Annals of Clinical Psychiatry, 19[4]:313–317, 2007

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230701653617

informa
healthcare

Comparing Features of Bipolar Disorder to Major Depressive Disorder in a Tertiary Mood Disorders Clinic

ROGER S. MCINTYRE, MD, FRCPC

Mood Disorders Psychopharmacology Unit, University Health Network, University of Toronto, Toronto, ON, Canada

JOANNA K. SOCZYNSKA, HBSC, DEBORAH MANCINI, MSC, and HANNA O. WOLDEYOHANNES, HBSC

Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON

JAKUB Z. KONARSKI, MSC

Institute of Medical Science, University of Toronto, Toronto, ON, Canada

SIDNEY H. KENNEDY, MD, FRCPC

Department of Psychiatry and Institute of Medical Sciences, University of Toronto and Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada

Background. *We sought to describe features that distinguish individuals with bipolar disorder from major depressive disorder.*
Methods. *A retrospective chart review of adult outpatients (N = 1000) seeking evaluation and treatment was conducted at the Mood Disorders Psychopharmacology Unit (MDPU), University Health Network, University of Toronto between October 2002 and November 2005 was conducted. Sociodemographic parameters, illness-characteristics and therapeutic interventions were evaluated and compared.*
Results. *The MDPU referring diagnosis were major depressive disorder (52%), bipolar disorder (29%), and unspecified (19%). Of all individuals with a non-bipolar entry diagnosis (n = 699), 23% (n = 159) were subsequently diagnosed with bipolar disorder ($p < 0.001$); the majority of whom (n = 117, 74%) received a non-bipolar I disorder diagnosis [e.g. bipolar II disorder (n = 71); bipolar NOS disorder (n = 46) ($p < 0.001$)]. Higher rates of unemployment/disability, previous depressive episodes, psychiatric hospitalization, comorbid hypertension, and lifetime substance use disorders, as well as an earlier age of illness-onset were more frequently endorsed by individuals with a diagnosis of bipolar disorder. Fifteen percent of individuals who were newly-diagnosed with bipolar disorder reported a history of antidepressant-associated mania.*
Conclusions. *The majority of individuals with a newly-diagnosed bipolar disorder at this tertiary center have a non-bipolar I disorder (i.e., bipolar spectrum). Several indices of illness severity differentiate individuals with bipolar disorder from major depressive disorder.*

Keywords Major depressive disorder, Bipolar disorder, Bipolar II disorder, Bipolar spectrum

INTRODUCTION

Bipolar disorder (BD) is a major public health concern in North America and other industrialized nations (1–3). Under-recognition of BD, and consequent inappropriate treatment, are the most important modifiable deficiencies in the contemporary management of this disorder (4–6). There are no pathognomonic features or biomarkers for undeclared BD which reliably differentiate this condition from major depressive disorder (MDD) and other medical disorders (7,8). Consequently, several investigations have reported on features (e.g., sociodemographic, clinical) which

Address correspondence to Dr. Roger S. McIntyre, MD, FRCPC, Associate Professor, Department of Psychiatry and Pharmacology, University of Toronto, Head, Mood Disorders Psychopharmacology Unit, University Health Network, 399 Bathurst Street - Toronto, ON, Canada M5T 2S8. E-mail: roger.mcintyre@uhn.on.ca

may differentiate BD from other psychiatric disorders, notably MDD (9–12).

Hitherto, the largest sample comparing features of BD to MDD was comprised of 1551 subjects meeting DSM-IV criteria for a major depressive episode who were enrolled in one of three clinical trials evaluating disparate antidepressant treatments (i.e., duloxetine, paroxetine, olanzapine-fluoxetine combination) (9). This investigation reported that BD (vs. MDD) was associated with a family history of BD, earlier age of onset, and greater number of lifetime depressive episodes. An important limitation of this post-hoc analysis however is the non-representativeness of individuals who often participate in clinical trials (13).

The encompassing aim of this analysis was to describe and compare features of BD versus MDD in a large consecutive sample of representative individuals (N = 1000) seeking evaluation and treatment at a university-affiliated tertiary mood disorders program.

