Undiagnosed Bipolar Disorders in Patients with Major Depressive Episode: Iran's part of a Multicenter Cross-Sectional Study

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Objective: Bipolar spectrum disorders may often go undiagnosed or unrecognized. The aim of this study was to determine the proportion of bipolar disorder symptoms in Iranian patients with a major depressive episode .
Methods: 313 patients with a current DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders 4th ed. Text rev.) diagnosed with a major depressive episode entered this cross-sectional study. Thirty two items revised Hypomania/ mania Symptoms Checklist (HCL-32) was used to determine the frequency of bipolar episodes.
Results: Considerable proportion of patients (53.9%) previously diagnosed as major depressive disorder fulfilled the criteria for bipolar disorder by Bipolarity Specifier. The Bipolarity Specifier additionally identified significant association for manic / hypomanic states during antidepressants therapy ($p<0.0003$) and current mixed mood symptoms ($p<0.0001$)
Conclusion: Bipolar symptoms meeting the criteria for bipolar disorders in depressed patients who have not been previously diagnosed with bipolar disorder are frequent. Current DSM criteria may not be sufficient to diagnose more subtle or atypical forms of bipolar disorders.

Keywords: *Bipolar disorder, Major depressive disorder, Bipolar Spectrum, Mania, Hypomania, Bipolarity Specifier*

Iran J Psychiatry 2013; 8:1: 1-6

Considering the prevalence, chronicity and recurrent nature, mood disorders are amongst the most crucial topics in public and mental health issues. Major depressive disorders (MDD) are considered to be the most frequently encountered form of psychiatric problems that cause significant social and functional impairments (1).

On the basis of past hypomanic or manic features, a considerable number of patients who were initially diagnosed with major depressive disorder eventually turn out to be diagnosed with bipolar disorder (2). A misdiagnosis of unipolar depression in about 40% of bipolar patients has been reported (3). However, bipolar disorder diagnosis in patients presenting with depressive symptoms may not be easily attained. Patients often consider their hypomanic or even manic symptoms to be normal (4), whereas depressive symptoms are distressing to them, so rapidly seek treatment. Therefore, disorders with hypomanic or sub-threshold bipolar symptoms may not be recognized (5) and it may not be easy to ascertain past episodes of bipolar disorder, especially that bipolar II is a "soft" expression of the disorder (6). Hidden cases of bipolar disorders among depressive patients call for attention of clinicians to address this issue .Observations show that these patients had been visited by a mean of four physicians before receiving a definite diagnosis of bipolar disorder (7).

Some studies suggest that 50% of patients with major depressive disorder diagnosis conform to bipolar II pattern (8). Bipolar patients misdiagnosed with MDD have significantly lower quality of life and less functional outcome, having increased risk of attempting suicide, greater requirement for inpatient psychiatric care that account for higher total health care costs, and they also have more substance abuse and are more treatment refractory compared with accurately diagnosed bipolar disorder (9). Moreover, antidepressant treatment has the potential of switching the disorder to manic or hypomanic phase (10), while

mood stabilizer treatment can be more appropriate (11). According to DSM-IV-TR(Diagnostic and Statistical Manual of Mental Disorders 4th ed. Text rev.), mood disorders are classified into distinct categories of bipolar and depressive disorders. Bipolar disorders are divided into bipolar I, bipolar II, cyclothymic and bipolar NOS (Not Otherwise Specified). This categorical classification of mood disorders runs against Kraepelin's unitary classification of hypo-manic and depressive states under manic-depressive insanity. DSM-IV-TR reports that a categorical classification requires "clear boundaries" between classes. The validity of DSM-IV-TR classification of mood disorders has also been questioned on clinical grounds (12). Lack of clear boundaries between different DSM-IV-TR syndromes does not support categorical classification, while supports dimensional classification (13). Another problem is that DSM-IV definition of hypomania requiring four days of hypomanic symptoms for diagnosis of bipolar II, excludes a large group of young patients with bipolar symptoms who do not meet its diagnostic threshold, and this, causes bipolar II patients to be initially misdiagnosed with major depressive disorder which leads onto inappropriate treatments. There are some attempts in various researches to identify clinical features associated with bipolarity, including a family history of bipolar disorder, a history of antidepressant-induced hypomania, a hyperthymic personality, an early age of disease onset, a pattern of highly recurrent illness, a history of brief depressive episodes, atypical symptoms, postpartum onset, and psychotic features (14, 15). In addition, mood lability was proposed to be a strong indicator that patients diagnosed as unipolar would be more correctly diagnosed as bipolar II (16). Angst et al developed modified criteria to meet the reliability of differential diagnosis of major depressive disorder and bipolar disorder. This Bipolarity Specifier Criteria has a particular attention to family history and illness course (17, 18).

