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Sub-threshold bipolar disorder in medication-free young subjects with major depression: Clinical characteristics and antidepressant treatment response

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ABSTRACT

Background: This study, for the first time, compared illness and antidepressant response characteristics of young subjects with major depression (MDD) at low (LRMDD) or high-risk (HRMDD) for developing bipolar disorder with characteristics of young bipolar (BPD) subjects and healthy controls (HC).

Methods: One hundred and six young (15–30 yr), medication-free subjects MDD subjects (HRMDD, N = 51; LRMDD, N = 55) were compared with 32 BPD (Type I: 14; Type II: 18) as well as 49 HC subjects. Baseline illness characteristics and frequency of comorbid conditions were examined using Analysis of Variance and Cochran-Armitage trend test. Additionally, in MDD subjects, the effect of open-label antidepressant treatment for up to 24 months with periodic assessments was compared between HRMDD and LRMDD groups for treatment response, remission and (hypo)mania switch while controlling for attrition.

Results: Significant gradation from LRMDD to HRMDD to BPD groups was found for increasing occurrence of alcohol dependence ($p = 0.006$), comorbid PTSD ($p = 0.006$), borderline personality traits ($p = 0.001$), and occurrence of melancholic features ($p < 0.005$). Antidepressant treatment response was similar between the two groups except that for the 12-month period HRMDD showed a trend for a lower response. Switch to (hypo) mania was infrequent in both groups though the HRMDD showed a higher occurrence of spikes in (hypo)mania symptoms (> 25% increase in YMRS scores)($p = 0.04$).

Conclusion: Findings of the study indicate that a substantial proportion of young MDD subjects share BPD illness characteristics. These HRMDD subjects, if treated with antidepressants, need to be monitored for development of BPD.

Trial registration: NCT01811147.

1. Background

It has been estimated that 30–55% of patients presenting with major depression (MDD) have sub-threshold hypo(manic) symptoms (Angst et al., 2010; Benazzi, 1997; Hoertel et al., 2013; Kukopulos et al., 1980; Zimmermann et al., 2009). Sub-threshold symptoms, family history of bipolar disorder (BPD) (Coryell et al., 1995; Fiedorowicz et al., 2011) or a history of mood-related psychosis are reported as risk factors for the development of BPD (Goldberg et al., 2001). MDD patients with these characteristics can be classified as high-risk MDD (HRMDD) as there is a frequent concern that they might convert to BPD. The risk for conversion to BPD is thought to be particularly high if HRMDD patients are treated with antidepressants without the cover of mood stabilizer treatment (Nusslock and Frank, 2011; Viktorin et al., 2014). Consequently, many depressed patients with sub-threshold hypo(mania) symptoms are not adequately treated. Subjects who do not have these characteristics are low-risk MDD (LRMDD) as they are thought to be less likely to convert to BPD.

Sub-threshold symptoms are particularly important in adolescents and young adults presenting with depression. Various studies have reported that MDD patients with sub-threshold hypo(manic) symptoms have an earlier age of onset (Angst et al., 2003; Zimmermann et al., 2009), recurrent episodes (Leonpacher et al., 2015), difficulties in diagnosis and treatment delay (Angst et al., 2010), more frequent comorbid psychiatric illnesses such as anxiety (Angst et al., 2003; Faravelli et al., 2006), substance use (Angst et al., 2003; Faravelli et al.,

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2006; Zimmermann et al., 2009), personality disorders (Faravelli et al., 2006) and a higher frequency and lethality of suicide attempts (Angst et al., 2003), leading to poor treatment outcomes compared to patients with MDD alone (Dudek et al., 2013; Park and Lee, 2016; Perlis et al., 2011). Importantly, it is known that in adolescents and young adults, BPD first manifests often as depression and a history of mania or (hypo) mania is either not available or difficult to elicit. Even though sub-threshold symptoms may be present, it is only after years of misdiagnosis and inappropriate treatment, that a proportion of these young depressed subjects exhibit overt (hypo)mania and are then correctly diagnosed with BPD. Complications arising from sub-threshold symptoms can be particularly devastating in late adolescence and young adulthood in terms of educational, occupational and social effects making early interventions crucial (Vieta et al., 2018). As discussed above, clinicians inadequately treat many of these young subjects due to the difficulty of making a diagnosis. A reluctance to use antidepressant monotherapy in this population also plays a role as there is not sufficient clinical indication to start these patients on mood stabilizers such as lithium, anticonvulsants or neuroleptics. To the best of our knowledge, until present, no study has investigated the frequency of sub-threshold (hypo)manic symptoms specifically in young depressed subjects and prospectively examined the effects of antidepressant treatment in this population.

For bipolar I and II depression, a number of studies and meta-analyses have indicated a possible lower response to antidepressants, though most studies in these analyses have included subjects on concomitant medications such as mood stabilizers and neuroleptics (Gijsman et al., 2004; McGirr et al., 2016; Sidor and Macqueen, 2011). A more recent large randomized study also reported lower antidepressant treatment efficacy in depressed subjects with subthreshold symptoms (Jha et al., 2018). However, it is not known if the efficacy of antidepressant monotherapy in young depressed subjects with subthreshold symptoms is similar to those with unipolar or bipolar depression.

