (SD)	1.05 (4.78) b	7.24 (10.57) b	5.85 (10.93) b	< 0.01

SDS: Sheehan Disability Scale; HDRS17: 17-item Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale
*p-value obtained in the ANOVA or Kruskal-Wallis test for the quantitative variables or Chi-square test or Fisher exact test for the qualitative variables
**Equal letters for the same variable indicate that there are no differences between the means or percentages among the groups, and different letters for the same variable indicate that there is such a difference

Table 3: Medication Adherence Rating Scale, in Bipolar Depression (BDD) Major Depressive Disorder (MDD).

Mars Questionnaire	Bipolar Disorder - BDD (n=86)		Major Depressive Disorder - MDD (n=47)		p-value*
	Non-Compliance	Compliance	Non- Compliance	Compliance	
Do you ever forget to take your medication?	18 (64.3%)	10 (35.7%)	9 (45.0%)	11 (55.0%)	0.24
Are you careless at times about taking your medication?	26 (92.9%)	2 (7.1%)	13 (65.0%)	7 (35.0%)	0.02
When you feel better, do you sometimes stop taking your medication?	25 (89.3%)	3 (10.7%)	19 (95.0%)	1 (5.0%)	0.63
Sometimes if you feel worse when you take the medication, do you stop taking it?	25 (89.3%)	3 (10.7%)	18 (90.0%)	2 (10.0%)	1
I take my medication only when I am sick	24 (85.7%)	4 (14.3%)	18 (90.0%)	2 (10.0%)	1
It is unnatural for my mind and body to be controlled by medication	22 (78.6%)	6 (21.4%)	16 (80.0%)	4 (20.0%)	1
My thoughts are clearer on medication	15 (53.6%)	13 (46.4%)	12 (60.0%)	8 (40.0%)	0.77
By staying on medication, I can prevent getting sick	9 (32.1%)	19 (67.9%)	12 (60.0%)	8 (40.0%)	0.08
I fell weird, like a 'zombie' on medication	26 (92.9%)	2 (7.1%)	20 (100.0%)	0 (0.0%)	0.5
Medication makes me feel tired and sluggish	20 (71.4%)	8 (28.6%)	16 (80.0%)	4 (20.0%)	0.74

Mars: Medication Adherence Rating Scale. Compliance=No to questions 1-6, 9-10; Answer Yes to questions 7,8.
*p-value obtained by Chi-square test or Fisher exact test

the three groups with respect to ethinicity (p=0.07), marital status (p=0.34) and Body Mass Index (BMI) (p=0.07). Individuals with BDD presented significantly higher unemployment rates than MDD and CONs. BDD patients are currently receiving disability payments than CONs (p<0.01). When it comes to mean education years, individuals with MDD rated 9.09 (SD=5.15); BDD, 10.39 (SD=4.46); and CONs, 12.63 (SD=5.71) (p<0.01).

BDD experienced significantly more childhood sexual abuse compared to MDD and CONs. MDD and BDD experienced significantly more emotional and physical abuses than CONs.

MDD presented higher percentage of smokers compared to BDD and CONs. There are no significant differences related to pack-years between the groups.

Medication and clinical characteristics, and functional impairment

Medication, severity of depressive and anxious symptoms, and functional impairment are shown in Table 2.

There were significant differences in medication use among the groups. BDD took significantly more lithium, atypical antipsychotic medicines, and other mood stabilizers than MDD and CONs. Both BDD and MDD took more antidepressants than CONs.

There were no significant differences between both groups (BDD and MDD) in functional impairment, however, there were significant differences in both groups (BDD and MDD) compared

Table 4: Biomarkers in Bipolar Depression (BDD) Major Depressive Disorder (MDD) and Controls.

Variables	Controls - CONs (n=81)	Bipolar Disorder	Major Depressive	p-value*
		BDD (n=86)	Disorder - MDD (n=47)	
Waist Circumference; mean (SD)	90.32 (20.85)	94.08 (17.62)	90.80 (12.66)	0.18
BM1 ≥ 30; n (%)	22 (26.6%)	32 (36.8%)	9 (18.2%)	0.08
hs-CRP mg/L; mean (SD)	3.73 (3.85)	4.47 (4.50)	4.47 (7.42)	0.65
Leptin ng/mL; mean (SD)	2205.85 (2287.79) a**	3692.88 (3001.87) b	2332.33 (2364.40) a	< 0.01
s TNF-R1 pg/mL; mean (SD)	408.92 (333.03)	498.34 (383.02)	369.38 (339.22)	0.15
s TNF-R 2 pg/mL; mean (SD)	8146.73 (4625.73) a	8262.54 (5668.82) a	5941.58 (4190.78) b	0.04

