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Depression in bipolar disorder versus major depressive disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions

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Abstract

Objectives—To compare the clinical features and course of major depressive episodes (MDE) occurring in subjects with bipolar I disorder (BD-I), bipolar II disorder (BD-II), and major depressive disorder (MDD).

Methods—Data were drawn from the National Epidemiologic Survey on Alcohol and Related Conditions (2001–2002), a nationally representative face-to-face survey of more than 43,000 adults in the United States, including 5,695 subjects with lifetime MDD, 935 with BD-I and lifetime MDE, and 494 with BD-II and lifetime MDE. Differences on sociodemographic characteristics and clinical features, course, and treatment patterns of MDE were analyzed.

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Results—Most depressive symptoms, family psychiatric history, anxiety disorders, alcohol and drug use disorders, and personality disorders were more frequent—and number of depressive symptoms per MDE were higher—among subjects with BD-I, followed by BD-II, and MDD. BD-I individuals experienced a higher number of lifetime MDE, had the worst quality of life, and received significantly more treatment for MDE than BD-II and MDD subjects. Individuals with BD-I and BD-II experienced their first mood episode about 10 years earlier than those with MDD (21.2, 20.5, and 30.4 years, respectively).

Conclusions—Our results support the existence of a spectrum of severity of MDE, with highest severity for BD-I, followed by BD-II and MDD, suggesting the utility of dimensional assessments in current categorical classifications.

Keywords

bipolar disorder; clinical classifications; depression; epidemiology

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Among subjects with bipolar disorder (BD), depression is much more prevalent (1, 2) and has stronger effects on mortality and psychosocial impairment than mania or hypomania (3, 4). Recently, the clinical, biological, and treatment characteristics of major depressive episodes (MDE) in BD as compared to major depressive disorder (MDD) have been a focus of attention for researchers and clinicians (5–21). However, specific clinical or biological markers for bipolar depression are still lacking. In current diagnostic systems, the same diagnostic criteria apply to MDE occurring during MDD or during the course of BD (22).

In comparisons of MDD and depressed BD patients, atypical features, such as hypersomnia or leaden paralysis (5, 6, 9, 20), psychotic symptoms (13, 16, 17, 19), psychomotor retardation (5, 13, 16), shorter depressive episodes (13, 14), higher number of depressive recurrences (9, 18–20), family history of mood disorders (9, 14), comorbidity with substance abuse (8, 17), and earlier age at onset (7, 9, 18) are reported more frequently in BD; whereas, somatic disturbances (5, 6, 18), anxiety (7, 13), sleep loss (5, 6, 9, 11, 13, 14, 18), and appetite loss (5, 6, 14, 17) are reported more frequently in MDD. However, findings in one sample have seldom been replicated in another, resulting in conflicting results across studies. Most studies report on samples of bipolar I disorder (BD-I) patients or on heterogeneous samples comprising of mostly BD-I patients (5, 6, 13, 14, 16–18); only a few have addressed differences between bipolar II disorder (BD-II) and MDD (9–11, 23); and even fewer have compared BD-I and BD-II with MDD (19, 20). Those studies used clinical samples, which preclude extrapolation of their results to the general population, and did not account for the impact of severity of depression on the clinical presentation and treatment patterns.

Current categorical classifications do not rely on specific clinical correlates to discriminate between different mood disorders. In fact, DSM-IV differences between MDD, BD-II, and BD-I are based on lifetime presence of increasing number and duration of manic symptoms (22). This, together with the absence of genetic or other biomarkers supporting boundaries between conditions (21, 24, 25), suggests that dimensional approaches may contribute to describe mood disorders more accurately.

We used data from a large national representative survey, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (26), to address some of the gaps in previous research. Specifically, among individuals with a lifetime history of MDE, we compared those with lifetime BD-I, BD-II, and MDD on sociodemographic and clinical characteristics, symptoms of MDE, and lifetime treatment patterns, and explored whether the different mood diagnoses arrayed along a dimension. Our aim was to expand the knowledge regarding the differential features of MDE occurring in BD-I, BD-II, and MDD,

which could aid in the clinical decision-making and the characterization of mood disorders in DSM-V.

Methods

Sample

Wave 1 of the NESARC was a face-to-face survey conducted by the U.S. Census Bureau under the direction of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (Bethesda, MD, USA) in 2001–2002 (26). The NESARC target population was the non-institutionalized, adult civilian population residing in the United States. The housing unit sampling frame was the U.S. Bureau of the Census Supplementary Survey, which included the group quarters sampling frame derived from the Census 2000 Group Quarters Inventory. Blacks, Hispanics, and young adults (ages 18–24) were oversampled to provide more precision on the estimates of these groups.

The research protocol, including informed consent procedures, was approved by the Census Bureau's Institutional Review Board and the U.S. Office of Management and Budget. The final sample included 43,093 respondents, and the overall survey response rate was 81.0%. The NESARC sample was weighted to adjust for the probabilities of selection of: a sample housing unit or housing unit equivalent from the group quarters sampling frame, nonresponse at the household or person levels, selection of one person per household, and oversampling of young adults. The weighted data were then adjusted for sociodemographic variables based on the 2000 Decennial Census. Because of the results of these procedures, the NESARC offered a nationally representative sample of the non-institutionalized adult U.S. population.

Sociodemographic and clinical assessment

All diagnoses in the NESARC were made according to the DSM-IV (22) criteria using the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV version (AUDADIS-IV) (27), a valid and reliable fully-structured diagnostic interview designed for use by non-clinicians. AUDADIS-IV has similar structure and content to other DSM-IV-based diagnostic interviews, such as the Structured Clinical Interview for DSM Disorders (SCID-IV) (28).

Axis I diagnoses included in the AUDADIS-IV were mood disorders (MDD, dysthymia, BD), anxiety disorders (panic disorder, social anxiety disorder, specific phobia, generalized anxiety disorder), substance use disorders (any alcohol abuse/dependence, any drug abuse/dependence, nicotine dependence), and conduct disorder. Avoidant, dependent, obsessive-compulsive, paranoid, schizoid, histrionic, and antisocial personality disorders were also assessed in Wave I. We included mood and anxiety diagnoses defined in the DSM-IV as primary or independent diagnoses, i.e., not substance-induced and not due to a general medical condition (22). MDE entirely accounted for by bereavement were also not included. As we aimed to compare MDE, we included all NESARC respondents with lifetime history of MDE and BD-I (n = 935), BD-II (n = 494), or MDD (n = 5,695). Questions pertaining to MDE symptoms referred to respondents' most severe lifetime MDE.