In light of the gaps in knowledge listed above, this study was designed to identify behavioral and biological markers of bipolarity in young MDD subjects. We studied baseline characteristics of young subjects, 15–30 years of age, with MDD or BPD or with no psychiatric illness (healthy controls (HC)). In addition, we studied the effects of open-label real-world antidepressant treatment in subjects with MDD and compared treatment response between HRMDD and LRMDD groups.

In this report, we present findings from the behavioral data and the effect of antidepressant treatment. We hypothesized that young depressed subjects with HRMDD would be similar to the BPD group in terms of baseline characteristics. We also hypothesized that the HRMDD group would have a lower response to antidepressants and a higher rate of side effects including precipitation of (hypo)mania (Park and Lee, 2016; Sharma et al., 2005).

2. Methods

This prospective longitudinal study was carried out at Indiana University School of Medicine (October 2011–2012) and the Cleveland Clinic (2012–2017). The patients were either referred to the clinic, were self-referred volunteers or responded to an advertisement. All subjects signed an informed consent approved by the institutional review board (IRB). Subjects under the age of 18 signed an assent with additional parental consent. All participants were evaluated by a trained research coordinator and a psychiatrist for inclusion eligibility for the study, Inclusion criteria for MDD and BPD patients: 1) ages 15–30 years (inclusive) and able to give voluntary informed consent (consent taken from both parents and child for children under the age of 18); 2) satisfy criteria for Diagnostic and Statistical Manual 4th edition Text Revision (DSM-IV-TR) depressive episode-current; 3) 17-item Hamilton Depression Rating Scale > 15 but < 25; 4) Young Mania Rating Scale score < 10; 5) able to be managed as outpatients during the study as ascertained by the following – i. Clinical Global Severity Scale < 5 (moderately ill); ii. no significant suicidal or homicidal ideation or severe disability.

BPD patients met Diagnostic and Statistical Manual 4th edition (DSM-IV-TR) criteria for Bipolar I or II disorder. Exclusion criteria for MDD and BPD participants were: 1) meeting DSM-IV criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, mental retardation, pervasive developmental disorder; 2) history of receiving electroconvulsive therapy in the past 1 year; 3) use of neuroleptics, mood stabilizers or benzodiazepines in the past 2 weeks; 4) use of antidepressants in the past 2 weeks; 5) if on fluoxetine in the past, then should not have been on this medication for 5 weeks; 6) acutely suicidal or homicidal or requiring inpatient treatment; 7) meeting DSM-TR criteria for other substance/alcohol dependence within the past 6 months or abuse in the past 3 months, excluding caffeine or nicotine. The criteria were evaluated by interview and urinary toxicology screening; 8) use of alcohol in the past 1 week; 9) no serious acute or chronic medical or neurological illness, including previously known HIV positive status (due to possible CNS involvement) as assessed by history, physical examination and laboratory examination including EKG, CBC and blood chemistry; 10) current pregnancy or breastfeeding; 11) metallic implants or another contraindication to MRI.

Inclusion criteria for healthy subjects: Healthy subjects matched for age, gender and ethnicity were included: 1) ages 15–30 years (inclusive) and able to give voluntary informed consent (consent taken from both parents and child for children under the age of 18); 2) no current or past history of psychiatric illness or substance abuse or dependence; 3) no current or past history of psychiatric illness or substance abuse or dependence in a first-degree relative. Exclusion criteria for healthy subjects were the same as that for patients regarding pregnancy, contraindications to MRI, taking any psychotropic medications, any significant medical or neurological illness and use of alcohol in the past 1 week.

Baseline Assessments: As part of screening for the study, detailed history and physical examination, routine blood tests, urine toxicology and electrocardiogram were performed. The following assessments were conducted: 1) Mini-international Neuropsychiatric Interview (MINI) for diagnosis as well as co-morbid illnesses (Sheehan et al., 1998); 2) Childhood Traumatic Events Scale (CTES)(Pennebaker and Susman, 2013); 3) Life Events Checklist (Gray et al., 2004); 4) Family Interview for Genetic Studies (FIGS)(Maxwell, 1992); 5) Mania Syndrome Checklist of schedule for Affective Disorders and Schizophrenia (MSC); 6) 17-Item Hamilton Depression Scale (HAM-D); 7) Hamilton Anxiety Scale (HAM-A)(Hamilton, 1976); 8) Young Mania Rating Scale (YMRS)(Young et al., 1978); 9) Columbia Suicide Severity Rating Scale (CSSRS)(Posner et al., 2011); 10) Scale for Suicide Ideation (MSSI) (Beck et al., 1979); 11) Interview for DSM-IV Personality Disorders (SCID-II)(First et al., 1997);12) Toronto Side Effects Scale (TSES) (Vanderkooy et al., 2002); and 13) Clinical Global Impression Severity Scale for BPD (CGI-BP)(Spearing et al., 1997).