hs-CRP: high-sensitivity C-Reactive Protein; sTNF-R1: soluble Tumour Necrosis Factor α Receptor 1; sTNF-R2: Soluble Tumour Necrosis Factor α Receptor 2
*p-value obtained in the ANOVA or Kruskal-Wallis test for the quantitative variables or Chi-square test or Fisher exact test for the qualitative variables
**Equal letters for the same variable indicate that there are no differences between the means or percentages among the groups, and different letters for the same variable indicate that there is such a difference

to CONs. There were no significant differences between BDD and MDD in depression severity on HDRS17 scale and anxiety severity on HAM-A, and both presented higher means compared to CONs.

Medication Adherence Rating Scale (MARS)

Table 3 summarizes Medication Adherence Rating Scale in BDD and MDD.

No significant differences were found between BDD and MDD groups in nine questions of MARS. However, there was significant difference between BDD and MDD in question 2 "Are you careless at times about taking your medication?". BDD patients presented significantly worse treatment adherence.

Biomarker and antrophometric measures

Table 4 summarizes biomarker and anthropometric measures. There were significant differences in leptin and sTNF-R2 levels. BDD patients presented higher leptin levels than MDD and CONs. MDD presented lower levels of sTNF-R2 levels than other groups.

There were no significant differences in BDD, MDD and CON groups regarding BMI, waist circumference, and levels of hs-CRP and sTNF-R1.

Discussion

This study provides findings that individuals with BDD differ from MDD and individuals without mood disorders, as BBD have experienced more childhood sexual abuse and usually present lower adherence treatment. These results are in accordance with a study that found that poor therapeutic alliance was associated to childhood sexual abuse [25]. Another previous study reported that child sexual abuse was more frequent in BD patients [38]. Individuals who suffered adverse childhood experiences had their brain structure and functioning altered, which contributes to health-risk behaviors, including smoking cigarettes, drinking alcohol, and eating high-fat and high-sugar foods [39]. Although MDD and BDD had experienced more childhood emotional and physical abuses than CONs, there were no alterations on their BMI and pack-years smoking.

Our study also found that mood disorders, either BDD or MDD, had similarities such as higher rates of functional impairment and more severity in depressive and anxious symptoms than individuals without mood disorders. On the other hand, there were more cases of BDD patients receiving disability payments than CONs. In addition, there was a higher rate of unemployment among BDD patients than MDD and CONs. There is evidence that recurrent depressive, manic or hypomanic episodes may lead to cognitive dysfunction and decline in psychobiosocial function in BD patients [40-42]. Moreover, both BD and MDD patients might present cognitive impairment, so such mood disorders could affect their learning and working skills [43-45]. MDD and BD are associated with increased levels of inflammatory biomarkers that contribute to both being considered progressive diseases [46,47]. The functional impairment persists even during disease remission phases or even when severity of depressive symptoms decreases [48]. Approximately 30% of all BD patients show severe impairment in their working skills [5,49]. Likewise, MDD functional impairment may cause complete incapacity to meet basic self-care needs [5].

The present study also showed that BDD patients had higher levels of leptin than other groups. Leptin is an adipokine that increases the production of pro-inflammatory cytokine, and higher leptin levels are a trait in BD in all phases: manic, depressive and remission [50]. Leptin resistance may be the pathway that connects obesity and depression, since there is a link between leptin, abdominal obesity and onset of depression [51,52]. Leptin resistance is like a regulator of food intake and obesity that might develop mental disorders such as anxiety, depression and neurocognitive functions [53]. Our study found that BDD patients took more lithium, other mood stabilizers and atypical antipsychotic medicines. Obesity and overweight in BD are partly related to prescribed drugs that could contribute to weight gain [54].

Mood disorders (either BD or MDD) have been reported with a low-grade of inflammation. However, patients with BD had significantly higher sTNF-R1 levels than MDDs and controls [16]. Higher sTNF-R1 levels in the depressive and manic phases could lead to neuroprogression caused by inflammatory mechanisms capable of inducing neuronal cell death through caspases and apoptotic machinery activation [55]. High sTNF-R1 and sTNF-R2 levels in individuals with BD are associated with cognitive impairment that could be a possible consequence of the pro-inflammatory process [56]. Conversely, in our study, MDD had significantly lower sTNF-R2 levels than BDD and individuals without mood disorders. Furthermore, BDD patients have shown higher levels of sTNF-R1 and sTNF-R2 than the other groups, although no significant differences were observed between the three groups.