The test-retest reliabilities of AUDADIS-IV werefair to good for mood and anxiety disorders (from $\kappa = 0.42$ for specific phobia, to $\kappa = 0.59$ for BD-I, $\kappa = 0.65$ for MDD, and $\kappa = 0.69$ for BD-II) and personality disorders ($\kappa = 0.40$–0.67), and excellent for drug diagnoses ($\kappa > 0.79$) (26, 29). The agreement between the AUDADIS-IV and the best estimate diagnosis given by psychiatrists for lifetime MDD showed a sensitivity of 75.7 and a specificity of 92.9 (29). The good test-retest reliabilities of the AUDADIS-IV mood sections were comparable to those obtained with the SCID (MDD: $\kappa = 0.64$ in patients and κ

= 0.42 in non-patients) (28), the computerized DSM-IV version of the Composite International Diagnostic Interview (CIDI) (any BD: $\kappa = 0.64$) (30), or the Schedule for Affective Disorders and Schizophrenia (SADS) by highly trained psychiatrists (hypomania $\kappa = 0.72$) (31). In addition, validity of MDD, BD-I, and BD-II diagnoses were assessed using the Mental Component, Social Functioning, Role Emotional Functioning, and Mental Health scores of the Short Form-12v2 (SF-12v2), a reliable and valid impairment measure in population surveys (32). Linear regression analyses of NESARC data on associations between MDD (33), BD-I (34), and BD-II (available upon request) controlling for age and comorbid psychiatric disorders showed highly significant relationships ($p < 0.001$) between each disability and mental impairment score and current or lifetime MDD, BD-I, and BD-II diagnoses. SF-12v2 was also used to measure impairment in our analyses.

We measured the severity of the most severe depressive episode, according to the number of depressive symptoms present during this episode. International classifications (ICD-10) (35) define episode severity according to the number of depressive symptoms present, and previous studies have found good correlation between number of symptoms of depression and other measures of severity (36).

Data were collected on sociodemographic characteristics, course of illness, and lifetime psychiatric family history among first-degree relatives (alcohol problems, drug problems, and depression). Ages at onset of manic, hypomanic, and MDE were defined as the first age at which the requisite number of symptoms for each diagnosis clustered in time. Respondents were classified as receiving treatment for a MDE if they (i) visited a counselor, therapist, doctor, psychologist, or other health professional to get help for an episode; (ii) were hospitalized for at least one night in relation to an episode; (iii) visited an emergency room to get help for an episode; or (iv) were prescribed medications for an episode. Use of alcohol, drugs, or non-prescribed medications to relieve symptoms of depression was also recorded, although not coded as receiving treatment.

Statistical analyses

One-way analysis of variance was used to compare differences across groups in dimensional measures and χ^2 analyses in categorical measures. To take into account the effect of covariates, we repeated the analyses adjusting for sociodemographic factors and severity (measured as the number of depressive symptoms in the most severe MDE). To further examine whether MDD, BD-II, and BD-I arrayed along a dimension of mood disorders, and to check for the presence of a severity trend across diagnoses, we tested for linear trends in the frequency of depressive symptoms, psychiatric family history, psychiatric comorbidity, and provision of treatment. To test for a predictive model of MDD, BD-I, and BD-II diagnoses, we performed a multinomial logistic regression analysis with diagnosis as the outcome, setting MDD as the reference category, and including symptoms of depression, psychiatric family history, lifetime comorbidities, age of onset of mood disorders, sociodemographic characteristics, use of drug or alcohol as self-medication, SF-12v2, number of lifetime depressive episodes, and number of depressive symptoms as predictors. From this model, we calculated expected probability for each diagnosis for each person. Accurate prediction was defined when the highest probability from the model coincided with the DSM-IV diagnoses. Standard errors (SE) and 95% confidence intervals (CI) for all analyses were calculated using Survey for Data Analysis (SUDAAN) (37), to adjust for the effects of the complex survey design. Significance was set at 0.05.

Results

Sociodemographic characteristics and impairment

Compared to BD-I and BD-II, individuals with MDD were more likely to be women, older than 45 years of age, and married or cohabiting, whereas those with BD-I or BD-II were more likely to have never been married. BD-II individuals were more likely than BD-I or MDD to be 18–29 years old. Education and personal income were highest among subjects with MDD, intermediate among those with BD-II, and lowest among those with BD-I. There were significantly more Black individuals with BD-I or BD-II than with MDD, and more Asians with BD-I than with MDD, with comparable proportions across diagnoses for other racial/ethnic groups. Individuals with BD-I and BD-II were more likely than those with MDD to report alcohol or drug use to relieve depression. Drug use for this purpose was also more likely in BD-I than BD-II (Table 1). SF-12v2 physical component, social functioning, role emotional, and mental health scores were significantly lower in BD-I compared to BD-II and MDD individuals. The physical component summary was lower in MDD than BD-II, but social functioning was lower in BD-II than MDD subjects (Table 1).

Symptoms of depression and psychiatric family history

During the most severe MDE, all symptoms of depression, except depressed mood and low energy, were more common in BD-I than MDD individuals. BD-II individuals were significantly more likely than those with MDD to report psychomotor retardation, feelings of guilt, irritability, restlessness, and a history of suicide attempts. Increased appetite or weight gain, hypersomnia, anhedonia, feelings of guilt, restlessness, worthlessness, thoughts about death, suicidal ideation, and suicide attempts were more common among BD-I than BD-II individuals. No symptoms of depression were reported more frequently by MDD than either BD-I or BD-II individuals, or by BD-II than BD-I individuals. The number of symptoms of depression in the most severe MDE was also higher in individuals with BD-I than those with BD-II, and in BD-I and BD-II compared to MDD subjects (Table 2). A family history of depression, alcohol problems, and drug problems was more common in subjects with BD-I or BD-II than MDD. Furthermore, individuals with BD-I presented with significantly more family history of alcohol problems than those with BD-II (Table 2).

In the adjusted analyses, most symptoms of depression (hypersomnia, increased appetite/weight gain, guilt, thoughts about death, suicidal ideation, suicide attempt, irritability, insomnia, restlessness, worthlessness, and difficulty making decisions) remained significantly more common among BD-I than MDD subjects; BD-II showed significantly more irritability, insomnia, and difficulty making decisions than MDD individuals; and increased appetite or weight gain, suicide attempt, irritability, restlessness, and worthlessness were more frequent among BD-I than BD-II subjects. Depressed mood was more common in MDD than in BD-I and BD-II individuals, and low energy was more frequent in MDD than BD-I subjects ($p < 0.05$ for all comparisons). Family history yielded essentially comparable results. The adjusted trend analyses revealed that most clinical symptoms of depression were more frequent in BD-I, followed by BD-II, and least frequent in MDD; while only depressed mood was more frequent in MDD, followed by BD-II and BD-I (Table 2). Linear trends were also found for family history of depression, alcohol problems, and drug problems with higher frequencies for BD-I, followed by BD-II and MDD individuals (Table 2).

Psychiatric comorbidity

Panic disorder, social anxiety disorder, specific phobia, and generalized anxiety disorder all co-occurred more frequently in BD-I than in MDD or BD-II. Panic disorder was also more common in BD-II than MDD subjects. Alcohol and drug use disorders were significantly

more likely among BD-I and BD-II individuals than MDD individuals, and drug abuse was also more likely in BD-I compared to BD-II. Rates of comorbidity with conduct disorder and alcohol abuse were not significantly different among the three diagnostic groups. All personality disorders assessed were more common in BD-I than MDD. This was also true in BD-II compared to MDD subjects, with the exception of dependent panic disorder. Avoidant, dependent, obsessive-compulsive, paranoid, and schizoid personality disorders were more prevalent in BD-I than BD-II individuals (Table 3). The adjusted analyses resembled the above results, also finding linear trends for all psychiatric comorbidities (except alcohol abuse and conduct disorder), with higher frequencies for BD-I, followed by BD-II, and MDD individuals (Table 3).