The primary aim of this study was to determine the frequency of bipolar symptoms in a sample of Iranian patients consulting a psychiatrist for current major depressive episode (MDE). Bipolarity was defined on the basis of DSM-IV-TR and Bipolarity Specific Criteria.

Materials and Methods

This study was Iran's part of a BRIDGE (Bipolar Disorders, Improving Diagnosis, Guidance and Education) project which was a multicenter, cross-sectional diagnostic study conducted by 521 hospital-based or community psychiatrists in Asia, Europe and Africa from April 1, 2008 to April 30, 2009 (19). As in each center, a key senior psychiatrist was selected for Iran's part as the national coordinator. To follow the policy of the main project, the participating local centers were both psychiatric departments of hospitals / hospital clinics (Roozbeh, Imam Hossein, Razi hospitals in Tehran and other university hospitals in other major cities)as well as independent psychiatric clinics running by specialist psychiatrists to provide representative impression of health care services in each area of the practice. In each psychiatric ward or clinic, 10-20 adult patients were included in the study. Persian translation and back translation of 32-item revised Hypomania /Mania Symptoms Checklist (HCL-32) (20) and Mini International Neuropsychiatric Interview (MINI) (21) were performed by the authors.

Three hundred and thirteen adults meeting DSM-IV-TR criteria for major depressive episode at the time of evaluation were recruited. Singed written informed consent was obtained. The participant psychiatrists completed the questionnaire provided by the committee of the main project on patients' clinical features and socioeconomic variables. All selected patients were screened for study inclusions. The exclusion criteria were as follows: Emergency situations, suicidal ideas, drug and current substance abuse, medical conditions, non-psychiatric emergencies and inability to complete the checklist (HCL-32).

Data collection

Socio-demographic variables as well as the following data were collected: a) previous psychiatric history, any previous hospitalization, features of bipolar symptoms according to DSM-IV-TR criteria for bipolar disorders, any risk factors for bipolar disorders, any response to antidepressants and current treatment; b) family history of mania, hypomania or any bipolar features in parents, siblings or children; c) co-morbidity with or history of substance abuse and addictions, panic disorder, obsessive-compulsive disorder, social phobias, generalized anxiety disorders , eating disorders, borderline personality disorders and attention-deficit hyperactivity disorder using the MINI questionnaire and symptoms checklist according to DSM-IV-TR.; d)functional status determined by using the DSM defined Global Assessment of Functioning(GAF) (22); e) completed HCL-32 (by the patients) .

Outcome Measures

The primary aim of this study was to determine the frequency of bipolar disorders in patients diagnosed as being in major depressive episode. This was determined as a percentage of patients fulfilling the criteria for bipolar disorder according to the DSM-IV-TR criteria and the bipolar specifier proposed by Angst et al (17, 18).Bipolarity Specifier attributes bipolar disorder in patients who previously experienced an episode of elevated/irritable mood or increased activity which affected their social/occupational functioning or led to hospitalization, while no exclusion criteria were applied. Bipolar Specifier includes all cases of bipolar 1-II disorders and additional cases excluded by DSM-IV-TR criteria.

Statistical Analysis

The following characteristics known to be associated with the diagnosis of bipolar disorders were considered as independent variables: sex, age younger than 30 at

the time of development of first symptoms, seasonal pattern of mood episodes, 2 or more previous mood episodes, history of suicide attempts, presence of hypomania/mania among the first-degree relatives, manic/hypomanic switching or mood lability following antidepressant treatment, duration of current depressive episode of 1 month or less, current depressive symptoms featured atypical, mixed or psychotic and current psychiatric co-morbidities .A multivariable stepwise logistic regression analysis was performed to assess the association of these variables with assigned bipolar diagnoses. The strength of the association was presented as odds ratios (ORs) with 95% confidence intervals .

All statistical tests were 2-sided and a probability level of 0.05 was established as statistically significant. The association between an assigned diagnosis of bipolar disorder according to DSM-IV-TR or the Bipolar Specifier criteria and patient characteristics was explored.