The co-occurrence of MDD and tobacco use disorder is high in

clinical practice People with current nicotine dependence exhibit greater prevalence and severity of several depressive symptoms compared to people with no history of nicotine dependence [57,58]. Depressed smokers have higher levels of pro-inflammatory cytokines than non-depressed smokers, including tumor necrosis factor-alpha, interleukin-6, and acute phase proteins such as C-Reactive Protein (CRP) [59,60].

The present study should be interpreted regarding the strengths and limitations. First, childhood-trauma data were retrospective, so they could be based on recall biases. Second, individuals with BD or MDD attended less school year than individuals without mood disorders. Third, although the current study was based on a small sample, it was from clinical practice sample. Finally, participants were in the age group between 18 to 65 years, thus we cannot generalize these findings to older, or younger, populations.

Conclusion

Our findings suggest clinical practice implications. Similarities between individuals with MDD and BDD were high rates of functional impairment, childhood physical and emotional abuse reports, and severity of depressive and anxiety symptoms. The differences between unipolar and bipolar depression were that patients with BDD had experienced more childhood sexual abuse and the rate of unemployment among them was higher, as well as the levels of leptin.

The patients of the present study are clinically representative of BDD and MDD patients seen in psychiatric settings. BDD patients took more lithium, other mood stabilizers and atypical antipsychotic medicines, and had poor compliance to treatment. Similarities in both BDD and MDD were that both kind of patients took more antidepressants.

Taken together, unipolar and bipolar depression showed similarities and differences in clinical features, adverse childhood experiences and biomarkers. The awareness of such differences and similarities is relevant for clinical practice. Further studies are required to investigate if BDD and MDD present different or similar etiology and phenomenology.

References

1. Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, et al. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. Epidemiologia e Psichiatria Sociale. 2009; 18: 23-33.
2. Vos T, Abajobir AA, Abbafati C, Abbas KM, Abate KH, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017.
3. Smith DJ, Craddock N. Unipolar and bipolar depression: Different or the same? British Journal of Psychiatry. 2011; 199: 272-274.
4. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet (London, England). 2015.
5. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5 (5th ed.). Arlington, VA: American Psychiatric Association Pub. 2013.
6. Liu CS, Carvalho AF, Mansur RB, McIntyre RS. Obesity and bipolar disorder: synergistic neurotoxic effects? Advances in Therapy. 2013; 30: 987-1006.
7. Bauer IE, Pascoe MC, Wollenhaupt-Aguiar B, Kapczinski F, Soares JC. Inflammatory mediators of cognitive impairment in bipolar disorder. Journal of Psychiatric Research. 2014; 56: 18-27.
8. Cao B, Chen Y, Brietzke E, Cha D, Shaukat A, Pan Z, et al. Leptin and adiponectin levels in major depressive disorder: A systematic review and meta-analysis. Journal of Affective Disorders. 2018; 238: 101-110.
9. Fernandes BS, Dash S, Jacka F, Dodd S, Carvalho AF, Köhler CA, et al. Leptin in bipolar disorder: A systematic review and meta-analysis. European Psychiatry. 2016; 35: 1-7.
10. Stern JH, Rutkowski JM, Scherer PE. Adiponectin, Leptin, and Fatty Acids in the Maintenance of Metabolic Homeostasis through Adipose Tissue Crosstalk. Cell Metabolism. 2016; 23: 770-784.
11. Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. Neuroscience and Bio behavioral Reviews. 2012; 36: 764-785.
12. McNamara RK, Lotrich FE. Elevated immune-inflammatory signaling in mood disorders: a new therapeutic target? Expert Review of Neurotherapeutics. 2012; 12: 1143-1161.
13. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: A meta-analysis of 30 studies. Biological Psychiatry. 2013; 74: 15-25.
14. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: A review of the interactions between inflammation and mood disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2014; 53: 23-34.
15. Rosenblat JD, McIntyre RS. Bipolar Disorder and Inflammation. Psychiatric Clinics of North America. 2016; 39: 125-137.
16. Bai YM, Su TP, Li CT, Tsai SJ, Chen MH, Tu PC, et al. Comparison of pro-inflammatory cytokines among patients with bipolar disorder and unipolar depression and normal controls. Bipolar Disorders. 2015; 17: 269-277.
17. Danese A, Mc Ewen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiology and Behavior. 2012; 106: 29-39.
18. Heim C, Plotsky PM, Nemeroff CB. Importance of studying the contributions of early adverse experience to neurobiological findings in depression. 2004.
19. Heim C, Shugart M, Craighead WE, Nemeroff CB. Neurobiological and psychiatric consequences of child abuse and neglect. Developmental Psychobiology. 2010; 52: 671-690.
20. Krug EEG, Mercy JA, Dahlberg LL, Zwi AB. The world report on violence and health. The Lancet. 2002; 360: 1083-1088.
21. Danese A, Baldwin JR. Hidden Wounds? Inflammatory Links between Childhood Trauma and Psychopathology. Annual Review of Psychology. 2017; 68: 517-544.
22. Aas M, Henry C, Andreassen OA, Bellivier F, Melle I, Etain B. The role of childhood trauma in bipolar disorders. Int J Bipolar Disord. 2016; 4: 2.
23. Brown GR, McBride L, Bauer MS, Williford WO.. Impact of childhood abuse on the course of bipolar disorder: A replication study in U.S. veterans. Journal of Affective Disorders. 2005; 89: 57-67.
24. Mandelli L, Petrelli C, Serretti A. The role of specific early trauma in adult depression: A meta-analysis of published literature. Childhood trauma and adult depression. European Psychiatry. 2015; 30: 665-680.
25. Keller SM, Zoellner LA, Feeny NC. Understanding factors associated with early therapeutic alliance in PTSD treatment: Adherence, childhood sexual abuse history, and social support. Journal of Consulting and Clinical Psychology. 2010; 78: 974-979.
26. Del-Ben CM, Vilela JAA, Crippa JA, de S, Hallak JEC, Labate CM, et al. Confiabilidade da "Entrevista Clínica Estruturada para o DSM-IV - Versão Clínica" traduzida para o português. Revista Brasileira de Psiquiatria. 2001; 23: 156-159.
27. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders Diagnostic criteria for research. 1992; 263.
28. Hamilton M. A rating scale for depression. Journal of Neurology, Neurosurgery,