Course of illness

Subjects with BD-I and BD-II had their first mood episode significantly earlier than individuals with MDD. There was a difference of about 10 years between the first mood episode in subjects with BD-I or BD-II and those with MDD. Differences in age of onset between BD-I or BD-II and MDD individuals remained significant with respect to MDE only. Age of onset of MDE, manic or hypomanic episodes, or any mood episode was not significantly different between subjects with BD-I and BD-II (Table 4).

Lifetime number of depressive episodes was higher for BD-I than MDD [8.9 (SE 0.6) versus 4.7 (SE 0.2), $p < 0.001$] or BD-II individuals [8.9 (SE 0.6) versus 5.9 (SE 0.9), $p = 0.009$], with nonsignificant differences between BD-II and MDD ($p = 0.18$). The proportion of subjects whose first mood episode was a MDE was higher among BD-I than BD-II (69.5% versus 55.7%, $p = 0.0001$).

Treatment of depressive episodes

Only 66.6% of those with BD-I, 44.4% with BD-II, and 54.2% with MDD received treatment for depression. Only 57.4% of subjects with BD-I, 36.3% with BD-II, and 43.9% with MDD were ever prescribed any psychotropic medication for depression (Table 5).

BD-I individuals were significantly more likely than the other two groups to report any mental health treatment, psychiatric hospitalization, emergency room visit, or prescription of medications for depression. Additionally, BD-II individuals were less likely than those with MDD to receive any mental health treatment or prescribed medication for depression (Table 5). Although age at first treatment for a MDE was younger in BD-I and BD-II than in MDD, significantly more time elapsed between diagnosis of depression and first treatment for individuals with BD-I than for those with MDD (Table 5). Treatment patterns remained unchanged in the adjusted analyses; also, a linear trend emerged with frequencies increasing from MDD to BD-II and BD-I (Table 5).

Gender and race/ethnicity analyses

To further explore whether our results were based on differences of gender or race/ethnicity, we repeated all our analyses stratifying by gender and by racial/ethnic subgroups (data not shown). Separate analyses of males and females yielded the same results that appeared when both sexes were analyzed together. Results for Whites, Hispanics, and Blacks were similar to those reported for the whole sample, although some became nonsignificant due to the smaller sample sizes. Some exceptions included, among Hispanics and Blacks, the proportion of females in the BD-I group and MDD group was comparable; and among Hispanics, time from diagnosis until first treatment of depression was longer in BD-II than MDD subjects, with no differences between diagnoses in age at first treatment for depression. Sample size constraints limited the reliability of comparisons of Native American or Asian subpopulations.

Predictive model of BD-I and BD-II diagnoses

The results of a multinomial regression analysis with diagnosis as the dependent variable, using MDD as the reference group, and using symptoms of depression, family history, comorbidities, course of illness, and sociodemographic characteristics as predictors, found that BD-I was significantly associated with restlessness [odds ratio (OR) = 1.73, 95% CI: 1.12–2.67)], absence of depressed mood (OR = 0.40, 95% CI: 0.19–0.87), presence of any anxiety disorder (OR = 1.42, 95% CI: 1.09–1.84) and any personality disorder (OR = 2.17, 95% CI: 1.70–2.77), earlier age of onset (OR = 1.05, 95% CI: 1.04–1.06), male sex (OR = 1.54, 95% CI 1.18–2.00), being foreign-born (OR = 1.56, 95% CI: 1.01–2.44), and having lower income (ORs ranging from 1.59 to 2.50); whereas BD-II was associated with absence of depressed mood (OR = 0.49, 95% CI: 0.26–0.92) and absence of worthlessness (OR = 0.50, 95% CI: 0.31–0.82), presence of any personality disorder (OR = 1.74, 95% CI: 1.28–2.38), earlier age of onset (OR = 1.06, 95% CI: 1.05–1.09), male sex (OR = 1.43, 95% CI: 1.02–2.00), and being Black (OR = 1.82, 95% CI: 1.20–2.77). When all factors were included in the model, the predictive power was 89.93%, standard error (SE) = 0.24, ($p < 0.001$), suggesting that the combination of clinical and demographic variables can be helpful in accurately identifying individuals with BD-I and BD-II.

Discussion

To our knowledge, this is the first study to compare the sociodemographic characteristics, clinical correlates, and treatment patterns of MDE in individuals with lifetime BD-I, BD-II, or MDD in a nationally representative sample. We found that: (i) most depressive symptoms, family history of depression and substance use disorders, comorbidity with anxiety, substance use, and personality disorders were more common in BD-I, followed by BD-II, and least common in MDD subjects; (ii) subjects with BD-I and BD-II had their first mood episode significantly earlier than those with MDD, and subjects with BD-I had a higher number of depressive episodes than those with BD-II and MDD; (iii) individuals with BD-I had higher treatment rates for MDE than individuals with BD-II or MDD; and (iv) analyses controlling by sociodemographic factors and number of symptoms of depression showed comparable results and identified a severity trend across diagnoses (higher for BD-I, followed by BD-II, and last, MDD). These results did not substantially change when stratifying the analyses by gender or race/ethnicity.

The most salient differences in symptoms were between BD-I and MDD, with higher frequencies of most of them in BD-I (6, 13, 16, 18), even after controlling by potential confounders. As in previous reports, BD-II presented more frequently with irritability, restlessness, worthlessness, and suicide attempts than MDD subjects (9, 10, 38). The higher frequency of insomnia in BD-II and comparable frequency of atypical symptoms between BD-II and MDD are in contrast with previous findings linking atypical symptoms to BD-II (9, 11, 20). Although higher frequencies of other characteristics have been previously reported in MDD (5, 6, 18, 20), only depressed mood and low energy appeared more frequently in MDD than in BD-I or BD-II subjects in the controlled analyses. Regarding differences in BD subtypes, increased appetite, irritability, restlessness, worthlessness, and suicide attempts were all more common among BD-I than BD-II individuals, although previous reports found greater frequencies of atypical symptoms, higher depression scores, and higher suicide attempt rates in BD-II than BD-I (12, 20). As previously documented, history of depression (9, 19) and substance use disorders (39) were more common in relatives of BD subjects, especially BD-I, than in relatives of MDD subjects; there were higher rates of comorbid anxiety disorders (40), alcohol and drug use disorders (41), and comorbid DSM-IV Axis II disorders in BD (particularly BD-I) than in MDD; and both BD-I and BD-II individuals had their first mood episode earlier than MDD subjects (5, 6, 9, 18–20).

BD individuals, especially BD-I, had a higher frequency of depressive symptoms, including suicidal behavior, and a higher frequency of comorbid anxiety and substance use disorders, presentations that are related to greater severity and poorer outcomes (42). In BD, a higher degree of impairment, greater social disadvantage, and greater number of depressive episodes (18, 20) compared to MDD add to their clinical severity. A higher proportion of elderly respondents with MDD could also reflect lower survival of individuals with BD, suggesting greater severity in BD. The direct comparison of the three disorders revealed a severity trend from MDD to BD-II and from BD-II to BD-I, measured by an increasing overall frequency of depressive symptoms, psychiatric family history, and psychiatric comorbidity even after controlling for number of symptoms of depression.