Antidepressant treatment: After baseline assessments, all depressed subjects who wanted treatment were immediately started on open-label real-world treatment with an antidepressant. The default starting medication used was fluoxetine. An SSRI was chosen as this class of medications has been reported to not be different from placebo for precipitation of mania in bipolar depression (Sidor and Macqueen, 2011). Fluoxetine was chosen as it has been the most studied medication for effectiveness and long-term safety in young depressed subjects (March et al., 2007).If for some reason fluoxetine was contraindicated *because of previously* reported side effects or treatment resistance, another antidepressant was used. Depending on response and tolerance, antidepressant dosage was increased or a combination of antidepressants was used. The goal of clinical treatment was to treat the depression adequately to achieve a euthymic or near euthymic state. For data analysis, the dose of all antidepressants used was converted to

fluoxetine equivalent dose (Hayasaka et al., 2015).

Follow-up for MDD patients: After the baseline visit, visit 3 was a week later followed by visit 4 and 5 every 2 weeks, visit 6–10 every 1 month and visit 11–20 every 3 months up to 24 months. At each follow-up visit, a psychiatrist and a research coordinator assessed the patient for antidepressant response and side effect including emergence of any (hypo)mania symptoms. Patients were rated on the following items: MINI mood episode sections to assess for a switch into (hypo)mania, 17-item HAM-D scale, YMRS, MSC-SAD, HAM-A, C-SSRS, BSSI, TSES, and CGI-S. Patients who fulfilled criteria for (hypo)mania, or mania and therefore a diagnosis of BD, were discontinued from the study.

Depression HRMDD and LRMDD subgroup ascertainment: Final classification of the HRMDD and LRMDD subjects was done after the study had come to a close so that the classification did not affect the treatment of subjects or the behavioral ratings conducted by the raters. Three psychiatrists (AA, MA and PK) independently reviewed all available clinical information from the screening interview of all subjects to make a final determination regarding classification of MDD subjects as HRMDD or LRMDD. Subsequently, the classification of each of the subjects was discussed and a best-estimate consensus classification was decided upon (Nurnberger et al., 2011). The criteria for HRMDD was based on the presence of at least one of the following criteria: A) family history of BPD in the first-degree relative; B) history of psychosis during a mood episode; or C) subthreshold symptoms: history of periods of euphoric mood or increased irritability along with at least 2 mania symptoms with the former or 3 symptoms if only the latter was present, as well as duration of mania symptoms being less than 4 days. Other MDD subjects who did not satisfy any of these characteristics were ascertained to be LRMDD. Subsequently, statistical comparison of the groups was conducted on the behavioral and treatment response measures.

Statistical Analysis: Baseline characteristics were summarized as means and standard deviations for continuous variables and frequencies and percentages for categorical variables. ANOVA or the Chi-square test were used to compare baseline characteristics among the patient groups. Pairwise comparisons were performed with linear contrasts in the ANOVA models or Chi-squared test on the reduced contingency table for two groups. In addition, to investigate whether each baseline variable has a trend across the mood spectrum (LRMDD-HRMDD-BPD II-BPD I), we applied linear regression to continuous variables. For trends for dichotomous variables, e.g., presence or absence of a history of post-traumatic stress disorder (PTSD), we used the Cochran-Armitage test (Armitage, 1955; Cochran, 1954) to examine whether the binomial proportion has a significant increasing or decreasing trend.

The analyses of treatment data were restricted to HRMDD and LRMDD patients. We compared the times to attrition, switch to (hypo) mania, response and remission between the two groups. Kaplan-Meier curves of time to attrition were compared using the log-rank test (Fig. 1). As this was a real-world follow-up, we also considered that drop-out from the study could be due to non-random factors such as greater worsening of depressive or mania symptoms in one group compared to another or differences in tolerability due to side effects. Therefore, in our analyses for switch, response and remission, we distinguished censoring due to attrition and administrative censoring (end of study duration or study termination due to switch to (hypo)mania), where the data then follow semi-competing risk framework in the sense that attrition censored the observation of other outcomes but not vice versa. The cause-specific cumulative incidence curves are shown in Fig. 1.

For 17-item HAM-D, YMRS, MSC-SAD, HAM-A, C-SSRS, BSSI, TSES, and CGI-S, the linear mixed-effects models were used to fit the longitudinal data of each outcome to assess the changes over time, where the results were adjusted by age, employment status, baseline score and average dose. Missing data were assumed to be missing at random in the mixed-effects models. In addition, as above, we also considered that dropout from the study could be due to non-random factors such as greater worsening of depressive or mania symptoms in one group compared to another. For this possibility, we conducted a sensitivity analysis, a comparison of the last observed value of each rating between the two groups.

Lastly, besides the diagnostic switch rates, we also compared spikes in mania symptoms as an indicator of acceleration of manic symptoms (26), between HRMDD and LRMDD patients. A spike was defined as an increase of 25% from baseline YMRS rating. This threshold was chosen so as to include all minor as well as major spikes. A logistic model was used to compare the spike while adjusting for age, dose and baseline YMRS score. Statistical significance was established with a two-sided p-value less than 0.05. All analyses were conducted with R-studio (Boston, MA) by Dr. Bo Hu, PhD.