and Psychiatry. 1960; 23: 53-62.

29. Moreno RA, Moreno DH. Escalas de depressão de Montgomery & Asberg (MADRS) e de Hamilton (HAM-D). Revista de Psiquiatria Clinica. 1998; 25: 262-272.

30. Hamilton M. The assessment of anxiety states by rating. British Journal of Medical Psychology. 1959; 32: 50-55.

31. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse & Neglect. 2003; 27: 169-190.

32. Grassi-Oliveira R, Stein LM, Pezzi JC. Tradução e validação de conteúdo da versão em português do Childhood Trauma Questionnaire. Revista de Saude Publica. 2006; 40: 249-255.

33. Sheehan KH, Sheehan DV. Assessing treatment effects in clinical trials with the discan metric of the Sheehan Disability Scale. Int Clin Psychopharmacol. 2008; 23: 70-83.

34. Sheehan DV. Harnett-Sheehan K, Raj BA. The measurement of disability. International Clinical Psychopharmacology. 1996.

35. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. Schizophrenia Research. 2000; 42: 241-247.

36. Moreira IC, Bandeira M, Pollo TC, Oliveira MS. De Adaptação transcultural para o Brasil da medication adherence rating scale para pacientes psiquiátricos. Jornal Brasileiro de Psiquiatria. 2014; 63: 273-280.

37. Core Team R. R A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. 2020.

38. Jansen K, Cardoso TA, Fries GR, Branco JC, Silva RA, Kauer-Sant'Anna M, et al. Childhood trauma, family history, and their association with mood disorders in early adulthood. Acta Psychiatrica Scandinavica. 2016; 134: 281-286.

39. Duffy KA, Mclaughlin KA, Green PA. Early life adversity and health-risk behaviors: Proposed psychological and neural mechanisms. Annals of the New York Academy of Sciences. 2018; 1428: 151-169.

40. Berk M. Neuroprogression: Pathways to progressive brain changes in bipolar disorder. International Journal of Neuropsychopharmacology. 2009; 12: 441-445.

41. Fries GR, Pfaffenseller B, Stertz L, Paz AV, Dargel AA, Kunz M, et al. Staging and neuroprogression in bipolar disorder. Curr Psychiatry Rep. 2012; 14: 667-675.

42. Zarate CA, Tohen M, Land M, Cavanagh S. Functional impairment and cognition in bipolar disorder. Psychiatr Q. 2000; 71: 309-329.