In the multinomial regression, several predictors were significantly associated with BD-I and BD-II diagnoses. Some of these variables, such as earlier age of onset and lifetime comorbid anxiety disorder, have also been related to BD diagnosis in a Canadian population-based comparison of subjects with BD and MDD (43), although other factors identified by that report were not replicated in our analyses. The fact that we reported differences between MDD and bipolar subtypes, instead of considering BD as a whole, may limit the comparability with previous studies. Although the multinomial regression provides a model for discriminating between diagnoses, differences between particular variables were small, especially between symptoms of depression; the combination of clinical, sociodemographic, and severity factors being necessary to adequately classify patients in each diagnostic group. Besides lack of clear-cut differences, we did not identify a particular set of symptoms of depression differentially associated with each diagnosis, but a continuum of symptoms and clinical and severity correlates more frequent in BD-I than BD-II and MDD subjects.

Although they have clinical utility, without clearly identified etiological, biological, or clinical validators, syndromes such as MDD or BD may be seen as categorizations imposed on a continuum of symptoms (44). Earlier studies comparing recurrent MDD and BD-I have shown that, regardless of diagnostic category, the more symptomatic depressions had a higher likelihood of presenting manic/hypomanic features and greater severity (45). Subsyndromal manic symptoms, such as irritability in depressed BD-I and BD-II subjects, also confer higher severity (46). These, and our own findings, are consistent with a dimensional view and may have implications for DSM-V concerning the classification of mood disorders. The American Psychiatric Association DSM-V Work Group has underscored the usefulness of dimensionally assessing behavioral domains and has proposed adding a unitary dimension of symptom severity, owing to its predictive value for treatment response of depression across mood disorders (42). The National Institute of Mental Health (NIMH) has also launched The Research Domain Criteria project (RDoC), a research initiative to develop new ways of classifying psychopathology based on dimensions of observable behavior and neurobiological measures (47). Aware that implementation of dimensional classifications involves feasibility problems, we have previously suggested that, as a first step, categorical classifications incorporate severity assessments of critical dimensions, including clinical symptoms, comorbidity, and family psychiatric history (44).

Despite recent increases in treatment-seeking for depression (48), the NESARC showed that many individuals with MDE did not receive treatment. Treatment rates for MDE were particularly low in BD-II, possibly reflecting under detection or lack of perceived need of treatment by patients or clinicians, despite its severity. Strategies aimed to facilitate diagnoses of BD in clinical settings could help diminish decline in functioning and lethality associated with this condition. Higher rates of psychiatric hospitalizations and emergency room visits for MDE in BD-I than MDD individuals confirm previous reports (17) and

underscore the greater morbidity and overall level of illness severity. Across diagnoses, treatment was more frequent in subjects with more symptomatic presentations, as expected.

Our study has the limitations common to most large-scale surveys. First, clinical information was based on retrospective self-report, and subject to recall bias. Second, to maximize our sample size, we included all subjects aged 18 years and older with at least one lifetime MDE, and, although more than two-thirds were older than 30 years and had therefore passed the peak age for conversion to BD, we may have included some individuals under MDD who would subsequently develop BD. Misclassification error would decrease rather than increase differences across groups, suggesting that our results are robust, although differences in comorbidity profile between early and late onset BD cannot be ruled out. Third, the NESARC did not collect data on types of psychotropic medication or treatment adherence, nor formally assessed psychotic disorders. Fourth, as other epidemiologic surveys, the NESARC did not use a clinician-administered interview, but relied on the AUDADIS-IV, a fully structured interview that assessed DSM-IV symptomatology. Although this could have precluded finding subtle differences between diagnostic categories possibly present using clinician-administered instruments, the AUDADIS-IV diagnoses led to significant between-group differences, suggesting that they were adequate for the purposes of our study and able to generate informative results. The National Comorbidity Survey Replication (NCS-R) group reported combined prevalences of BD-I and BD-II higher than those reported in our study, up to 3.9% (49), although subsequent analyses of the same group lowered those figures to 2.1–2.7% (50, 51). It is possible that the NESARC may have also assigned a diagnosis of BD to individuals who would not receive that diagnosis in a clinical interview. However, potential misclassification should have biased our results towards the null, decreasing, rather than increasing, any potential differences among the groups. Moreover, we assessed other clinical correlates (comorbidity, treatment variables), not relying only on DSM-IV criteria for MDE. The test-retest reliabilities of the AUDADIS-IV mood sections (BD-I: $\kappa = 0.59$, MDD: $\kappa = 0.65$, and BD-II: $\kappa = 0.69$), large sample size of the study, and consistency across analytic strategies provide additional support for the validity of our results.

The NESARC constitutes the largest nationally representative survey to date to include information on MDD, BD-I, and BD-II in adults. We found a gradient of more frequent depressive symptoms, comorbidities, family history, and treatment, and greater severity of MDE from BD-I to BD-II and then to MDD. Although the combination of clinical, sociodemographic, and severity variables had a predictive power of 89.93%, differences in particular characteristics were small, without clear-cut differences between groups. In conjunction with the lack of differential biological or etiological markers, our results are consistent with the existence of a continuum of depressive clinical syndromes and suggest the need to include a dimensional assessment in the current categorical classifications.

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References

1. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry. 2003; 60:261–269. [PubMed: 12622659]
2. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry. 2002; 59:530–537. [PubMed: 12044195]
3. Rosa AR, Reinares M, Franco C, et al. Clinical predictors of functional outcome of bipolar patients in remission. Bipolar Disord. 2009; 11:401–409. [PubMed: 19500093]
4. Marangell LB, Bauer MS, Dennehy EB, et al. Prospective predictors of suicide and suicide attempts in 1,556 patients with bipolar disorders followed for up to 2 years. Bipolar Disord. 2006; 8:566–575. [PubMed: 17042830]
5. Mitchell PB, Goodwin GM, Johnson GF, Hirschfeld RMA. Diagnostic guidelines for bipolar depression: a probabilistic approach. Bipolar Disord. 2008; 10:144–152. [PubMed: 18199233]
6. Mitchell PB, Malhi GS. Bipolar depression: phenomenological overview and clinical characteristics. Bipolar Disord. 2004; 6:530–539. [PubMed: 15541069]
7. Bowden CL. A different depression: clinical distinctions between bipolar and unipolar depression. J Affect Disord. 2005; 84:117–125. [PubMed: 15708408]
8. Muzina DJ, Kemp DE, McIntyre RS. Differentiating bipolar disorders from major depressive disorders: treatment implications. Ann Clin Psychiatry. 2007; 19:305–312. [PubMed: 18058287]
9. Benazzi F. Clinical differences between bipolar II depression and unipolar major depressive disorder: lack of an effect of age. J Affect Disord. 2003; 75:191–195. [PubMed: 12798259]
10. Benazzi F. Psychomotor changes in melancholic and atypical depression: unipolar and bipolar-II subtypes. Psychiatry Res. 2002; 112:211–220. [PubMed: 12450630]
11. Hantouche EG, Akiskal HS. Bipolar II vs. unipolar depression: psychopathologic differentiation by dimensional measures. J Affect Disord. 2005; 84:127–132. [PubMed: 15708409]
12. Brugue E, Colom F, Sanchez-Moreno J, Cruz N, Vieta E. Depression subtypes in bipolar I and II disorders. Psychopathology. 2008; 41:111–114. [PubMed: 18059112]
13. Mitchell PB, Wilhelm K, Parker G, Austin MP, Rutgers P, Malhi GS. The clinical features of bipolar depression: a comparison with matched major depressive disorder patients. J Clin Psychiatry. 2001; 62:212–216. [PubMed: 11305713]
14. Mitchell P, Parker G, Jamieson K, et al. Are there any differences between bipolar and unipolar melancholia? J Affect Disord. 1992; 25:97–105. [PubMed: 1644992]
15. Furukawa TA, Konno W, Morinobu S, Harai H, Kitamura T, Takahashi K. Course and outcome of depressive episodes: comparison between bipolar, unipolar and subthreshold depression. Psychiatry Res. 2000; 96:211–220. [PubMed: 11084217]
16. Parker G, Roy K, Wilhelm K, Mitchell P, Hadzi-Pavlovic D. The nature of bipolar depression: implications for the definition of melancholia. J Affect Disord. 2000; 59:217–224. [PubMed: 10854638]
17. Olfson M, Das AK, Gameroff MJ, et al. Bipolar depression in a low-income primary care clinic. Am J Psychiatry. 2005; 162:2146–2151. [PubMed: 16263856]
18. Perlis RH, Brown E, Baker RW, Nierenberg AA. Clinical features of bipolar depression versus major depressive disorder in large multicenter trials. Am J Psychiatry. 2006; 163:225–231. [PubMed: 16449475]
19. Solomon DA, Leon AC, Maser JD, et al. Distinguishing bipolar major depression from unipolar major depression with the screening assessment of depression-polarity (SAD-P). J Clin Psychiatry. 2006; 67:434–442. [PubMed: 16649831]
20. Serretti A, Mandelli L, Lattuada E, Cusin C, Smeraldi E. Clinical and demographic features of mood disorder subtypes. Psychiatry Res. 2002; 112:195–210. [PubMed: 12450629]
21. Phillips ML, Vieta E. Identifying functional neuroimaging biomarkers of bipolar disorder: toward DSM-V. Schizophr Bull. 2007; 33:893–904. [PubMed: 17562698]
22. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. Washington, DC: American Psychiatric Association; 1994.