Results

From 313patients participated in this study, 207 (66.1%) were female and 106 (33.9%) were male. The mean age of the subjects was 38.4±12.3 years. Of the subjects, 66.1% were married, and 33.9% single, divorced or widowed. A part of study performed in hospitals (inpatients or outpatients) was 37.4% and it was 62.6% in psychiatrists' private clinics. A total of 57 (18.2%) patients fulfilled DSM-4-TR criteria for bipolar disorder, whereas 169 (53.9%) met the Bipolarity Specifier criteria. The bipolarity specifier additionally identified significant associations for manic / hypomanic states during antidepressant therapy, current mixed mood symptoms and substance use disorder. Table 1 and 2 demonstrate variables in bipolar and unipolar subjects based on Bipolarity Specifier and bipolarity "other definitions"

Frequency of Bipolar Disorders

Based on DSM-IV-TR criteria, 57 patients (18.2%) fulfilled the criteria for bipolar disorders. According to Bipolarity Specifier, 169 patients (53.9%) met the criteria for a bipolar disorder. All patients who met DSM-IV-TR criteria for bipolar disorders also fulfilled the criteria for the Bipolarity Specifier.

Frequency of Bipolar Spectrums

For each bipolar symptom, rates were similar to the 2 bipolar groups. Duration of elevated and irritable mood was similar, mostly having a hypomanic episode lasting more than one week.

Table 1: Variables in bipolar and unipolar subjects based on HCL-32 Bipolarity Specifier

Bipolarity	**Bipolar (no=168)**		**Unipolar (no=145)**		**p-value**
Variables	*Yes*	*No*	*Yes*	*No*	
Male	59	109	47	98	0.61
Married	94	74	113	32	0.00002
Postpartum depression(females)	23	86	19	79	0.7
Seasonality of mood episodes	43	124	26	119	0.09
Previous psychiatric hospitalizations	49	119	47	98	0.76
Family history of bipolarity	49	118	26	119	0.01
The episode occurred with use of antidepressants	31	137	17	128	0.09
Resistance to antidepressant treatment	49	117	40	105	0.7
Mood lability due to antidepressants use	60	107	26	119	0.0004
First antidepressant treatment	14	153	27	116	0.0065
Atypical depression	44	124	26	119	0.08
Mixed features	89	79	45	100	0.0001
Psychotic features	26	142	15	130	0.17
Substance abuse	13	154	4	141	0.051
Anxiety disorder	62	105	43	102	0.016
Borderline personality disorder	29	139	4	141	<0.0001
ECT (current treatment)	21	147	15	130	0.5
Anxiolytic drugs (current treatment)	90	78	96	49	0.02
Antidepressants use(current treatment)	130	38	134	11	0.0003
Antipsychotics use(current treatment)	68	100	47	98	0.14
Mood stabilizers use(current treatment)	102	66	51	94	<0.0001
Mood episodes with free interval	114	33	73	37	0.004
	Means	**SD**	**Means**	**SD**	
Age (year)	35.4	11.9	41.7	11.9	<0.0001
Number of depressive symptoms	7.2	1.3	7.2	1.3	0.82
Total number of mood episodes	3.6	1.4	3	1.5	0.0002
GAF	48.4	17.2	49.2	14.9	0.84
Number of suicidal attempts	1.6	1.1	1.3	0.8	0.02

Table 2: Variables in bipolar and unipolar subjects based on bipolarity "other definitions"

Bipolarity variables	Bipolar (no=169)		Unipolar(no=144)		p-value
	Yes	*No*	*Yes*	*No*	
Male	64	105	42	102	0.1
Married	98	71	109	35	0.004
Postpartum depression(females)	25	80	17	85	0.2
Seasonality of mood episodes	46	122	23	121	0.01
Previous psychiatric hospitalizations	51	108	35	109	0.07
Family history(bipolarity)	56	112	19	125	<0.0001
the episode occurred with use of antidepressant	42	127	6	138	<0.0001
Resistance to antidepressant treatment	53	114	36	108	0.19
Mood lability due to antidepressants use	70	98	16	128	<0.0001
First antidepressant treatment	20	147	21	122	0.48
Atypical depression	48	121	22	122	0.005
Mixed features	99	70	35	109	0.0001
Psychotic features	29	140	12	132	0.02
Substance abuse	11	157	6	138	0.35
Anxiety disorder	66	103	39	104	0.02
Borderline personality disorder	29	140	4	140	<0.0001
ECT (current treatment)	19	150	17	127	0.87
Anxiolytic drugs (current treatment)	92	77	94	50	0.05
Antidepressant (current treatment)	130	39	134	10	0.0001
Antipsychotics (current treatment)	76	93	39	105	0.001
Mood stabilizers (current treatment)	114	55	39	105	<0.0001
Mood episodes with free interval	121	32	66	38	<0.0001
	means	**SD**	**means**	**SD**	
Age (year)	36.4	11.9	40.5	12.4	0.004
Number of depressive symptoms	7.3	1.3	7.1	1.2	0.22
Number of days with depression in last year	159.11	102.83	193.51	112.38	0.006
Total number of mood episodes	3.8	1.3	2.8	1.4	<0.0001
Number of suicidal attempts	1.7	1.1	1.3	0.8	0.009
GAF	46.5	16.4	51.5	15.5	0.84

Antidepressant Therapy Patients

In DSM-IV-TR criteria, hypomanic episodes which occurred in the presence of another disorder or during antidepressant treatment were excluded. However, in our sample, 115 patients (36.7%) had experienced episodes of elevated or irritable mood triggered by antidepressants.