43. Pan Z, Park C, Brietzke E, Zuckerman H, Rong C, Mansur RB, et al. Cognitive impairment in major depressive disorder. CNS Spectrums. 2019; 24: 22-29.

44. Kapczinski NS, Narvaez JC, Magalhães PV, Bücker J, Peuker AC, Loredo AC, et al. Cognition and functioning in bipolar depression. Revista Brasileira de Psiquiatria. 2016; 38: 201-206.

45. Solé B, Bonnin CM, Torrent C, Balanzá-Martínez V, Tabarés-Seisdedos R, Popovic D, et al. Neurocognitive impairment and psychosocial functioning in bipolar II disorder. Acta Psychiatrica Scandinavica, 2012; 125: 309-317.

46. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, et al. So depression is an inflammatory disease, but where does the inflammation come from? BMC Medicine. 2013; 11: 200.

47. Moylan S, Maes M, Wray NR, Berk M. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. Molecular Psychiatry. 2013; 18: 595-606.

48. Cohen RM, Greenberg JM, IsHak WW. Incorporating Multidimensional Patient-Reported Outcomes of Symptom Severity, Functioning, and Quality of Life in the Individual Burden of Illness Index for Depression to Measure Treatment Impact and Recovery in MDD. JAMA Psychiatry. 2013; 70: 343.

49. Ávila CC, Cabello M, Cieza A, Vieta E, Ayuso-Mateos JL. Functioning and disability in bipolar disorders: A systematic review of literature using the ICF as a reference. Bipolar Disorders. 2010; 12: 473-482.

50. Fernandes BS, Dash S, Jacka F, Dodd S, Carvalho AF, Köhler CA, et al. Leptin in bipolar disorder: A systematic review and meta-analysis. European Psychiatry. 2016; 35: 1-7.

51. Milaneschi Y, Lamers F, Bot M, Drent M, Penninx BWJH. Leptin Dysregulation Is Specifically Associated With Major Depression With Atypical Features: Evidence for a Mechanism Connecting Obesity and Depression. Biological Psychiatry. 2017; 81: 807-814.

52. Milaneschi Y, Simonsick EM, Vogelzangs N, Elsa S, Yaffe K, Harris TB, et al. Leptin, abdominal obesity and onset of depression in older men and women. Journal of Clinical Psychiatry. 2012; 73: 1205-1211.

53. Wędrychowicz A. Peptides from adipose tissue in mental disorders. World Journal of Psychiatry. 2014; 4: 103.

54. Torrent C, Amann B, Sánchez-Moreno J, Colom F, Reinares M, Comes M, et al. Weight gain in bipolar disorder: Pharmacological treatment as a contributing factor. Acta Psychiatrica Scandinavica. 2018; 118: 4-18.

55. Barbosa IG, Rocha NP, Huguet RB, Ferreira RA, Salgado JV, Carvalho LA, et al. Executive dysfunction in euthymic bipolar disorder patients and its association with plasma biomarkers. Journal of Affective Disorders. 2012; 137: 151-155.

56. Doganavsargil-Baysal O, Cinemre B, Aksoy UM, Akbas H, Metin O, Fettahoglu C, et al. Levels of TNF-α, soluble TNF receptors (sTNFR1, sTNFR2), and cognition in bipolar disorder. Human Psychopharmacology. 2013; 28: 160-167.

57. Nunes SOV, de Castro MRP, Vargasa HO, Vargas MM, de Batista Fonseca IC, Dodd S, et al. Clinical characteristics and smoking cessation: an analysis of sex and depressive disorders differences. Addictive Disorders & Their Treatment. 2013; 12: 158-165.

58. Ziedonis D, Hitsman B, Beckham JC, Zvolensky M, Adler LE, Audrain-McGovern J, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. Nicotine & Tobacco Research : Official Journal of the Society for Research on Nicotine and Tobacco. 2008; 10: 1691-1715.

59. Nunes SOV, Vargas HO, Brum J, Prado E, Vargas MM, de Castro MRP, et al. A comparison of inflammatory markers in depressed and nondepressed smokers. Nicotine & Tobacco Research : Official Journal of the Society for Research on Nicotine and Tobacco. 2012; 14: 540-546.

60. Nunes SOV, Vargas HO, Prado E, Barbosa DS, de Melo LP, Moylan S, et al. The shared role of oxidative stress and inflammation in major depressive disorder and nicotine dependence. Neuroscience and Bio behavioral Reviews. 2013; 37: 1336-1345.