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Research report

Treatment-induced manic switch in the course of unipolar depression can predict bipolarity: Cluster analysis based evidence

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ABSTRACT

Background: Antidepressants are known to induce manic switch in patients with depression. Treatment-induced mania is not considered as bipolar disorder in DSM IV. The aim of this study was to assess whether clinical characteristics of patients with unipolar depression with a history of treatment-induced mania were similar to those of patients with bipolar disorder.

Method: The study included 217 consecutive patients with DSM-IV mood disorders, diagnosed as: bipolar disorder type I (BP-I, n = 58) or type II (BP-II, n = 18) whose first episodes were depression, recurrent (unipolar) major depressive disorder with a history of antidepressant treatment-induced mania (switchers = sUD; n = 61) and without such an event (rUD; n = 80). First, the groups were compared with regard to clinical features and course specifiers using variance and chi-square analysis. Variables that differed significantly between the four groups were included in two-step cluster analysis to explore naturally occurring subgroups in all diagnoses. Subsequently, the relationship between the naturally occurring clusters and pre-defined DSM-IV diagnoses were investigated.

Results: Two-step cluster analysis revealed two different naturally occurring groups. Higher severity of depressive episodes, with higher rate of melancholic features, higher number of hospitalization and suicide attempts were represented in one cluster where switchers (77%), bipolar I (94.8%) and II (83.3%) patients clustered together.

Conclusion: The findings of this study confirm that treatment-induced mania is a clinical phenomenon that belongs within the bipolar spectrum rather than a coincidental treatment complication, and that it should be placed under “bipolar disorders” in future classification systems.

Limitations: The study includes the limitations of any naturalistic retrospective study.

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1. Introduction

Bipolar disorder begins with a depressive episode in about 20–70% of cases (Goodwin and Jamison, 1990; Perugi et al., 2000; Suppes et al., 2001) and depressive symptoms tend to dominate the course of the illness (Judd et al., 2003; Suppes et al., 2001). Diagnosis of bipolar disorder is delayed for a long time when the first episode is depression (Akiskal et al., 1995;

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Ghaemi et al., 1999; Manning and Ahmed, 2002) and treatment of these patients with antidepressant monotherapy may lead to manic switch (Bowden, 2005; Ghaemi et al., 1999; Ghaemi et al., 2008; Goldberg and Truman, 2003; Thase and Sachs, 2000; Post et al., 2006). Antidepressant associated manic switch was reported to be higher in bipolar type I than unipolar depression (Bond et al., 2008; Ghaemi et al., 2004; Perlis et al., 2010; Tondo et al., 2010) or bipolar type II (Altshuler et al., 2006), and antidepressant induced mania during the course of unipolar depression is considered as a sign of latent bipolar disorder (Akiskal and Pinto, 1999; Angst, 1985; Benazzi, 1997; Ghaemi et al., 2001; Joseph et al., 2009). The presence of psychotic, melancholic and atypical features in a depressive episode are considered risk factors for treatment-induced mania (Akiskal et al., 1983; Ghaemi et al., 2001; Goldberg and Harrow, 2001; Mitchell et al., 2001; Perugi et al., 1998).

There is insufficient evidence regarding a more precise differential diagnosis between bipolar and unipolar depression. DSM-IV (American Psychiatric Association, 2001) specifiers such as atypical, melancholic and psychotic features present more frequently in bipolar depression than in unipolar depression (Agosti and Stewart, 2001; Benazzi, 1999; Brockington et al., 1982; Mitchell et al., 2001; O'Donovan et al., 2008; Perris, 1966). Early onset depression with atypical features may be predictive for bipolar disorder (Akiskal, 1996; Akiskal et al., 1983; Goodwin and Jamison, 1990; Koukopoulos and Koukopoulos, 1999; Manning and Ahmed, 2002; Weissman et al., 1996). Postpartum onset and seasonality are also more common in bipolar depression (Bowden, 2005; Freeman and Keck, 2001; Goodwin and Jamison, 1990; Kelly and Sharma, 2010; Roeklein et al., 2010; Shin et al., 2005). The presence of these specifiers in different types of bipolar disorder requires evidence-based validation to offer some reconsideration for DSM-5 (Colom and Vieta, 2009).

Despite widespread recognition among experts that treatment-induced mania should be classified under bipolar disorder (Akiskal et al., 1983; Akiskal and Pinto, 1999; Altshuler et al., 1995; Benazzi, 1997; Chun and Dunner, 2004; Goldberg and Harrow, 2001; O'Donovan et al., 2008; Youngstrom, 2009), neither DSM-IV nor ICD 10 (World Health Organisation, 1993) allow the diagnosis of bipolar disorder among patients who experience treatment-induced mania; Such cases are coded under “drug-induced mood disorders” in DSM-IV.