23. Benazzi F. Bipolar versus unipolar psychotic outpatient depression. J Affect Disord. 1999; 55:63–66. [PubMed: 10512608]
24. Parsey RV, Hastings RS, Oquendo MA, et al. Lower serotonin transporter binding potential in the human brain during major depressive episodes. Am J Psychiatry. 2006; 163:52–58. [PubMed: 16390889]
25. Konarski JZ, McIntyre RS, Kennedy SH, Rafi-Tari S, Soczynska JK, Ketter TA. Volumetric neuroimaging investigations in mood disorders: bipolar disorder versus major depressive disorder. Bipolar Disord. 2008; 10:1–37. [PubMed: 18199239]
26. Grant BF, Dawson DA, Stinson FS, Chou PS, Kay W, Pickering R. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. Drug Alcohol Depend. 2003; 71:7–16. [PubMed: 12821201]
27. Grant, BF.; Dawson, DA.; Hasin, DS. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version. Bethesda: National Institute on Alcohol Abuse and Alcoholism; 2001.
28. Williams JB, Gibbon M, First MB, et al. The Structured Clinical Interview for DSM-III-R (SCID). II. Multisite test-retest reliability. Arch Gen Psychiatry. 1992; 49:630–636. [PubMed: 1637253]
29. Canino G, Bravo M, Ramirez R, et al. The Spanish Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS): reliability and concordance with clinical diagnoses in a Hispanic population. J Stud Alcohol. 1999; 60:790–799. [PubMed: 10606491]
30. Wittchen HU, Lachner G, Wunderlich U, Pfister H. Test-retest reliability of the computerized DSM-IV version of the Munich-Composite International Diagnostic Interview (M-CIDI). Soc Psychiatry Psychiatr Epidemiol. 1998; 33:568–578. [PubMed: 9803825]
31. Simpson SG, McMahon FJ, McInnis MG, et al. Diagnostic reliability of bipolar II disorder. Arch Gen Psychiatry. 2002; 59:736–740. [PubMed: 12150650]
32. Ware, JE.; Kosinski, M.; Turner-Bowker, DM.; Gandek, B. How to Score Version 2 of the SF-12 Health Survey. Lincoln: Quality Metrics; 2002.
33. Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry. 2005; 62:1097–1106. [PubMed: 16203955]
34. Grant BF, Stinson FS, Hasin DS, et al. Prevalence, correlates, and comorbidity of bipolar I disorder and Axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2005; 66:1205–1215. [PubMed: 16259532]
35. World Health Organization. [Last accessed August 11, 2011.] International Statistical Classification of Diseases and Related Health Problems 10th Revision Version for 2007. Available from: http://apps.who.int/classifications/apps/icd/icd10online/
36. Brennan PA, Hammen C, Andersen MJ, Bor W, Najman JM, Williams GM. Chronicity, severity, and timing of maternal depressive symptoms: relationships with child outcomes at age 5. Dev Psychol. 2000; 36:759–766. [PubMed: 11081699]
37. Research Triangle Institute. Software for Survey Data Analysis (SUDAAN) Version 9.0. Research Triangle Park: Research Triangle Institute; 2004.
38. Benazzi F. Symptoms of depression as possible markers of bipolar II disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2006; 30:471–477. [PubMed: 16427176]
39. Wilens TE, Biederman J, Adamson J, et al. Association of bipolar and substance use disorders in parents of adolescents with bipolar disorder. Biol Psychiatry. 2007; 62:129–134. [PubMed: 17481590]
40. Coryell W, Solomon DA, Fiedorowicz JG, Endicott J, Schettler PJ, Judd LL. Anxiety and outcome in bipolar disorder. Am J Psychiatry. 2009; 166:1238–1243. [PubMed: 19797434]
41. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA. 1990; 264:2511–2518. [PubMed: 2232018]
42. American Psychiatric Association. [Last accessed August 11, 2011.] DSM-V Development. Available from: http://www.dsm5.org/

43. Schaffer A, Cairney J, Veldhuizen S, Kurdyak P, Cheung A, Levitt A. A population-based analysis of distinguishers of bipolar disorder from major depressive disorder. J Affect Disord. 2010; 125:103–110. [PubMed: 20223522]
44. Vieta E, Phillips ML. Deconstructing bipolar disorder: a critical review of its diagnostic validity and a proposal for DSM-V and ICD-11. Schizophr Bull. 2007; 33:886–892. [PubMed: 17562693]
45. Cassano GB, Rucci P, Frank E, et al. The mood spectrum in unipolar and bipolar disorder: arguments for a unitary approach. Am J Psychiatry. 2004; 161:1264–1269. [PubMed: 15229060]
46. Goldberg JF, Perlis RH, Bowden CL, et al. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. Am J Psychiatry. 2009; 166:173–181. [PubMed: 19122008]
47. [Last accessed August 11, 2011.] NIMH Website. Available from http://www.nimh.nih.gov
48. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289:3095–3105. [PubMed: 12813115]
49. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005; 62:593–602. [PubMed: 15939837]
50. Kessler RC, Akiskal HS, Angst J, Guyer M, Hirschfeld RM, Merikangas KR, et al. Validity of the assessment of bipolar spectrum disorders in the WHO CIDI 3. 0. J Affect Disord. 2006; 96:259–269. [PubMed: 16997383]
51. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007; 64:543–552. [PubMed: 17485606]