METHOD

This investigation was conducted at the Mood Disorders Psychopharmacology Unit (MDPU), University Health Network, University of Toronto. The MDPU is an academic outpatient specialty research program providing clinical service to adults (18–65 years) seeking evaluation and treatment for MDD or BD.

The data for this analysis were procured from consecutive medical charts (N = 1000) of patients who were assessed at the MDPU between October 2002 and November 2005. The mood disorder diagnosis was established by an MDPU consultant, all of whom have demonstrated adequate diagnostic interrater-reliability.

The primary aim of this investigation was to compare the demographic, clinical, and treatment features of individuals with BD to MDD. Toward this aim, we partitioned the full analysis set into three groups: 1) Individuals with an entry and discharge diagnosis of BD (confirmed BD); 2) Individuals with an entry and discharge diagnosis of MDD (confirmed MDD); 3) Individuals with an entry diagnosis of MDD or unspecified, who were subsequently discharged from the MDPU with a diagnosis of BD (newly-diagnosed BD). Data were not available regarding all variables of interest across the subgroups and as such there were some discrepancies between total number of subjects per group and number of patients endorsing a specific factor.

Data from the medical charts were initially captured with a case report form and scanned with automated capture software (TELEFORM Version 8) prior to storage and statistical analysis. Statistical analysis was conducted using SPSS for Windows, Version 12.0 (Chicago, IL). Dichotomous variables were analyzed using the Chi–Square and Kruskal-Wallis statistic for nominal and ordinal variables and univariate ANOVA for continuous variables. All tests were two-tailed with statistical significance set at $p < 0.05$.

This retrospective chart review was approved by the Research Ethics Board of the University Health Network, University of Toronto. Written informed consent was only required for patients actively receiving care at the MDPU.

RESULTS

Of the 1000 medical charts reviewed, most individuals were referred to the MDPU by a primary-care provider (PCP) (n = 597); the remaining patients were referred by psychiatrists or other mental-health care professionals (n = 403). Eighteen charts were excluded from the analysis due to incomplete recording of diagnostic information at MDPU entry leaving 982 medical charts for the analysis herein.

Summary statistics of the demographic and clinical illness variables for the three groups are presented in Table 1. Individuals with an entry or discharge diagnosis of a non-mood disorder (e.g., anxiety disorders) were also excluded from this analysis.

At entry to the MDPU, 285 (29%) individuals had a diagnosis of BD, while 509 (52%) had a diagnosis of MDD, and 190 (19%) had an unspecified diagnosis (i.e., were seeking diagnostic clarity). Thirty-one individuals (3%) with an entry diagnosis of BD were subsequently discharged from MDPU with a non-bipolar diagnosis (e.g., anxiety disorder).

A large number of individuals with an MDPU entry diagnosis of MDD or unspecified (n = 688) subsequently received a discharge diagnosis of BD (newly-diagnosed BD) (n = 159, 23%; $p < 0.001$) (Table 2). The majority (n = 117; 74%) of individuals in this newly-diagnosed BD group received a bipolar spectrum diagnosis, i.e., bipolar II disorder (n = 71); bipolar NOS disorder (n = 46) ($\chi^2 = 19.03$, df = 3, $p < 0.001$).

Almost half (46%) of the individuals with confirmed BD (n = 218), were unemployed at index consultation, versus 30% of individuals with newly-diagnosed BD (n = 159) and 39% of those with confirmed MDD (n = 358) ($p = 0.003$). Individuals with an earlier BD diagnosis at discharge (confirmed and newly-diagnosed) also had a younger age of illness-onset compared to persons with confirmed MDD ($p = 0.001$), and a greater frequency of recurrent depressive episodes (vs. single or chronic) ($p < 0.001$) (Table 1).