The aim of the present study was to assess the clinical characteristics of recurrent unipolar depression patients with and without history of treatment-induced mania (groups sUD and rUD, respectively) and bipolar disorder type I or II patients (groups BP-I and BP-II, respectively) with first episode depression. We hypothesized that the clinical characteristics of patients with a history of treatment-induced mania would be similar to those of patients with bipolar disorder.

2. Methods

This is a naturalistic, retrospective, cross-sectional study comparing patients with recurrent (unipolar) depression with or without a history of treatment-induced mania, and patients with bipolar disorder type I or II whose first episodes were depression. The study was approved by Dokuz Eylul University Ethics Committee.

2.1. Diagnostic tools

All participants were interviewed using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1997) for DSM-IV diagnosis. Clinical features and course of illness were investigated through patient and family interviews and retrospective screening of all available medical records.

2.2. Participants

Two hundred and thirty-six consecutive patients aged 18 years and older, diagnosed by their physicians as having either bipolar disorder or major depressive disorder, with or without a history of treatment-induced mania, were referred to the study from the inpatient and outpatient units of Dokuz Eylul University Medical School Department of Psychiatry during a two year period. Patients with bipolar disorder were referred to the study because the first episode they experienced in the past was depression, as documented in their medical records at the bipolar disorders outpatient unit. Potential underlying medical conditions for mood disorders were excluded by the referring physician. All patients provided written informed consent. Manic switch was defined as meeting full DSM-IV manic episode criteria within the first eight weeks of antidepressant or electroconvulsive therapy (ECT) initiation (Angst et al., 1992) or increasing medication dose (Goldberg and Truman, 2003). Due to the sensitivity and validation problems related to definition of hypomania, hypomanic switches were excluded (Angst, 2008). We also excluded mixed episodes, to avoid any diagnostic confusion and to keep the switching phenomena as homogeneous as possible. Nineteen patients were excluded from the study due to diagnostic mismatch after the SCID-I interviews. The remaining 217 patients with bipolar disorder type I (BP-I, $n = 58$) or type II (BP-II, $n = 18$), recurrent (unipolar) major depressive disorder with a history of antidepressant treatment-induced mania (switchers = sUD; $n = 61$) and without such an event (rUD; $n = 80$) comprised the study group.

2.3. Clinical variables

Groups were compared with regard to sex, age, age of illness onset, duration (weeks), severity, frequency and number of past episodes, number of lifetime suicide attempts and hospitalizations, as well as the presence of course specifiers. Frequency of past depressive episodes was formulated as the total number of past episodes divided by the total number of years between illness onset and time of study enrollment. Three different types of course specifiers were defined: (1) Severity of an episode: mild, moderate, severe without psychotic features, severe with psychotic features; (2) Clinical features of an episode: catatonia, melancholia or atypical features; and (3) Longitudinal course specifiers seasonal pattern or postpartum onset. For the episode-related categorical features, the existence of a feature during an episode, regardless of how many times it occurred, was considered as positive for that feature. For severity, the mean severity of past episodes was entered as the lifetime severity. Therefore, all types of features are considered as lifetime course specifiers, based on the heterogenic quality of the DSM-IV-TR specifiers (Colom and Vieta, 2009).

2.4. Statistical analyses

Groups (BP-I, BP-II, rUD, sUD) were compared for age, age of illness onset, number, and the duration and frequency of past episodes using Kruskal–Wallis analysis of variance. The Mann–Whitney *U* test was used for comparison of two independent groups. Categorical data such as the presence or absence of a suicide attempt, hospitalization, and course specifiers were analyzed using chi-square tests.

Two-step cluster analysis with log-likelihood distance measure was used to explore naturally occurring subgroups in all diagnoses. The two-step method allows the creation of cluster models based on both continuous and categorical variables. Since the cluster features tree and final solutions are very sensitive to order effects, we randomly ordered cases by a randomization list generated by PASW Statistics 18.0 (IBM SPSS Inc, 2009, Chicago, IL). The two-step algorithm was then applied to automatically determine the number of clusters using Bayesian Information Criterion (BIC). The predicted cluster profile was saved as a new variable for each case and, subsequently, the relationship between the naturally occurring clusters and pre-defined DSM-IV diagnosis was investigated. Two-tailed significance level was set to 0.05.