3. Results

A total of 106 MDD, 32 BPD and 49 HC took part in the study. Out of the 106 MDD subjects, 51 (48%) were ascertained to be HRMDD and 55 (52%) LRMDD. Out of 51 HRMDD subjects, 45 subjects satisfied the criteria A of subthreshold symptoms: 38 with subthreshold symptoms only, 3 with additional mood episode related psychosis, and 4 with additional family history. Five subjects had only a family history of bipolar disorder and 1 subject had only a history of mood-related psychotic symptoms. Out of the 32 BPD subjects, 14 satisfied DSM-IV-TR criteria for BPD I and 18 for BPD II.

3.1. Sociodemographic profile

There was a significant difference for age between the groups ($F_{3,134} = 4.39$, $p = 0.006$) with the HRMDD being the youngest (Table 1).

Between-group significant differences for illness characteristics, comorbid disorders and symptom profile (Table 2): For the onset of first depressive episode a significant overall difference was found between groups ($F_{3,134} = 2.82$, $p = 0.041$) and there was a significant trend ($p = 0.005$) for increasing age-of-onset from LRMDD at one end and BPD group on the other with HRMDD in between.

Co-morbid disorders as ascertained by responses on the MINI revealed several significant differences. Current alcohol dependence history was also significantly different ($\chi^2 = 17.3$, $df = 3$, $p = 0.001$) with a significant trend ($p = 0.006$) for increasing use from LRMDD group to the BPD groups with HRMDD in between.

The prevalence of current PTSD was also significant between groups ($\chi^2 = 8.1$, $df = 3$, $p = 0.044$) with a significant gradation for increasing proportion of PTSD symptoms from the LRMDD group to the BPD groups with HRMDD showing an intermediate prevalence ($p = 0.006$). No difference was found between the four groups for the occurrence of specific childhood traumatic events measured with the CTES. However, in the life event checklist four items (severe human suffering; assault with a weapon; exposure to toxic substance; serious accident at work, home or during recreational activity) with a significant trend ($p < 0.05$) for increasing occurrence of these events from the LRMDD group to the BPD groups and HRMDD showing intermediate occurrence.

The incidence of panic disorder was significant among groups ($\chi^2 = 8.9$, $df = 3$, $p = 0.03$). However, in this instance, the trend test was not significant as 57% of BPD I, 27.8% of BPD II and 25.5% of LRMDD subjects satisfied DSM-IV-TR criteria, while only 17.6% of HRMDD did.

For SCID-II rating analysis, a personality trait was ascertained to be present if a subject had a majority of the characteristics in a particular personality cluster. There was an increasing trend for differences in occurrence of borderline traits among the four groups ($\chi^2 = 12.7$, $df = 3$, $p = 0.005$) with a significant increasing trend ($p = 0.001$) from LRMDD to BPD groups with occurrence in HRMDD in between. Paranoid traits also showed a significant difference between groups