Table 1

Differences among subjects with bipolar disorder and lifetime major depressive episodes and subjects with major depressive disorder by sociodemographic characteristics

	BD-I (n = 935)	BD-II (n = 494)	MDD (n =5695)			BD-I versus MDD		BD-II versus MDD		BD-I versus BD-II	
Characteristic	**% (SE)**	**% (SE)**	**% (SE)**	**χ^2 (df)**	**p-value**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Sex: female	60.2 (2.0)	58.2 (2.8)	67.3 (0.8)	8.0 (2)	0.001	0.7	0.6–0.9	0.7	0.5–0.9	1.1	0.8–1.4
Race/ethnicity				2.8 (8)	0.010						
White/non Hispanic	75.0 (1.9)	71.7 (2.5)	78.1 (1.2)			1.0	1.0–1.0	1.0	1.0–1.0	1.0	1.0–1.0
Black/non Hispanic	10.0 (1.2)	12.7 (1.4)	7.5 (0.6)			1.4	1.1–1.8	1.9	1.4–2.4	0.8	0.5–1.1
Native American	4.5 (0.8)	3.9 (1.2)	3.1 (0.3)			1.5	1.0–2.3	1.4	0.7–2.7	1.1	0.5–2.3
Asian/Pacific Islander	1.9 (0.7)	2.1 (0.8)	2.9 (0.4)			0.7	0.3–1.4	0.8	0.4–1.6	0.9	0.3–2.5
Hispanic	8.5 (1.1)	9.7 (1.6)	8.4 (0.9)			1.1	0.9–1.3	1.3	1.0–1.7	0.8	0.6–1.2
Birthplace: USA	90.9 (1.6)	91.5 (1.6)	91.1 (1.0)	0.1 (2)	0.946	1.0	0.7–1.3	1.1	0.7–1.5	0.9	0.6–1.5
Marital status				11.5 (4)	< 0.001						
Married/cohabiting	49.6 (1.9)	44.1 (2.6)	56.2 (0.9)			1.0	1.0–1.0	1.0	1.0–1.0	1.0	1.0–1.0
Widowed/separated/divorced	21.8 (1.5)	19.4 (2.0)	24.8 (0.7)			1.0	0.8–1.2	1.0	0.8–1.3	1.0	0.7–1.4
Never married	28.6 (1.7)	36.5 (2.6)	19.0 (0.7)			1.7	1.4–2.1	2.5	1.9–3.2	0.7	0.5–0.9
Education				5.5 (4)	0.001						
Less than high school	19.1 (1.6)	16.6 (1.9)	13.4 (0.6)			1.7	1.3–2.1	1.4	1.0–1.8	1.2	0.9–1.8
High school graduate	29.9 (1.8)	28.8 (2.8)	26.9 (0.9)			1.3	1.1–1.6	1.2	0.9–1.5	1.1	0.8–1.5
Some college or higher	51.1 (2.1)	54.7 (2.7)	59.7 (0.9)			1.0	1.0–1.0	1.0	1.0–1.0	1.0	1.0–1.0
Personal income				8.4 (6)	< 0.001						
$0–19,999	64.9 (2.0)	53.4 (3.3)	50.1 (1.0)			1.0	1.0–1.0	1.0	1.0–1.0	1.0	1.0–1.0
$20,000–34,999	18.4 (1.6)	24.6 (2.5)	22.6 (0.8)			0.6	0.5–0.8	1.0	0.7–1.4	0.6	0.4–0.9
$35,000–69,999	14.0 (1.4)	17.9 (2.0)	20.4 (0.9)			0.5	0.4–0.7	0.8	0.6–1.1	0.6	0.4–1.0
$70,000+	2.7 (0.6)	4.2 (1.3)	6.9 (0.6)			0.3	0.2–0.5	0.6	0.3–1.1	0.5	0.3–1.1
Urbanicity				0.8 (2)	0.439						
Urban	77.0 (2.5)	80.7 (2.9)	78.8 (1.7)			1.0	1.0–1.0	1.0	1.0–1.0	1.0	1.0–1.0
Rural	23.0 (2.5)	19.3 (2.9)	21.2 (1.7)			1.1	0.9–1.4	0.9	0.6–1.2	1.3	0.9–1.8
Age at assessment				16.4 (6)	< 0.001						
18–29 years	32.2 (1.9)	42.6 (2.9)	19.8 (0.7)			1.0	1.0–1.0	1.0	1.0–1.0	1.0	1.0–1.0
30–44 years	34.2 (1.9)	36.7 (2.7)	32.8 (0.8)			0.6	0.5–0.8	0.5	0.4–0.7	1.2	0.9–1.7
45–64 years	30.3 (1.7)	18.2 (2.2)	37.4 (0.8)			0.5	0.4–0.6	0.2	0.2–0.3	2.2	1.5–3.2

Characteristic	BD-I (n = 935) % (SE)	BD-II (n = 494) % (SE)	MDD (n =5695) % (SE)	χ^2 (df)	p-value	BD-I versus MDD OR	95% CI	BD-II versus MDD OR	95% CI	BD-I versus BD-II OR	95% CI
65 years and older	3.4 (0.6)	2.5 (0.7)	10.1 (0.5)			0.2	0.1–0.3	0.1	0.1–0.2	1.8	0.9–3.7
Any alcohol use to relieve symptoms of depression	34.3 (2.0)	28.3 (2.7)	17.9 (0.7)	28.5 (2)	< 0.001	2.4	2.0–2.9	1.8	1.4–2.4	1.3	1.0–1.8
Any drug use or non-prescribed medications to relieve symptoms of depression	18.2 (1.8)	9.3 (1.6)	5.4 (0.4)	20.0 (2)	< 0.001	3.9	3.0–5.2	1.8	1.2–2.7	2.2	1.4–3.4
	Mean (SE)	Mean (SE)	Mean (SE)	Wald *F*(df)	p-value	*t*-test	p-value	*t*-test	p-value	*t*-test	p-value
SF-12v2											
Physical component summary	48.5 (0.5)	51.8 (0.6)	49.7 (0.2)	10.5 (65)	< 0.001	−2.1	0.043	3.9	< 0.001	−4.4	< 0.001
Social functioning scale	43.1 (0.6)	46.4 (0.7)	48.1 (0.2)	31.6 (65)	< 0.001	−7.8	< 0.001	−2.4	0.019	−3.7	< 0.001
Role emotional scale	41.6 (0.6)	47.1 (0.6)	47.5 (0.2)	51.8 (65)	< 0.001	−10.1	< 0.001	−0.7	0.482	−7.0	< 0.001
Mental health scale	41.4 (0.5)	45.2 (0.6)	46.3 (0.2)	47.0 (65)	< 0.001	−9.7	< 0.001	−1.6	0.118	−4.9	< 0.001

BDI-I = bipolar I disorder; BD-II = bipolar II disorder; MDD = major depressive disorder; SE = standard error; OR = odds ratio; CI = confidence interval; SF-12v2 = Medical Outcomes Study 12-item short form.