3. Results

3.1. Diagnostic and treatment considerations

Two hundred and thirty six patients who gave written informed consent were interviewed with SCID-I. Diagnosis of bipolar disorder in 76 patients, (bipolar I, $n=58$, 74.3%; bipolar II, $n=18$, 23.7%) whose first episodes were depression and diagnosis of major depressive disorder recurrent type (rUD) in 80 patients were confirmed after the structured interview. Out of 80 patients who were referred to the study for treatment-induced mania/hypomania (switchers), 19 (23.8%) were diagnosed as having bipolar disorder. Fourteen patients had BP-I (17.5%), 5 had BP-II (6.5%) disorder. Three of fourteen BP I patients (21.4%) had spontaneous manic episodes before treatment-induced mania. Thirteen of these fourteen patients (94.3%) experienced spontaneous manic episodes after switching. Four of five patients with BP-II (80%) had past hypomanic episodes. One patient cycled into spontaneous hypomanic referred episode after switching.

In the whole switchers group ($n=80$), treatment-induced mania occurred 3.59 ± 5.81 years after the first depressive episode. Patients were evaluated 4.38 ± 5.16 years after switching. Those patients who kept cycling had their first post-switching manic/hypomanic episode 5.86 ± 3.9 years after switching.

In order to continue with homogeneous groups, switchers with the diagnosis of bipolar disorder were excluded from statistical analysis. The remaining 61 patients consisted of the sUD group (Fig. 1).

The main treatment modality in the sUD group was pharmacotherapy. Only one patient in this group switched into mania under electroconvulsive therapy (ECT). The top five antidepressants taken by patients at the time of switching were venlafaxine ($n=14$, 19.7%), citalopram ($n=12$, 16.4%), paroxetine ($n=11$, 14.1%), fluoxetine ($n=10$, 12.8%) and sertraline ($n=8$, 10.3%); followed by ($n=4$, 6.6%),

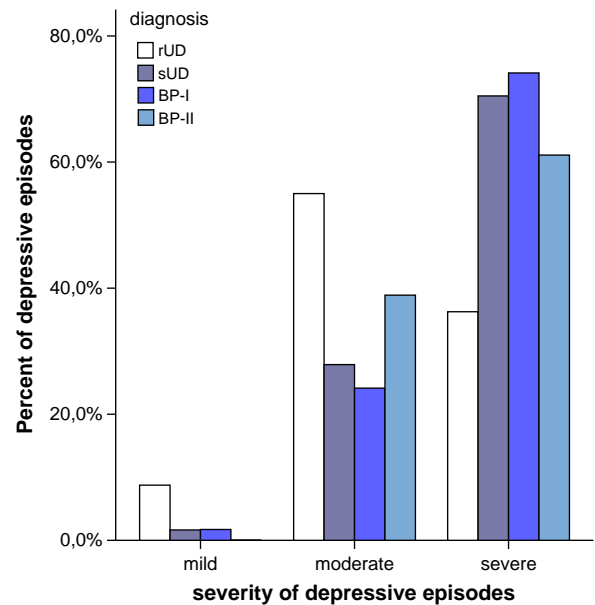


Fig. 1. Severity of the depressive episodes among four diagnoses. BP-I (Bipolar type I); BP-II (Bipolar type II); sUD (antidepressant induced mania, switchers); and rUD (recurrent unipolar depression).

maprotiline ($n=2$, 3.3%) and clomipramine, escitalopram, imipramine, moclobemide, and nefazodone ($n=1$, 1.6% in each antidepressant group) followed those.

There was a major change in treatment modality after switching. Thirty-six (59%) of 61 sUD patients were receiving mood stabilizers, either alone ($n=16$), or in combination with SSRIs ($n=12$) or second-generation antipsychotics ($n=8$). Twenty-five patients (41%) were still on antidepressants (mainly SSRIs), 12 (20%) were on monotherapy, and 13 (21.6%) were on combination treatment. Nine (14.8%) patients were taking second-generation antipsychotics.

The main antidepressant in the rUD group was an SSRI ($n=60$, 75%) either alone ($n=57$) or in combination with another psychotrop ($n=3$).

3.2. Age and gender

There was a significant age difference between the four groups ($\chi^2=10.391$, $df=3$, $p=0.016$). sUD patients were significantly younger than BP-II patients ($z=2.030$, $p=0.042$) at the time of study enrollment (Table 1).

The number of female patients was higher than males in all four groups and the rUD group had the highest F/M ratio (Table 1).

3.3. Age of illness onset

Age of illness onset differed significantly between the study groups ($\chi^2=24.734$, $df=3$, $p=0.000$). BP-I patients had the earliest illness onset, which differed significantly from that of the BP-II ($z=3.151$, $p=0.002$), sUD ($z=-3.175$, $p=0.002$) and rUD ($z=-4.670$, $p=0.000$) groups. There was no significant difference between the latter three groups (Table 1).