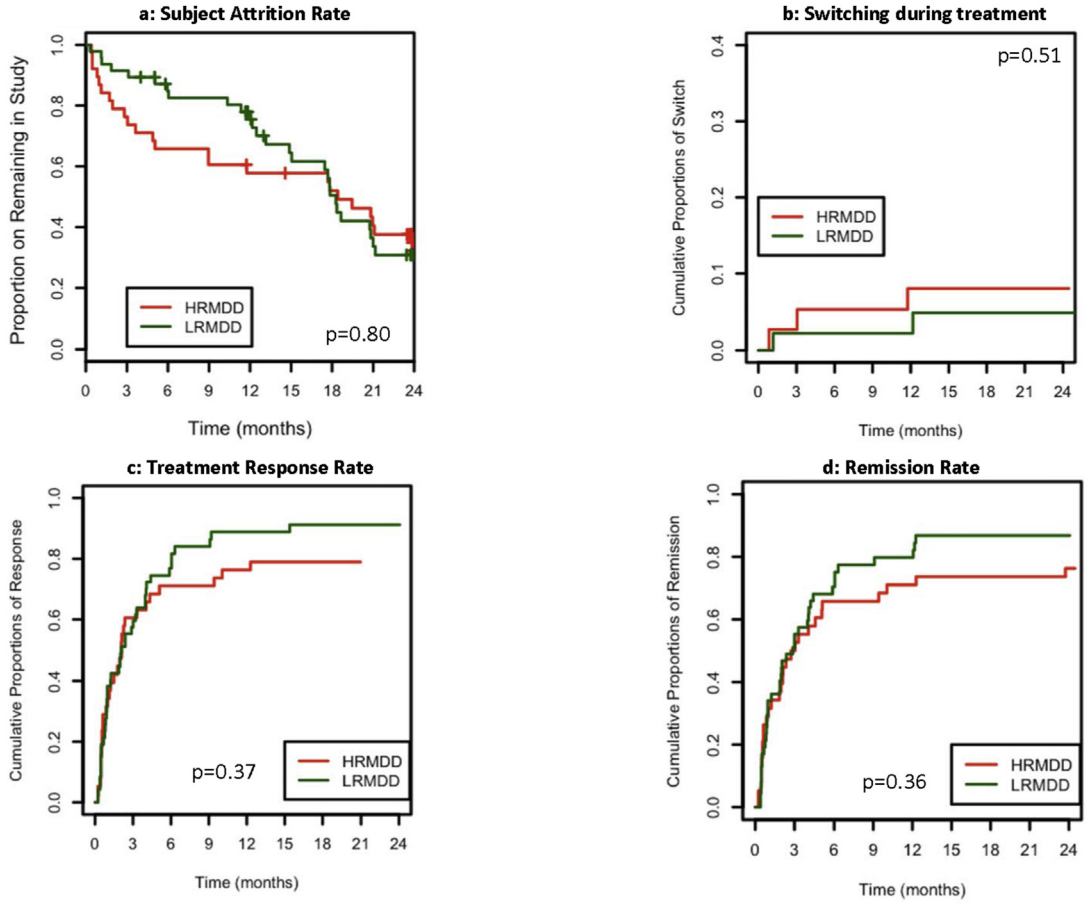

Fig. 1. Kaplan Meier Curves for Switching (a), Response (b) and Remission (c) rates while controlling for Attrition (d) rates over the 24-month period. Number of subjects at each time point: were 3 months (HRMDD:29, LRMDD:43), 6 months (HRMDD:24, LRMDD:38), 9 months (HRMDD:25, LRMDD:36), 12 months (HRMDD:22, LRMDD:36), 15 months (HRMDD:21, LRMDD:24), 18 months (HRMDD:18, LRMDD:19), 24 months (HRMDD:13, LRMDD:11).

(χ^2 = 9.9, df = 3, p = 0.02) with a significant trend for an increase of occurrence from the LRMDD to the BPD groups (p = 0.03), however, in this case, HRMDD group had the highest percentage of subjects with paranoid traits (44.7%).

Finally, the prevalence of MDD with melancholic subtype was significantly different between the groups and (p = 0.03) showed an increasing trend (p = 0.005) of occurrence from LRMDD to the BPD groups with HRMDD group showing intermediate frequency. An active suicidal attempt was reported in 7% of BPD I subjects in contrast to none in the other groups.

3.2. Antidepressant treatment response for HRMDD and LRMDD subjects

Out of 106 MDD subjects 85 (HRMDD: LRMDD; 38:47), subjects agreed to start open-label clinical antidepressant treatment. The most frequently used antidepressant was fluoxetine or another SSRI; however, other antidepressants such as bupropion, venlafaxine, duloxetine, mirtazapine, were also used depending on patient tolerance and preference. In some instances, a combination of bupropion and an SSRI was also used. All antidepressant doses were converted to fluoxetine equivalent for the purpose of reporting (average starting dose: 13 ± 5 mg daily; overall average dose: 38 ± 17 mg daily (HRMDD: 35 ± 18 mg and LRMDD: 40 ± 17 mg); average maximum: 48 ± 23 mg daily). The average duration of treatment was 394 ± 258 days (HRMDD: 360 ± 286 days and LRMDD: 421 ± 233 days). There was no significant difference between HRMDD and LRMDD in terms of the starting dose, maximum dose, overall average dose and average duration of treatment at 24 months. Number of subjects at each time point were: 3 months (HRMDD: 29, LRMDD:43), 6 months (HRMDD: 24, LRMDD:38), 9 months (HRMDD:25, LRMDD:36), 12 months (HRMDD: 22, LRMDD:36), 15 months (HRMDD:21, LRMDD:24), 18 months (HRMDD:18, LRMDD:19), 24 months (HRMDD:13, LRMDD:11).

Kaplan-Meier survival curves for attrition, response and remission rates, and proportion of switch (2 in LRMDD and 3 in HRMDD group) to DSM-IV-TR bipolar diagnosis are presented in Fig. 1. HRMDD patients tend to have a higher attrition rate in the first six months (p = 0.04) but the overall attrition curve was not significantly different. Curves for response and remission were also not significantly different, though the rates were lower in HRMDD than LRMDD when examined at 3, 6, 9, 12 and 24 months intervals respectively (Supplement Table I).

3.3. Change in (hypo)mania and depression and scores

We examined if mania symptoms spikes (> 25% increase from baseline YMRS and MSC scores) were different between the two groups. HRMDD patients were more likely to have spikes compared to LRMDD group (OR = 3.03, CI = [1.04, 8.33], p = 0.04). However, on closer examination, it was revealed that the increase in spikes in HRMDD subjects was significant only for the first 3 months of treatment (OR = 5.50, CI = [1.25, 25.02], p = 0.03) (Supplement Table II). The finding of an increase in mania spikes within the HRMDD group remained significant at a trend level when alcohol dependence was controlled for (OR = 2.71, 95% = [0.95, 7.68], p = 0.06).No

Table 1
Socio-demographic profile of study subjects: Bipolar Disorder I (BPD I), Bipolar Disorder II (BPD II), High-Risk Major Depressive Disorder (HRMDD) and Low-Risk Major Depressive Disorder (LRMDD).