A significantly higher proportion of individuals with confirmed BD and newly-diagnosed BD reported a history of psychiatric hospitalizations compared to individuals with confirmed MDD (53% and 46% vs. 27%, respectively; $p < 0.001$). Bipolar individuals were also more likely to report a history of lifetime substance abuse ($p = 0.021$) and trended toward greater lifetime suicidality risk (defined as suicidal ideation or attempt) ($p = 0.051$). The newly-diagnosed BD group reported the highest suicidality rate relative to the confirmed BD and MDD groups (53% vs. 46% vs. 41%, respectively; $p < 0.051$). Anxiety was more frequently reported by individuals with confirmed MDD (72%) than in either of the confirmed and newly-diagnosed BD groups (55% and 57% respectively; $p < 0.001$).

Table 1 Demographic and Illness Characteristics

	MDD/U-BD (n = 159)	MDD-MDD (n = 358)	BD-BD (N = 218)	F	df	P value
Mean age	37.50 ± 11.34	41.30 ± 12.36	37.93 ± 11.25	8.298	2	<0.001
Age of illness onset	21.91 ± 9.13	26.24 ± 12.76	23.10 ± 11.55	6.915	2	0.001
n/Total N	MDD/U-BD (%)	MDD-MDD	BD-BD (%)	χ^2	df	p value
Marital status						
Single/Divorced/Separated	66	58	64	3.400	2	0.183
Married	34	42	36			
Females	59	64	54	7.680	2	<0.021
Males	41	36	46			
Employment						
Unemployed/disability/retired	30	39	46			
Working	62	54	42	11.928	2	0.003
Other (e.g., student)	8	7	12			
Education						
Less than high school	6	7	6			
High school graduate	48	40	46	2.857	4	0.582
Postsecondary graduate	46	53	48			
Number of depressive episodes						
Single	0	9	7			
Recurrent	90	54		54.642	4	<0.001
Chronic	10	37	11			

MDD/U-BD: Newly-diagnosed Bipolar Disorder.
MDD-MDD: Confirmed Major Depressive Disorder.
BD-BD: Confirmed Bipolar Disorder.
U: Unspecified diagnosis.

Table 2 Recognition of Bipolar Disorder in a Tertiary Care Mood Disorders Clinic

	Entry Diagnosis Prior to MDPU Visit			
MDPU Diagnosis n(%)	Major Depression or unspecified entry diagnosis (n = 688)	Bipolar Disorder (n = 281)	Anxiety (n = 6)	Other (n = 7)
Major Depressive Disorder	432 (63%)	32 (11%)	3(50%)	0 (0%)
Bipolar Disorder	159 (23%)	218 (76%)	0 (0%)	4 (57%)
Anxiety Disorders	9 (1%)	3 (1%)	2(33%)	1 (14%)
Seeking Diagnostic Clarity	23 (3%)	13 (5%)	1(17%)	1 (14%)
Other	65 (9%)	15 (5%)	0 (0%)	1 (14%)

$\chi^2 = 335.911$, df = 12, $p < 0.001$.

Sixteen percent of persons with confirmed MDD had two or more psychiatric comorbidities, similar to individuals with newly-diagnosed and confirmed BD (11% and 10%; p = 0.014). Individuals with confirmed BD, were more likely to have received a diagnosis of hypertension (p = 0.048).

The use of multiple psychotropic medications was reported more frequently in individuals with BD. A significantly higher proportion of individuals with confirmed BD (n = 61, 28%) received five or more (lifetime) psychotropic medications compared to 78 (22%) with confirmed MDD and 28 (18%) with newly-diagnosed BD (p = 0.021). There was a significant difference in the mean number of lifetime and current psychotropic medications received between the confirmed BD and confirmed MDD groups (p < 0.001).

A post-hoc Tukey test revealed that there was a significant difference in the number of current psychotropic medications between individuals with confirmed MDD and confirmed BD (p < 0.001), as well as between the newly-diagnosed and confirmed BD groups (p = 0.008), but not between the newly-diagnosed BD and confirmed MDD groups (p = 0.162). The

between-group differences in lifetime mean number of psychotropic medications remained significant only between the newly-diagnosed BD and confirmed BD groups ($p = 0.032$).