Table 2

Depressive symptoms and family history of subjects with bipolar disorder and lifetime major depressive episodes and subjects with major depressive disorder

	BD-I (n = 935)	BD-II (n = 494)	MDD (n = 5695)			BD-I versus MDD		BD-II versus MDD		BD-I versus BD-II		Linear trend test[a]	
Depressive symptoms	**% (SE)**	**% (SE)**	**% (SE)**	**χ^2 (df = 2)**	**p-value**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**χ^2 (df = 1)**	**p-value**
Hypersomnia	58.6 (1.9)	49.0 (2.8)	45.4 (0.9)	15.7	0.001	1.7	1.4–2.0	1.2	0.9–1.5	1.5	1.1–2.0	7.2	0.007
Increased appetite/weight gain	45.5 (2.1)	34.8 (2.6)	33.5 (0.8)	11.8	< 0.001	1.7	1.4–2.0	1.1	0.8–1.4	1.6	1.2–2.1	14.0	0.000
Anhedonia	94.6 (0.8)	89.9 (1.6)	87.6 (0.6)	19.9	< 0.001	2.5	1.8–3.4	1.3	0.9–1.8	2.0	1.3–3.0	0.0	0.973
Psychomotor retardation	51.9 (2.1)	46.1 (2.9)	38.4 (0.9)	15.4	< 0.001	1.7	1.4–2.1	1.4	1.1–1.8	1.3	0.9–1.7	0.4	0.531
Loss of appetite/weight	65.6 (1.8)	60.9 (2.8)	57.1 (0.8)	8.5	0.001	1.4	1.2–1.7	1.2	0.9–1.5	1.2	0.9–1.6	1.7	0.198
Feelings of guilt	75.0 (1.8)	66.0 (2.5)	57.3 (0.8)	34.1	< 0.001	2.2	1.8–2.7	1.5	1.1–1.8	1.5	1.2–2.1	12.0	0.001
Thoughts about death	73.2 (1.8)	56.9 (2.7)	54.2 (0.8)	34.4	< 0.001	2.3	1.9–2.8	1.1	0.9–1.4	2.1	1.6–2.7	5.6	0.018
Suicidal ideation	58.4 (2.2)	40.9 (2.7)	36.5 (0.8)	32.8	< 0.001	2.5	2.0–3.0	1.2	1.0–1.5	2.0	1.5–2.7	17.7	< 0.001
Suicide attempt	26.5 (1.7)	14.5 (1.9)	8.8 (0.4)	36.4	< 0.001	3.7	3.0–4.6	1.8	1.3–2.4	2.1	1.5–3.0	61.4	< 0.001
Depressed mood	93.7 (1.0)	92.9 (1.4)	95.0 (0.4)	1.5	0.222	0.8	0.5–1.1	0.7	0.4–1.1	1.1	0.7–1.9	26.1	< 0.001
Irritability	72.2 (1.9)	64.0 (2.6)	48.6 (0.8)	40.9	< 0.001	2.7	2.3–3.3	1.9	1.5–2.4	1.5	1.1–1.9	57.8	< 0.001
Insomnia	52.0 (2.0)	46.3 (2.9)	45.3 (0.8)	4.6	0.014	1.3	1.1–1.6	1.0	0.8–1.3	1.3	1.0–1.6	4.1	< 0.001
Low energy	88.0 (1.2)	84.7 (2.1)	85.0 (0.6)	2.4	0.097	1.3	1.0–1.7	1.0	0.7–1.4	1.3	0.9–2.0	4.8	0.015
Restlessness	68.1 (1.9)	47.5 (2.9)	36.9 (1.0)	44.3	< 0.001	3.6	3.0–4.5	1.6	1.2–2.0	2.4	1.8–3.2	44.3	< 0.001
Worthlessness	80.4 (1.4)	65.3 (2.6)	61.6 (0.8)	38.3	< 0.001	2.6	2.1–3.1	1.2	0.9–1.5	2.2	1.6–2.9	8.0	0.005
Poor concentration	92.5 (1.1)	89.0 (1.8)	84.6 (0.7)	15.7	< 0.001	2.2	1.6–3.1	1.5	1.0–2.2	1.5	0.9–2.5	2.7	0.100
Difficulty making decisions	86.3 (1.3)	80.4 (2.3)	75.3 (0.7)	22.4	< 0.001	2.1	1.6–2.6	1.4	1.0–1.8	1.5	1.0–2.3	6.7	0.010
Family history													
Depression	79.1 (1.7)	74.1 (2.5)	67.9 (0.9)	16.1	< 0.001	1.8	1.5–2.2	1.4	1.0–1.8	1.3	1.0–1.8	22.8	< 0.001
Alcohol problems	82.7 (1.7)	76.4 (2.1)	70.3 (0.8)	21.3	< 0.001	2.0	1.6–2.5	1.4	1.1–1.7	1.5	1.1–2.0	20.6	< 0.001
Drug problems	50.7 (2.0)	45.0 (2.7)	35.5 (0.8)	18.6	< 0.001	1.9	1.6–2.2	1.5	1.2–1.9	1.3	1.0–1.6	20.5	< 0.001
	Mean (SE)	Mean (SE)	Mean (SE)	Wald *F* (df = 65)	p-value	*t*-test	p-value	*t*-test	p-value	*t*-test	p-value		
No. of symptoms of depression	8.1 (0.0)	7.6 (0.1)	7.4 (0.0)	120.6	< 0.001	15.5	< 0.001	3.4	0.001	6.5	< 0.001		

BDI-I = bipolar I disorder; BD-II = bipolar II disorder; MDD = major depressive disorder; SE = standard error; OR = odds ratio; CI = confidence interval.

[a] Linear trend test adjusted by sociodemographic characteristics and severity.

Table 3

Psychiatric comorbidity of subjects with bipolar disorder and lifetime major depressive episodes and subjects with major depressive disorder