Factor	Healthy Control n = 49	Bipolar Disorder I n = 14	Bipolar Disorder II n = 18	High-risk Major Depressive Disorder n = 51	Low-risk Major Depressive Disorder n = 55	Overall p-value[b]	Bipolar Disorder I vsHigh-risk Major Depressive Disorder p-value	Bipolar Disorder II vs High-risk Major Depressive Disorderp-value	Bipolar Disorder I vs Bipolar Disorder II	Bipolar Disorder I vs Low-risk Major Depressive Disorder	Bipolar Disorder II vs Low-risk Major Depressive Disorder	High-risk Major Depressive Disorder vs Low-risk Major Depressive Disorder
Age in yr. (mean ± SD)	24.2 ± 3.3	23.9 ± 3.7	23.5 ± 3.9	22.7 ± 3.4	25.2 ± 3.6	***0.006***	0.26	0.40	0.79	0.23	0.09	< ***0.001***
Gender n(%)						0.07	0.55	***0.02***	***0.03***	0.17	0.19	0.20
Female n(%)	28 (57.1)	12 (85.7)	9 (50.0)	40 (78.4)	37 (67.3)							
Male n(%)	21 (42.9)	2 (14.3)	9 (50.0)	11 (21.6)	18 (32.7)							
Race n(%)						0.36	0.85	0.61	0.42	0.09	0.52	0.07
African-American n (%)	4 (8.2)	4 (28.6)	3 (16.7)	13 (25.5)	6 (10.9)							
Asian n(%)	8 (16.3)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)							
Caucasian n(%)	37 (75.5)	10 (72.4)	15 (83.3)	37 (72.5)	49 (89.1)							
Education n(%)	16.8 ± 2.5	14.2 ± 1.8	14.6 ± 2.9	14.0 ± 2.3	14.5 ± 2.3	0.65	0.83	0.42	0.66	0.57	0.98	0.24
Employment n(%)						***0.009***	***0.01***	0.78	0.053	***0.049***	0.35	***0.018***
Employed n(%)	26 (53.1)	7 (53.8)[a]	10 (55.6)	23 (46.9)	37 (69.8)							
Student n(%)	23 (46.9)	0 (0)	5 (27.8)	18 (36.7)	7 (13.2)							
Unemployed n(%)	0 (0)	6 (42.9)	3 (16.7)	8 (16.3)	9 (17.0)							
Rating Scales at Baseline (Mean score ± SD)												
17-Item Hamilton Depression Scale		17.6 ± 3.7	18.0 ± 5.9	18.7 ± 3.9	17.0 ± 3.1	0.18	0.37	0.58	0.84	0.51	0.36	***0.015***
Young Mania Rating Scale		2.4 ± 2.6	2.1 ± 2.6	2.1 ± 2.9	0.73 ± 1.3	***0.005***	0.74	0.97	0.73	< ***0.001***	***0.004***	***0.002***
Mania Syndrome Checklist of schedule for Affective Disorders and Schizophrenia		5.6 ± 1.3	6.8 ± 2.8	5.5 ± 1.4	5.1 ± 0.44	< ***0.001***	0.7	***0.013***	0.16	***0.009***	< ***0.001***	0.054
Clinical Global Impression Severity Scale for BPD		3.9 ± 0.49	3.8 ± 0.55	3.9 ± 0.51	3.9 ± 0.56	0.84	0.87	0.41	0.45	0.69	0.61	0.68
Scale for Suicide Ideation		8.0 ± 10.4	7.9 ± 10.1	5.1 ± 8.6	6.2 ± 9.9	0.62	0.29	0.25	0.99	0.54	0.51	0.56
Columbia Suicide Severity Rating Scale		2.9 ± 1.8	3.1 ± 1.7	3.1 ± 1.5	2.7 ± 1.6	0.59	0.72	0.97	0.76	0.62	0.32	0.19
Hamilton Anxiety Scale		14.9 ± 6.5	16.2 ± 7.0	16.0 ± 7.0	13.9 ± 4.5	0.28	0.61	0.91	0.59	0.49	0.1	0.067

[a] 1 patient had missing data.
[b] ANOVA was used for continuous variables while chi-squared test was used for categorical variables. Overall p-value was calculated excluding the Healthy Control group.

Table 2
Baseline Illness Characteristics, Comorbid disorders and symptoms profile of patients with Bipolar Disorder I (BPD I), Bipolar Disorder II (BPD II), High-Risk Major Depressive Disorder (HRMDD) and Low-Risk Major Depressive Disorder (LRMDD) (only significant overall differences).