A significantly higher proportion of individuals with confirmed MDD received multiple (4 or more) antidepressants during the course of their illness compared to persons with confirmed BD and newly-diagnosed BD (n = 89, 25%; n = 36, 17%; n = 28, 18%, respectively) ($p = 0.005$). In addition, there was a significantly higher proportion of persons in the confirmed MDD group who received multiple concomitant medications (non-psychotropic) compared to either the newly-diagnosed or confirmed BD group (21% vs. 9% and 9% respectively; $p < 0.001$). There was also a significantly higher proportion of persons with antidepressant induction of mania/hypomania in the confirmed BD and the newly-diagnosed BD groups compared to the confirmed MDD group (25% and 15% vs. 1%; $p < 0.001$).

DISCUSSION

The results of this investigation indicate that several indices of illness severity differentiate BD from MDD. A large proportion of individuals referred to the MDPU with MDD or an unspecified diagnosis were subsequently diagnosed with a bipolar spectrum disorder (notably Bipolar II Disorder).

Our results cohere with findings from several investigations. For example, Perlis et al. reported that individuals with BD vs. MDD are differentially affected by several indices of illness severity and multiple depressive episodes (9). Others have also reported that depressive symptoms (and episodes) are a common index presentation of BD, they comprise the majority of affectively ill days and result in greater impairment than hypo/manic symptoms at a corresponding level of severity.

To our knowledge, this is the largest sample comparing features of BD to MDD in a naturalistic setting. The results of this investigation are largely corroborative and document: 1) A significant proportion of depressed individuals referred to a tertiary mood clinic by PCPs are covertly bipolar; 2) Bipolar spectrum disorder is a common phenotypic expression of BD in tertiary care settings; 3) Bipolar disorder individuals manifest relatively more indices of illness severity when compared to MDD; 4) Medical and psychiatric comorbidity are prevalent in the BD population; 5) Anamnestic inquiry of depressed individuals often reveals a history of antidepressant-associated mania; 6) Polypharmacy, notably the use of antidepressants, is prevalent in BD (11,12,15–22).

There are several methodological factors which limit inferences and interpretations which can be drawn from this analysis: 1) Data were collected post-hoc and the diagnoses were not confirmed with a structured clinical interview, and instead were based on a clinical interview in accordance with DSM-IV-TR criteria; 2) Data were extracted from medical charts preventing a more detailed analysis of the variables of interest; 3) Illness-course was not supplemented with quantitative metrics (e.g., Life-Chart methodology); 4) Most of the information recorded in the medical chart was not corroborated by a third party; 5) The MDPU is a tertiary university-affiliated center, as such, our results may not be generalizable to other centers which provide clinical services to individuals with less complicated mood disorders; 6) The data herein are considered descriptive.

How do the results of this investigation inform clinical practice? Routine screening and surveillance for BD should be the standard of care in all depressed patients utilizing primary and mental-health services. Depressed individuals who report an early age of illness onset, a high frequency of depressive episodes and comorbidity, and who also have a history of multiple antidepressant trials, should be stratified as an at-risk group for covert BD. Clinicians should routinely inquire regarding the exacerbation of psychiatric symptoms with antidepressants (i.e., induction of mania) in all treated depressed patients.

ACKNOWLEDGMENT

This investigation was supported by an unrestricted grant from Janssen-Ortho, Canada Inc. The authors would like to thank Chris Lam, Seol Moon, and Bernadette DeFreitas for their assistance in the preparation of the data for this manuscript. We would like to thank Dr. David Muzina for his helpful comments regarding the manuscript preparation.

