Original Article

Brief major depressive episode as an essential predictor of the Bipolar Spectrum Disorder

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Abstract

BACKGROUND: A bipolar spectrum definition presented to help the designation of more appropriate diagnostic criteria for the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) is Ghaemi et al. Bipolar Spectrum Disorder (BSD). The present study evaluates the BSD frequency among inpatients with major depressive disorder (MDD) and tries to elucidate the contribution of second degree diagnostic items of BSD in the BSD definition.

METHODS: One hundred individuals aged 18-65 with current MDD consecutive admitted in three university affiliated psychiatric center were clinically interviewed. The patients with mental retardation or the history of substance dependence/ abuse were excluded. The interviews were carried out by a trained general practitioner according to an 11-item checklist comprised of criteria C (2 items) and D (9 items) of Ghaemi et al. BSD.

RESULTS: Fifty three males and 47 females entered the study. Patients' mean age was 34.16 ± 9.58. Thirty eight patients (39.2%: 18 males and 20 females) met the complete diagnostic criteria of BSD. Early-onset depression (53.0%), recurrent depression (40.0%) and treatment resistant depression (38.8%) were the most frequent accessory items of BSD, but using logistic regression three items -recurrent major depressive episodes (MDEs), treatment resistant depression, and brief MDE- had the significant weight to predict the BSD. Then, three mentioned items were simultaneously entered the logistic regression model: brief MDE ($\beta = 1.5$, EXP (β) = 4.52, p = 0.007), treatment resistant depression ($\beta = 1.28$, EXP (β) = 3.62, p = 0.01), and recurrent MDEs ($\beta = 1.28$, EXP (β) = 3.62, p = 0.01) had the highest strength in predicting BSD and account for 21-30% of BSD diagnosis variance in sum.

CONCLUSIONS: Regarding the greater diagnostic strength of some accessory items – especially brief MDE – to predict the BSD, it is suggested that these items were considered as the main ones in the BSD criterion C.

KEY WORDS: Bipolar spectrum disorder, brief depressive episode, recurrent depression, treatment resistant depression.

Many researchers have evaluated and described the characteristics of bipolar spectrum patients and presented various classifications. Akiskal and Pinto's bipolar prototypes,[1] Ghaemi, Ko and Goodwin's Bipolar Spectrum Disorder (BSD),[2] Akiskal and Benazzi's depressive mixed state,[3,4] Sachs' bipolarity index,[5] and Angst's minor bipolar disorder[6] are some examples of these descriptions. Thus, there is low agreement on using one of the described definitions of bipolar spectrum. Ghaemi et al. Bipolar Spectrum Disorder[2] is one of the bipolar spectrum forms designed as a disorder with certain criteria and aimed at helping presentation of appropriate diagnostic criteria for the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V). Patients with BSD have major depressive disorder (MDD) according to the DSM-IV criteria; it means that they have never experienced any spontaneous manic or hypomanic episode, but have some features in

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common with patients suffered from bipolar disorder (BD) standard criteria. On the BSD definition, "family history of bipolar disorder" and "antidepressant-induced mania /hypomania" (criterion C) have greater weight than other items. Second degree items (criterion D) include hyperthymic personality, recurrent major depressive episodes (> 3 MDEs), brief MDEs (< 3 months), atypical depressive symptoms, psychotic MDEs, early-onset MDE (< age 25), postpartum depression, antidepressant "wear- off" (acute but not continued response), and treatment resistant MDE (lack of response to 3 or more antidepressant treatment trials). The existence of at least one item from the criterion C and two items from the criterion D, OR two items from the criterion C and one item from the criterion D, OR six items from the criterion D without any item from the criterion C, has been considered the Bipolar Spectrum Disorder.[2]

In this definition of BD, some criteria with significant evidence from the literature have been utilized; although there are few contradicting findings for some of them, e.g. the studies on atypical depression by Posternak and Zimmerman,[7] and Parker.[8] Several studies have focused on either of the diagnostic items for BSD, but the studies on its total diagnostic criteria are sparse. Smith et al[9] assessed 87 consecutive patients referred to a university health service psychiatric clinic who had a current major depressive episode and the history of at least one early-onset depressive episode (< age 22). The sample comprised of 46 individuals with MDD, 27 individuals with Ghaemi et al. BSD,[2] and 14 individuals with DSM-IV BD. The mean score of hypomanic symptoms checklist in the BSD group was significantly more than MDD group and less than DSM-IV BD group.