Factor		Bipolar Disorder I n = 14	Bipolar Disorder II n = 18	High-risk Major Depressive Disorder n = 51	Low-risk Major Depressive Disorder n = 55	Overall p-value[b]	Bipolar Disorder I vs High-risk Major Depressive Disorder p-value	Bipolar Disorder II vs High-risk Major Depressive Disorder p-value	Bipolar Disorder I vs Bipolar Disorder II	Bipolar Disorder I vs Low-risk Major Depressive Disorder	Bipolar Disorder II vs Low-risk Major Depressive Disorder	High-risk Major Depressive Disorder vs Low-risk Major Depressive Disorder	Trend test[a]
Illness characteristics (mean ± SD)													
Age at First Depressive Episode in yrs.		14.1 ± 4.1	12.2 ± 3.0	14.9 ± 3.8	15.5 ± 5.0	***0.041***	0.49	***0.009***	0.15	0.39	***0.01***	0.48	***0.005***
Number of Mood Episodes		61.5 ± 89.0	55.6 ± 37.4	18.4 ± 21.8	31.5 ± 34.1	***0.001***	***0.003***	***< 0.001***	0.69	***0.02***	***0.03***	0.10	***0.01***
First degree family history of Bipolar Disorder n(%)		6 (42.9)	5 (27.8)	13 (25.5)	0	***< 0.001***	0.206	0.849	0.373	***< 0.001***	***0.016***	***0.026***	***0.012***
Comorbid disorders													
***Comorbid disorders (Current)* n(%)**													
Alcohol Dependence		1 (7.1)	4 (22.2)	1 (2.0)	0	***0.001***	0.32	***0.004***	0.24	***0.046***	***< 0.001***	0.3	***p = 0.006***
Post-Traumatic Stress Disorder		4 (28.6)	4 (22.2)	5 (9.8)	3 (5.5)	***0.044***	***0.07***	0.18	0.68	***0.01***	***0.03***	0.4	***p = 0.006***
Life Events Check List n(%)	Severe human suffering	7 (50)	9 (50)	10 (20%)	11 (20%)	***0.006***	**0.013**	***0.013***	0.833	**0.013**	**0.013**	*0.96*	***0.002***
	Assault with a weapon	5(36)	10 (56)	23 (45%)	13 (24%)	***0.04***	0.667	*0.445*	0.347	0.276	**0.011**	***0.02***	***0.04***
	Exposure to toxic substance	4 (29)	5 (28)	7 (14%)	3(6%)	***0.026***	0.146	*0.176*	0.856	**0.007**	**0.008**	*0.146*	***0.003***
	Serious accidental work home or during recreational activity	6 (43)	13 (72)	18(35%)	11 (20%)	***0.001***	0.47	***0.007***	0.141	**0.05**	**< 0.001**	0.078	***0.001***
***Comorbid disorders (Lifetime)* n(%)**													
Panic disorder		8 (57.1)	5 (27.8)	9 (17.6)	14 (25.5)	**0.03**	**0.003**	0.36	0.09	***0.02***	0.85	0.33	0.31
***Personality trait* n(%)**													
Paranoid		5 (35.7)	6 (33.3)	21 (44.7)	9 (16.7)	***0.019***	0.85	0.41	0.64	0.055	0.13	***0.002***	0.03
Borderline		6 (42.9)	10 (55.6)	13 (28.3)	9 (16.7)	***0.005***	0.15	***0.04***	0.77	***0.01***	***0.001***	0.16	***< 0.001***
Antisocial		1 (7.1)	0	0	0	***0.019***	***0.046***	–	0.21	***0.03***	–	–	0.31
***Depression Phenomenology* n(%)**													
Melancholic features		12 (85.7)	15 (83.3)	37 (72.5)	30 (54.5)	***0.029***	0.31	0.36	***0.85***	***0.033***	***0.029***	0.055	***0.005***
Active suicidal attempt (Active steps to injure or prepare for suicidal attempt)		1 (7.1)	0	0	0	***0.039***	0.06	–	0.25	0.052	–	–	0.32

[a] For the trend test, linear model was used for continuous variables while Cochran-Armitage test was used for categorical variables.
[b] ANOVA was used for continuous variables while the chi-squared test was used for categorical variables. Overall p-value was calculated excluding the Healthy Control group.

difference was noted for a change over time for 17-item HAM-D, which was the main outcome measure. No difference was seen for HAM-A, YMRS, MSC, C-SSRS, MSSI, and CGI severity. When examined at each 3, 6, 9, 12, 15, 18 and 24 months there were no significant differences between the two groups except for greater TSES score for antidepressant side effects in the HRMDD subjects at the 3-month time point ($p = 0.019$) and a trend for a significantly less decrease in 17-item HAM-D score in this group at the 12-month time point ($p = 0.054$) (Supplemental Table III). Differences in the last observed value before attrition for any of the behavioral measures were also not significantly different.