	BD-I (n = 935)	BD-II (n = 494)	MDD (n = 5695)			BD-I versus MDD		BD-II versus MDD		BD-I versus BD-II		Linear trend test[a]	
Comorbid psychiatric disorders	**% (SE)**	**% (SE)**	**% (SE)**	**χ^2 (df = 2)**	**p-value**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**χ^2 (df = 1)**	**p-value**
Any alcohol use disorder	58.4 (2.0)	54.1 (3.0)	40.3 (0.9)	30.1	< 0.001	2.1	1.8–2.5	1.7	1.4–2.2	1.2	0.9–1.6	38.8	< 0.001
Alcohol abuse	17.4 (1.7)	19.5 (2.1)	19.4 (0.7)	0.6	0.545	0.9	0.7–1.1	1.0	0.8–1.3	0.9	0.6–1.2	0.1	0.787
Alcohol dependence	41.0 (2.3)	34.5 (2.8)	21.0 (0.8)	30.5	< 0.001	2.6	2.1–3.2	2.0	1.5–2.6	1.3	1.0–1.8	41.9	< 0.001
Any drug use disorder	38.8 (2.1)	27.0 (2.5)	17.2 (0.6)	37.4	< 0.001	3.1	2.5–3.7	1.8	1.4–2.3	1.7	1.3–2.3	66.7	< 0.001
Drug abuse	29.5 (2.0)	20.0 (2.2)	14.1 (0.6)	23.0	< 0.001	2.6	2.1–3.1	1.5	1.2–2.0	1.7	1.2–2.3	34.7	< 0.001
Drug dependence	18.0 (1.8)	13.5 (1.9)	5.5 (0.4)	24.7	< 0.001	3.8	2.9–5.1	2.7	1.9–3.8	1.4	1.0–2.1	49.6	< 0.001
Nicotine dependence	47.1 (2.4)	42.2 (2.7)	30.0 (0.8)	28.5	< 0.001	2.1	1.7–2.5	1.7	1.4–2.1	1.2	0.9–1.6	23.1	< 0.001
Any anxiety disorder	65.1 (1.8)	48.0 (2.6)	41.4 (0.9)	37.8	< 0.001	2.6	2.2–3.2	1.3	1.0–1.6	2.0	1.5–2.6	71.2	< 0.001
Panic disorder	32.3 (1.8)	21.0 (2.2)	14.5 (0.6)	32.8	< 0.001	2.8	2.3–3.4	1.6	1.2–2.1	1.8	1.3–2.5	68.6	< 0.001
Social anxiety disorder	27.7 (2.0)	16.5 (2.0)	12.8 (0.6)	20.5	< 0.001	2.6	2.1–3.3	1.4	1.0–1.8	1.9	1.4–2.8	35.1	< 0.001
Specific phobia	34.3 (1.9)	21.9 (2.3)	20.4 (0.7)	18.7	< 0.001	2.0	1.7–2.4	1.1	0.8–1.4	1.9	1.4–2.6	33.2	< 0.001
Generalized anxiety disorder	31.6 (1.9)	18.7 (2.4)	15.0 (0.6)	27.8	< 0.001	2.6	2.2–3.2	1.3	0.9–1.8	2.0	1.4–2.9	69.4	< 0.001
Any personality disorder	67.0 (1.8)	52.9 (2.8)	30.8 (0.8)	74.5	< 0.001	4.6	3.9–5.4	2.5	2.0–3.2	1.8	1.4–2.4	187.2	< 0.001
Avoidant	23.2 (1.7)	10.5 (1.6)	6.5 (0.4)	35.5	< 0.001	4.3	3.5–5.4	1.7	1.2–2.4	2.6	1.8–3.8	76.7	< 0.001
Dependant	6.9 (1.1)	1.1 (0.5)	1.2 (0.2)	12.2	< 0.001	6.1	3.8–9.5	0.9	0.4–2.3	6.5	2.4–18.2	29.9	< 0.001
Obsessive compulsive	36.5 (1.8)	29.0 (2.6)	16.4 (0.7)	40.1	< 0.001	2.9	2.4–3.5	2.1	1.6–2.7	1.4	1.1–1.9	85.6	< 0.001
Paranoid	35.9 (2.0)	23.4 (2.3)	10.0 (0.5)	55.9	< 0.001	5.1	4.1–6.2	2.8	2.1–3.6	1.8	1.4–2.5	143.2	< 0.001
Schizoid	21.8 (1.6)	10.8 (1.7)	7.4 (0.5)	34.2	< 0.001	3.5	2.8–4.3	1.5	1.1–2.1	2.3	1.6–3.4	59.3	< 0.001
Histrionic	15.1 (1.3)	14.2 (1.9)	3.6 (0.4)	32.8	< 0.001	4.7	3.5–6.4	4.4	3.1–6.4	1.1	0.8–1.5	67.2	< 0.001
Antisocial	21.0 (1.7)	17.0 (2.1)	6.3 (0.4)	33.8	< 0.001	3.9	3.1–5.0	3.0	2.2–4.2	1.3	0.9–1.8	67.6	< 0.001
Conduct disorder	2.6 (0.6)	1.1 (0.5)	1.7 (0.2)	1.9	0.155	1.6	0.9–2.8	0.6	0.2–1.6	2.5	0.9–7.2	0.1	0.777

BDI-I = bipolar I disorder; BD-II = bipolar II disorder; MDD = major depressive disorder; SE = standard error; OR = odds ratio; CI = confidence interval.

[a]Linear trend test adjusted by sociodemographic characteristics and severity.

Table 4

Age of onset of affective episodes in subjects with bipolar disorder and lifetime major depressive episodes and subjects with major depressive disorder

	BD-I (n = 935)	BD-II (n = 494)	MDD (n = 5695)	BD-I versus MDD		BD-II versus MDD		BD-I versus BD-II	
Age of onset	**Mean (SE)**	**Mean (SE)**	**Mean (SE)**	***t*-test**	**p-value**	***t*-test**	**p-value**	***t*-test**	**p-value**
Age of first mood episode, years	21.3 (0.4)	20.2 (0.5)	30.3 (0.2)	−22.3	< 0.001	−18.8	< 0.001	1.9	0.059
Age of first depressive episode, years	23.6 (0.4)	23.9 (0.6)	30.4 (0.2)	−15.6	< 0.001	−10.7	< 0.001	−0.4	0.662
Age of first manic/hypomanic episode, years	24.9 (0.5)	23.5 (0.6)	–	–	–	–	–	2.0	0.053

BDI-I = bipolar I disorder; BD-II = bipolar II disorder; MDD = major depressive disorder; SE = standard error.

Table 5

Treatment of major depressive episodes of subjects with bipolar disorder and lifetime major depressive episodes and subjects with major depressive disorder

	BD-I (n = 935)	BD-II (n = 494)	MDD (n = 5695)			BD-I versus MDD		BD-II versus MDD		BD-I versus BD-II		Linear trend test[a]	
Treatment for depression	**% (SE)**	**% (SE)**	**% (SE)**	**χ^2 (df = 2)**	**p-value**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**χ^2 (df = 1)**	**p-value**
Any mental health treatment	66.6 (2.0)	44.4 (3.0)	54.2 (0.9)	66.6	< 0.001	1.7	1.4–2.0	0.7	0.5–0.9	2.5	1.9–3.2	20.3	< 0.001
Any psychiatric hospitalization	25.3 (1.7)	8.5 (1.5)	9.6 (0.5)	25.3	< 0.001	3.2	2.6–3.9	0.9	0.6–1.3	3.7	2.4–5.5	52.6	< 0.001
Any emergency room visit	22.6 (1.6)	8.4 (1.4)	8.0 (0.5)	22.6	< 0.001	3.4	2.7–4.2	1.1	0.7–1.5	3.2	2.2–4.6	50.2	< 0.001
Any prescribed psychotropic medication	57.4 (2.2)	36.3 (3.1)	43.9 (0.9)	57.4	< 0.001	1.7	1.4–2.1	0.7	0.6–1.0	2.4	1.8–3.1	26.5	< 0.001
	Mean (SE)	Mean (SE)	Mean (SE)	Wald *F*(df=2)	p-value	*t*-test	p-value	*t*-test	p-value	*t*-test	p-value	*t*-test	p-value
Age of first treatment for depression, years	28.4 (0.6)	28.0 (1.0)	33.5 (0.3)	37.4	< 0.001	−7.8	< 0.001	−5.5	< 0.001	0.4	0.725	13.5	< 0.001
Time from diagnosis of depression until first treatment for depression, years	4.7 (0.4)	4.3 (0.5)	3.4 (0.1)	5.9	0.004	3.3	0.002	1.8	0.074	0.7	0.496	20.1	< 0.001

BDI-I = bipolar I disorder; BD-II = bipolar II disorder; MDD = major depressive disorder; SE = standard error; OR = odds ratio; CI = confidence interval.

[a]Linear trend test adjusted by sociodemographic characteristics and severity.