REFERENCES

1. Yatham LN, Kennedy SH, O'Donovan C, Parikh S, Macqueen G, McIntyre R, Sharma V, Silverstone P, Alda M, Baruch P, Beaulieu S, Daigneault A, Milev R, Young LT, Ravindran A, Schaffer A, Connolly M, Gorman CP: Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: Consensus and controversies. *Bipolar Disord* 2005; 7(Suppl 3):5–69
2. McIntyre RS, Konarski JZ: Bipolar disorder: a national health concern. *CNS Spectr* 2004; 9:6–15
3. McElroy S, Allison D, Bray G: *Obesity and Mental Disorders*. New York: Taylor & Francis; 2006
4. Akiskal HS, Bourgeois ML, Angst J, Post R, Moller H, Hirschfeld R: Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J Affect Disord* 2000; 59(Suppl 1):S5–S30
5. Hirschfeld RM, Calabrese JR, Weissman MM, Reed M, Davies MA, Frye MA, Keck PE, Jr., Lewis L, McElroy SL, McNulty JP, Wagner KD: Screening for bipolar disorder in the community. *J Clin Psychiatry* 2003; 64:53–59
6. Hirschfeld RM: Bipolar spectrum disorder: Improving its recognition and diagnosis. *J Clin Psychiatry* 2001; 62 Suppl 14:5–9
7. Lenox RH, Gould TD, Manji HK: Endophenotypes in bipolar disorder. *Am J Med Genet* 2002; 114:391–406
8. Kendell R, Jablensky A: Distinguishing between the validity and utility of psychiatric diagnoses. *Am J Psychiatry* 2003; 160:4–12

9. 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
10. Hantouche EG, Angst J, Akiskal HS: Factor structure of hypomania: Interrelationships with cyclothymia and the soft bipolar spectrum. *J Affect Disord* 2003; 73:39–47
11. Akiskal HS, Hantouche EG, Bourgeois ML, Azorin JM, Sechter D, Allilaire JF, Lancrenon S, Fraud JP, Chatenet-Duchene L: Gender, temperament, and the clinical picture in dysphoric mixed mania: Findings from a French national study (EPIMAN). *J Affect Disord* 1998; 50:175–186
12. Goldberg JF, Harrow M, Whiteside JE: Risk for bipolar illness in patients initially hospitalized for unipolar depression. *Am J Psychiatry* 2001; 158:1265–1270
13. Zimmerman M, Mattia JI, Posternak MA: Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry* 2002; 159:469–473
14. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, Coryell W, Maser JD, Keller MB: Psychosocial disability in the course of bipolar I and II disorders: A prospective, comparative, longitudinal study. *Arch Gen Psychiatry* 2005; 62:1322–1330
15. Das AK, Olfson M, Gameroff MJ, Pilowsky DJ, Blanco C, Feder A, Gross R, Neria Y, Lantigua R, Shea S, Weissman MM: Screening for bipolar disorder in a primary care practice. *JAMA* 2005; 293:956–963
16. Ghaemi SN, Rosenquist KJ, Ko JY, Baldassano CF, Kontos NJ, Baldessarini RJ: Antidepressant treatment in bipolar versus unipolar depression. *Am J Psychiatry* 2004; 161:163–165
17. Frye MA, Ketter TA, Leverich GS, Huggins T, Lantz C, Denicoff KD, Post RM: The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. *J Clin Psychiatry* 2000; 61:9–15
18. Ghaemi SN, Lenox MS, Baldessarini RJ: Effectiveness and safety of long-term antidepressant treatment in bipolar disorder. *J Clin Psychiatry* 2001; 62:565–569
19. Ghaemi SN, Sachs G, Chiou AM, Pandurangi AK, Goodwin K: Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? *J Affect Disord* 1999; 52:135–144
20. Manning JS, Haykal RF, Connor PD, Akiskal HS: On the nature of depressive and anxious states in a family practice setting: The high prevalence of bipolar II and related disorders in 3a cohort followed longitudinally. *Compr Psychiatry* 1997; 38:102–108
21. McIntyre RS, Konarski JZ, Yatham LN: Comorbidity in bipolar disorder: A framework for rational treatment selection. *Human Psychopharmacology* 2004; 19:369–386
22. Beyer J, Kuchibhatla M, Gersing K, Krishnan KR: Medical comorbidity in a bipolar outpatient clinical population. *Neuropsychopharmacology* 2005; 30: 401–404