Given utilizing many valid indices of bipolar spectrum described in the literature – especially family history of bipolar disorder – in the Ghaemi et al. BSD,[2] using external validators to evaluate this definition of bipolar spectrum disorder would be difficult; because these validators themselves are among the criteria of

the BSD.[9] Thus, a way to assess validity of the criteria is identifying the relationship of each item of the criteria with the BSD, and clarifying position and weight of each item in diagnosing the BSD. It is also important to mention that there is not enough evidence on considering higher weight for the first two diagnostic items of BSD (family history of bipolar disorder and antidepressant-induced mania/hypomania) versus other items (e.g. recurrent MDEs, brief MDEs, and early-onset MDE).

Given the literature deficits on the diagnostic criteria of Ghaemi et al. BSD,[2] the present study evaluates the BSD frequency in inpatients with MDD and tries to assess the validity of second degree diagnostic items of the BSD (criterion D) and elucidate the contribution of these items in diagnosing the BSD.

Methods

One hundred patients consecutively admitted to two university affiliated psychiatric hospital and a psychiatric ward of a university affiliated general hospital in Tehran, Iran were cross-sectionally studied. The inclusion criteria included: 1. aged 18-65; 2. diagnosed as having current MDD by an attending psychiatrist (according to the DSM-IV criteria and based on the hospital records); and 3. giving informed consent. The exclusion criteria included: 1. history of substance dependence or abuse (exception of nicotine and caffeine); and 2. mental retardation.

The demographic characteristics (age and gender) were registered. A trained general practitioner carried out a clinical interview with the probands according to an 11-item checklist comprised of criteria C (2 items) and D (9 items) of Ghaemi et al. BSD.[2]

Family history of BD in first-degree relatives (parents, siblings, and offsprings) was evaluated using hospital records and clinical interview with the patients, and according to the DSM-IV criteria of bipolar disorders (bipolar disorders type I [BID] and type II [BIID], and bipolar disorder-not otherwise specified). The item "antidepressant-induced mania/ hypomania" was defined as occurring mania or

hypomania only during the period of antidepressant use or in one month or less from the last use of that. To assess hyperthymic personality, the Akiskal et al. definition[10] was utilized. To count the number of depressive recurrence – for identifying recurrent depression (more than three MDEs) – the definition of "at least 2 months partial or complete remission between two episodes" was considered. The episode duration was defined as the time interval from completion of MDE criteria to the beginning of "lack of completed criteria of MDE" to recognize brief MDE (< 3 months). The existence of two signs of increased appetite (or weight) and hypersomnia (DSM-IV criteria) in the current or previous MDE was considered as the definition of atypical depression. Psychotic depression was a current or previous MDE with any signs of hallucinations or delusions (DSM-IV definition of psychotic features). Postpartum depression was defined as an MDE occurred in 8 weeks after delivery. Rapid response to antidepressant drug use (during 10 days) with depressive relapse in 10 days after beginning the remission was considered as the definition of antidepressant wear off. Also, treatment resistant depression was defined as major depressive symptoms

reduction less than 50% in spite of doing at least three 4-week clinical trials using at least three different antidepressants.

The data were analyzed using descriptive statistical methods, chi-square test, Chronbach's alpha test, and logistic regression.

Results
One hundred inpatients with current MDD comprised of 53 males and 47 females were entered the study. The mean age was 34.16 ± 9.58 and ranged from 18 to 54.

Identification of some BSD items was not possible in five patients, and 38 patients (39.2%: 18 males and 20 females) met the complete diagnostic criteria of BSD. Based on chi-square test, there was not a significant relationship between gender and the diagnosis of BSD (p = 0.290). Table 1 displays the frequency of each BSD diagnostic item in patients with MDD.

Criterion D which includes 9 items showed a low internal consistency through the chronbach's alpha (0.3).

Logistic regression was used to evaluate the contribution of each item of criterion D in diagnosing BSD. As shown in Table 2, three items recurrent MDEs, treatment resistant depression, and brief MDE had the greatest weight to predict BSD. These items accounted

Table 1. Frequencies of Bipolar Spectrum Disorder criteria met in Major Depressive Disorder patients.