Table 1
Comparison of clinical characteristics and course specifiers of four diagnostic groups.

	BP-I		BP-II		sUD		rUD		Analysis of variance/ Chi-square		Significant difference*
	n = 58		n = 18		n = 61		n = 80		df	p values	
Gender (number, %)											
Female	36	62.1	15	83.3	45	73.8	66	82.5	3	0.042	rUD>BP-I = BP-II = sUD
Age (years) (mean, SD [†])	40.98	14.11	46.44	12.30	38.70	13.95	45.98	14.48	3	0.016	BP-I = BP-II = sUD<rUD*
Age of illness onset	25.24	8.68	33.66	9.10	31.90	12.38	35.38	13.29	3	0.000	sUD>BP-I, rUD = BP-II = sUD*
Early-onset (<21)	27	46.6	3	16.7	13	21.3	11	13.8	6	0.000	
Mid-onset (22–39)	27	46.6	10	55.6	28	45.9	34	42.5			BP-I<sUD = rUD**
Late-onset (>39) (number, %)	4	6.9	5	27.8	20	32.8	35	43.8			BP-I<BP-II***
Depressive episodes (mean, SD)											
Number	3.65	2.83	3.72	1.74	3.66	4.13	2.81	2.72	3	0.049	rUD<BP-II*, sUD = BP-I = BP-II
Duration (weeks)	11.41	4.42	10.17	4.86	17.11	27.14	15.33	20.48	3	0.001	sUD>BP-I*, rUD>BP-I*
Frequencys	0.44	0.43	0.34	0.14	0.63	0.44	0.47	0.33	3	0.000	UD>BP-I*, rUD*, BP-I = BP-II
Severity (number, %)											
Severe	43	74.1	11	61.1	43	70.5	29	36.3	6	0.000	BP-I = BP-II = sUD>rUD****
Moderate	14	24.1	7	38.9	17	27.9	44	55.0			
Mild	1	1.8	–	–	1	1.6	7	8.8			
Suicide attempts (number, %)	23	39.7	7	38.9	14	23.0	12	15.0	3	0.006	BP-I>rUD
Hospitalization (number, %)	46 79.3	6 33.3	22 36.1	11 13.8	3	0.000					BP-I>BP-II = sUD>rUD
Course specifiers (number, %)											
Presence of											
Psychotic	31	53.4	4	22.2	7	11.5	1	1.3	3	0.000	BP-I>BP-II = sUD,rUD
Melancholic	35	60.3	9	50.0	38	62.3	22	27.5	3	0.000	BP-I = BP-II = sUD>rUD
Atypical	6	35.5	2	11.8	8	47.1	1	5.9		NA	
Seasonal	6	10.3	1	5.6	7	11.5	2	2.5		NA	
Post-partum	4	6.9	–	–	2	3.3	–	–		NA	
Catatonic features	1	1.7	–	–	1	1.6	–	–		NA	

BP-I (Bipolar type I); BP-II (Bipolar type II); sUD (treatment induced mania = switchers); rUD (Recurrent Depression).

NS: Non significant; NA: not applicable: because expected counts were less than five in the cells.

[†] SD = Standard Deviation.

* Kruskal–Wallis, post hoc Mann–Whitney.

** Early vs Late onset 2 × 2 chi-square (df: 1; p = 0.000).

*** Early vs Late onset 2 × 2 chi-square (df: 1; p = 0.03).

**** Severe vs moderate 2 × 2 chi-square (df: 1; p = 0.001).

3.4. Number and duration of past episodes

Groups differed significantly in the number of past depressive episodes ($\chi^2 = 7.837$, $df = 3$, $p = 0.049$). rUD patients had the lowest number of past depressive episodes compared to sUD, BP-II, and BP-I groups. Only the difference between rUD and BP-II groups was significant ($z = -2.680$, $p = 0.007$). The sUD, BP-I and BP-II groups showed a similar number of past depressive episodes.

The four groups differed significantly in the duration of past depressive episodes ($\chi^2 = 8.842$, $df = 3$, $p = 0.001$). sUD patients had the longest duration of depressive episodes, followed by the rUD patients. Both groups differed significantly from BP-I patients with regard to length of depressive episodes (sUD vs BP-I; $z = -2.898$, $p = 0.004$; rUD vs BP-I; $z = -2.362$, $p = 0.018$). The length of depressive episodes was similar in BP-I and BP-II patients (Table 1).