Discussion

The results of this study indicate that 18.21% of patients with major depressive episode met DSM-IV-TR criteria for either bipolar 1 or bipolar II disorder, whereas with application of Bipolarity Specifier Criteria, this rate increased to 53.9%. Findings suggest that bipolar features are more frequent than symptoms indicated by DSM-IV-TR. These findings are consistent with previous studies which showed impulsivity and history of substance abuse, head trauma, or suicide attempts are increased in Mania Rating Scale amongst depressed patients (23). Also, similar to our findings, in a recent study, two-thirds of the subjects with bipolar depressed episodes had concomitant manic symptoms, most often distractibility, flight of ideas or racing thoughts, and psychomotor agitation. Patients with any mixed features were significantly more likely to have early age at illness onset, rapid cycling in the past year, bipolar I subtype, history of suicide attempts, and more days in the preceding year with irritability or mood elevation than those with pure bipolar depressed episodes (24).In this study, by using Bipolar Specifier Criteria, it was revealed that a number of variables in major depressive episode patients such as mood lability due to antidepressants, mixed mood features, borderline personality disorder, family history of bipolarity, anti depressant induced hypomanic/manic episode were associated with bipolarity.

Some hypomanic or even manic symptoms such as mood lability and co-morbidity with borderline personality disorder and anxiety disorders manifested more prominently during antidepressant treatment of MDD patients, are indicative of bipolarity.

Nearly none of these variables are included in DSM-IV-TR criteria for diagnosing bipolar disorder which

may be considered unjustified and a great pitfall for this classification.
On the contrary such variables as resistance to antidepressants, atypical features, presence of psychosis, seasonality of mood episodes and postpartum onset which may be more frequent in bipolar types could not differentiate the two groups.

Strengths and Limitations of the Study
Inclusion of hospital and community psychiatrists in the study increases generalizability of findings that can be considered as the strength factor of the study, whereas non-random selection of clinics and psychiatrists are limitations. Although training sessions were held for all participants, another limitation might be the limited training given to psychiatrists involved in the study. However, such training was not deemed necessary as all contributors were well-known skilled psychiatrists of different areas who were predominantly academic staff (assistant, associate and full professors practicing and teaching in psychiatric departments of reputable universities), that can almost be an indicator of lack of bias.

Implications of Treatment
Using mood stabilizers as prophylactic measures in bipolar disorders are more appropriate than those diagnosed as pure MDD patients (25). Many patients in major depressive episode are prescribed antidepressants in routine depression management. According to our findings, it is confirmed that treatment using antidepressant medications in MDE goes under question or at least requires detailed information to be collected. Present and past history of the patient as well as keen attention to symptoms of bipolar features should be traced attentively. Mood stabilizers can be considered more appropriate for such patients .A recent study proposed that either as mono-therapy or as adjunctive therapy to mood stabilizers, the role of antidepressants in treatment of depressive symptoms in bipolar disorders is of limited efficacy and with adverse consequences (26).

Conclusion

A high proportion of patients with MDE also have a sub threshold hypomania or mania. Findings suggest that bipolar features are more frequent than symptoms indicated by DSM-IV-TR, and exclusion criteria of mood disorders in this classification should be revised. DSM-IV classification appears to be too narrow or rigid to distinguish a more subtle and "softer" form of bipolar cases from pure unipolar ones.

Acknowledgements

We are grateful for the contribution of the following colleagues in the study:
Dr Ebrahim Abdollahian, Dr Reza Afsari,Dr Hamid Afshar Zanjani, Dr Gholamhossein Ahmadzadeh, Dr Mohammad Arbabi, Dr Abbas Attari, Dr Hadi Badr,Dr Gholamreza Barani, Dr Majid Barakatein, Dr AlirezaFarnam, Dr Mirfarhad Ghalebandi, Dr Mohammadreza Khodaie, Dr Safa Maghsoodloo, Dr Robabeh Mazinani, Dr Arash Mirabzadeh, Dr Shole Nakhjavani, Dr Victoria Omranifard, Dr Fatemeh Ranjbar, Dr Maryam Rasoulian, Dr Reza Rostami,Dr Shahrokh Sardarpour Goodarzi, Dr Mehran Zarghami.
Authors of this study also appreciate Iran Sanofi Pharmaceutical's assistance.
The main (International-multicenter) study has been funded by Sanofi.

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