Bipolar Spectrum Disorder criteria	Frequency (%)	Missing data	Age* mean (SD)	Male to female ratio*
First degree relative with bipolar disorder	23 (23.7)	3	37.08 (10.06)	11/12
Antidepressant-induced hypomania	15 (15.5)	3	33.26 (8.91)	8/7
Hyperthymic personality	20 (20.0)	0	36.20 (7.42)	14/6
Recurrent major depressive episodes	40 (40.8)	2	36.85 (9.56)	12/14
Brief major depressive episodes	26 (27.1)	4	31.80 (9.77)	18/14
Atypical depressive symptoms	19 (19.0)	0	38.31 (7.55)	20/11
Psychotic major depressive episodes	31 (32.0)	3	36.93 (9.44)	10/11
Early age of onset of major depressive episode	53 (53)	0	28.33 (7.29)	29/24
Postpartum depression**	3 (8.8)	0	37.33 (7.50)	---
Antidepressant 'wear-off'	17 (17.5)	3	32.38 (10.20)	9/8
Lack of response to antidepressants	35 (36.8)	5	36.05 (10.20)	19/16

* Among patients who had the criterion
** It is related to 34 females with history of at least one labor.

for 10-14%, 11-11.3%, and 10.8-11% of BSD diagnosis variance respectively. At the next stage, three mentioned items were entered the logistic regression model simultaneously. The analysis showed that brief MDE (β = 1.5, EXP (β) = 4.52, p = 0.007), treatment resistant depression (β = 1.28, EXP (β) = 3.62, p = 0.01), and recurrent MDEs (β = 1.28, EXP (β) = 3.62, p = 0.01) have the highest strength in predicting BSD and account for 21-30% of BSD diagnosis variance in sum.

Also, two essential diagnostic items of BSD (criterion C) were used as external validators for criterion D items (accessory diagnostic items). To evaluate the relationship of each criterion D item and the variable family history of bipolar disorder (one of the two essential items) logistic regression was used. From above nine items, only Recurrent MDEs significantly (β = 1.07, EXP (β) = 2.92, p = 0.03) and treatment resistant depression nearly significantly (β = 0.91, EXP (β) = 2.50, p = 0.06) accounted for the variable family history of bipolar disorder. Then, both factors – Recurrent MDEs and treatment resistant depression – were entered the analysis simultaneously and accounted for 8-12% of family history of bipolar disorder variance.

None of the nine items of criterion D significantly accounted for the variable antidepressant-induced hypomania.

Table 2. Logistic regression of the Bipolar Spectrum Disorder (BSD) criteria versus BSD

Criterion D	β	df	p-value	EXP (β)
Hyperthymic personality	-0.224	1	0.799	0.668
Recurrent major depressive episodes	1.43	1	0.001	4.20
Brief major depressive episodes	-1.34	1	0.005	3.84
Atypical depressive symptoms	0.419	1	0.416	1.521
Psychotic major depressive episodes	-0.596	1	0.206	0.778
Early age of onset of major depressive episode	0.285	1	0.497	1.329
Postpartum depression	-0.261	1	0.834	0.770
Antidepressant 'wear-off'	-0.351	1	0.058	0.646
Lack of response to antidepressants	1.41	1	0.002	4.09

Discussion

This study showed that 39% of 100 MDD inpatients were suffered from the BSD by definition of Ghaemi et al[2] which is in line with the finding of Smith et al[9] and close to the result of Kiejna et al. study.[11] The first study[9] showed the frequency of 37% for the BSD on 73 outpatients with early-onset MDD. The second study[11] found the rate of 28% on 112 outpatients with recurrent MDD using a modified definition of Ghaemi et al. BSD.[12] Using a hospitalized sample in the present study could be the main reason for higher rates of the BSD.

Because criterion D items have lower diagnostic weight than criterion C counterparts by definition of the BSD, criterion D was settled apart from more important diagnostic items (criterion C).