4. Discussion

The results of our study show that 42% of young subjects presenting with a depressive episode have subthreshold (hypo)manic symptoms present for less than four days. This percentage is in-line with the 30–55% of patients reported to have subthreshold symptoms in other retrospective studies and community surveys (1–5). Five subjects out of 106 MDD converted to BPD diagnosis over two years which is similar to conversion rates calculated by Fiedorowicz and colleagues (Fiedorowicz et al., 2011) of 2.5% per year. This low rate of precipitation of (hypo)mania has also been noted in previous reviews and randomized trials (*Joseph et al., 2009*; Schneck et al., 2017) of antidepressant treatment for high-risk young depressed subjects.

To investigate the behavioral profile of the HRMDD group in comparison to BPD I, BPD II and LRMDD groups, we compared these four groups on a broad array of variables for illness characteristics, development trauma, comorbid disorders, personality traits, family history and symptoms of depression including suicidality. Overall, the four groups were similar in terms of demographics and severity of depression. However, significant differences were also seen between the groups.

Furthermore, trend test analysis revealed a gradation of values from the LRMDD to HRMDD to the BPD groups in terms of an earlier age of onset, tendency to develop alcohol dependence, borderline and paranoid traits and melancholic symptoms of depression. The increased childhood trauma events and frequency of PTSD associated with bipolarity could represent an increased allostatic load stemming from chaotic early childhood environment secondary to the presence of BPD in other family members as well as increased behavioral problems and risky behaviors including substance use in the index subject (Kapczinski et al., 2008). The gradation of values from BPD I to BPD II to HRMDD and then to LRMDD group, confirmed statistically significant on tests of trend, lend support to the bipolar spectrum concept (Akiskal et al., 2006) in this late adolescent and young adult population.

Regarding antidepressant treatment response, in the literature, there have been reports that BPD depression has a lower response than that for MDD (Park and Lee, 2016; Sharma et al., 2005). After accounting for attrition as a non-random event, we did observe a non-significant lower response and remission rate in the HRMDD compared to LRMDD group (Fig. 1). A trend for a smaller decrease in 17-item HAM-D scores in HRMDD group for the 12-month time point was also noted. These results suggest an intermediate antidepressant response in HRMDD subjects compared to what has been reported in low-risk MDD subjects and bipolar depression. In addition, within the first 3 months of treatment, HRMDD group reported more side effects as measured by the TSES scores than LRMDD group suggesting a possible decreased tolerability for antidepressants. This decreased tolerability may be related to increased attrition rates in the HRMDD group. *Adverse events from antidepressants have been noted to occur more in children and adolescents (*Strawn et al., 2014*). However, in this study, no relationship to age for attrition, response, remission and total TSES score was found, possibly due to an older population sample.*

During the treatment phase over 24 months for MDD subjects, the HRMDD did exhibit an overall higher number of spikes of in mania symptoms from baseline though for the individual time points this was significant only at 3 months. However, the conversion to frank (hypo) mania or mania requiring a change in diagnosis was not significantly different between the HRMDD and LRMDD groups. Therefore, the findings of this study suggest that HRMDD subjects are likely to report some increase in (hypo)mania symptoms with antidepressant treatment but the conversion rate to bipolar diagnosis is less than what has been reported in studies of BPD patients (Altshuler et al., 2006; Gijsman et al., 2004; Liu et al., 2017; McGirr et al., 2016).

Limitations of the study include the small number of BPD I and BPD II compared to the MDD subjects. However, as BPD is less prevalent than MDD, the relative ratio of the numbers of subjects studied is not very different from larger community surveys of these groups (Angst et al., 2010; Zimmermann et al., 2009). The overall sample size was not big enough to conduct a multiple comparison correction for the large number of baseline characteristics studied. The goal of the study was to leverage the rigorous and comprehensive phenotyping to provide a comprehensive comparison of these groups, which yielded a number of important findings that can be confirmed in future more extensive studies. This study was conducted in medication-free outpatients. Therefore, the sample of both unipolar and bipolar subjects consisted of moderately ill subjects. The generalizability of these findings to more severely ill cohorts will also need to be studied in future investigations. A limitation of the treatment response aspect of the study was the real-world nature and lack of blinding or randomization. However, by keeping the ascertainment of the HRMDD or LRMDD group membership at the conclusion of the study, the raters were kept blind to the classification thereby decreasing the effect of bias on the ratings. Another limitation was the substantial attrition rate over time in both groups and it is possible that some of the HRMDD subjects who exited the study may have converted if they had stayed in the study. We accounted for this possibility by using attrition rates and events as covariates in the analyses of response and remission rates.

5. Conclusion

In summary, the results of this study of young subjects with depression found that the group with subthreshold symptoms of bipolar disorder was intermediate between low-risk MDD group and the BPD groups in terms of illness characteristics and comorbid illness. Furthermore, in regard to treatment response and mania switch rates, the high-risk group displayed properties similar to what has been reported in the literature for BPD. Therefore, these subjects, if treated with antidepressants, need to be monitored closely for the development of BPD. Future studies with a randomized design need to be conducted.

Conflicts of interest

This project was funded by the NIMH to AA (R01MH093420). None of the authors have any financial conflicts to declare which are relevant to the conduct of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2018.12.006.

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