On logistic regression, the most strength item in predicting the BSD was brief MDE, and after that treatment resistant depression and recurrent MDEs were the next items respectively. Being recurrent was one of the main features of Kraepeline's manic-depressive illness.[13] In an 11-year prospective study on 559 MDD cases, Akiskal et al[14] reported that recurrent depression and being early-onset of first MDE (< 25 age) identified a subgroup of MDD patients who switch to BIID. Benazzi[15] by studying 89 MDD and 151 BIID patients, demonstrated that the clinical features of highly recurrent MDD (> 4 MDEs) are between low

recurrent MDD and BIID. Also another study on 336 BIID and 224 MDD individuals using multivariable logistic regression showed higher rate of recurrent depression (> 4 MDEs) in BIID group [OR = 2.15 (1.42–3.24)].[16] Despite these findings, an investigation on 284 BIID and 196 MDD patients demonstrated that although the most frequent bipolar index (70.4%) is recurrent depression (> 4 MDEs), this index have the least positive predictive value (PPV; 66.5%) to predict BIID.[17] The relationship of treatment resistant depression and BD has been reported in several studies. The frequency of bipolar disorders in patients with treatment refractory depression has been reported as 46%[18] and the longitudinal study of 21 treatment resistant MDD sufferers in one to seven years found that 24% of patients were switched to BD.[19] This rate was more than 12.5% switch rate which was obtained through follow up of 599 patients with non-refractory depression.[14] The rate of brief MDE in BD sufferers has been higher than MDD patients on naturalistic studies.[20] Also self-reported daily assessment of 203 BD patients using chronoRecord software indicated high frequency of short depressive episodes.[21] A longitudinal study on BD probands by Judd et al[22,23] ascertained that "depression" which was subsyndromal in many cases was the main characteristic of bipolar disorders. Besides, Angst et al showed that 30% of MDD patients would experience recurrent brief depressive disorder[24] and also it was suggested that the chance of improvement on lithium was higher for very short depressive episodes.[25]

Hyperthymic personality, atypical depressive symptoms, psychotic major depressive episodes, postpartum depression, and antidepressant 'wear-off' are other criterion D items which did not reach a significant level in predicting BSD on logistic regression. The literature includes some evidence in support of and/or against the relationship between each above indices and bipolar disorder.[2,7,8,26-35] However, despite lack of significant role for each remained criterion D items in predicting the BSD in the present study, the findings are not able to rule out the contribution of each mentioned BSD indices in developing a BSD, because of some methodological limitations that will be pointed out.

In spite of growing evidence for some indicators of bipolar spectrum – especially three important indices mentioned above – less attention has been paid to the brief MDE as a predictor of bipolar disorder in the literature. In two recent studies by Benazzi[16,17] in which early-onset MDE (< 20 age) was found to have the highest PPV after the family history of BD; and the early-onset MDE (< 21 age) was found to have more strength to identify MDD cases close to BIID, the brief MDE was not assessed. At the present study, although early-onset MDE was the most frequent among evaluated indices, it had no significant contribution in predicting BSD. However, this research unlike the above-mentioned studies did not evaluate individuals with classic BD and focused only on Ghaemi et al. BSD.[2] Therefore the difference seen between the findings of the present study and the Benazzi's[16,17] findings regarding the weight attributed to predictive factors for bipolar disorders could be at least in part because of BIID–BSD difference. However, the difference in research setting (inpatient vs. outpatient) would be important in creating different results too.

Another important finding of the present study is the low internal consistency of criterion D nine items (alpha = 0.3). It may be resulted from existing heterogeneous items in criterion D and suggests the hypothesis that there are several subtypes of bipolar spectrum disorder.

Several methodological limitations should be cited when resulting from the findings of this study including the cross-sectional evaluation, relying on information obtained from interview with patient and hospital records and not using interview with patient's family members, and relying on patient memory to get old information. To increase validity of the findings, the study replication on outpatients, longitudinal assessment of probands, and com-

paring two samples of unipolar depression and standard bipolar disorder are suggested.

According to our findings and considering different weights of three diagnostic items (brief MDE, treatment resistant depression, and recurrent MDEs) relative to other accessory diagnostic items of BSD, it is suggested to include these three items in the main diagnostic item list in addition to the two main items of "family history of bipolar disorder" and "antidepressant-induced mania / hypomania". Certainly, further research needs to be done on this subject, in order to precisely identify the position of each BSD diagnostic item.

Acknowledgements

Conflict of interest
Authors have no conflicts of interest.

Authors' Contributions
ASh carried out the design and coordinated the study, and prepared the manuscript.
FZ provided assistance in the design of the study, coordinated and carried out all the interviews with the patients and participated in manuscript preparation.
MA provided assistance in analyzing the data and participated in manuscript preparation.
All authors have read and approved the content of the manuscript.

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