3.5. Frequency of depressive episodes (total number of past depressive episodes/total number of years between illness onset and time of study enrollment)

The BP-I, BP-II, sUD, and rUD groups differed significantly in the frequency of depressive episodes ($\chi^2 = 19.027$, $df = 3$, $p = 0.000$). The sUD group had the highest episode frequency and differed significantly from the BP-I ($z = -3.947$, $p =$

0.000), BP-II ($z = -2.846$, $p = 0.004$), and rUD ($z = -0.574$, $p = 0.010$) groups; The BP-I, BP-II and rUD groups did not differ from each other (Table 1).

3.6. Depressive episode course specifiers

3.6.1. Severity of depressive episodes

The severity of past depressive episodes differed significantly between the groups ($\chi^2 = 28.093$, $df = 6$, $p = 0.000$). The BP-I, BP-II and sUD groups contained similar proportion of patients with severe episodes. Patients with moderately severe episodes clustered mainly in the rUD group (Table 1 and Fig. 1).

3.6.2. Melancholic features

The presence of melancholic features differed significantly between the four groups ($\chi^2 = 22.036$, $df = 3$, $p = 0.000$). The proportion of patients with melancholic features was highest in the sUD group, followed by BP-I, BP-II, and rUD groups. As the BP-I, BP-II and sUD groups were similar with regard to the presence of melancholic features, the BP-I and sUD groups had significantly higher proportions of patients with melancholic features compared to the rUD group ($\chi^2 = 14.961$, $df = 1$, $p = 0.001$ and $\chi^2 = 17.141$, $df = 1$, $p = 0.000$ respectively) (Table 1).

3.6.3. Psychotic features

There was a significant group difference for the presence of psychotic features ($\chi^2 = 61.381$, $df = 3$, $p = 0.000$) in past depressive episodes. Psychotic features occurred most frequently in the BP-I, followed by the BP-II, sUD and rUD groups. The presence of psychotic features was significantly higher in the BP-I group compared to sUD ($\chi^2 = 24.10$, $df = 1$, $p = 0.000$), and rUD ($\chi^2 = 51.43$, $df = 1$, $p = 0.000$) groups. rUD patients also had significantly lower rates of psychotic features than BP-II ($\chi^2 = 13.35$, $df = 1$, $p = 0.000$) and sUD ($\chi^2 = 6.76$, $df = 1$, $p = 0.009$) groups (Table 1).

3.6.4. Atypical features

Atypical features were most common in the sUD group (Table 1).

Seasonality was present in 10.3% of the BP-I, 5.6% of the BP-II, 2.5% of the rUD, and 11.5% of the sUD groups. Postpartum depression occurred neither in BP-II nor in rUD, but presented in 6.88% ($n = 4$) of the BP-I, and in 3.29% ($n = 2$) of the sUD patients. Catatonic features were observed only in BP and sUD groups, with one patient in each group (Table 1). Due to the small numbers of patients presenting with atypical, catatonic and seasonality features, no group comparisons were done.

3.7. Suicide attempts

Nearly 40% of patients in both the BP-I and BP-II groups had attempted suicide. The difference between the four groups was significant ($\chi^2 = 12.558$, $df = 3$, $p = 0.006$). The proportion of patients with past suicide attempt was significantly higher in the BP-I group compared to rUD ($\chi^2 = 10.797$, $df = 1$, $p = 0.001$) (Table 1).

3.8. Hospitalizations

The difference between the groups was significant with regard to the number of patients who had at least one psychiatric hospitalization in the past ($\chi^2 = 61.420$, $df = 3$, $p = 0.000$).

The rate of hospitalization was higher in the BP-I group compared to BP-II ($\chi^2 = 13.44$, $df = 1$, $p = 0.000$), sUD ($\chi^2 = 22.704$, $df = 1$, $p = 0.000$), and rUD groups ($\chi^2 = 59.61$, $df = 1$, $p = 0.000$). As the BP-II and sUD groups had similar rates of past hospitalizations, the sUD group contained significantly higher rates of hospitalization than the rUD group ($\chi^2 = 9.614$, $df = 1$, $p = 0.002$).

3.9. Findings of cluster analyses

Cluster analysis was performed using age of illness onset; gender; severity, duration and frequency of depressive episodes; number and frequency of all episodes; presence of melancholic, psychotic, atypical features in depressive episodes; presence of hospitalization and suicide attempts. Normality was tested with the Shapiro–Wilk test. Despite certain transformations (Box–Cox family of power transforms or the cube-root transformation), we achieved normality only in the BP-II group for the number of depressive/and total episodes, frequency of depressive episodes and duration of depressive episodes ($df = 18$, Shapiro–Wilk = 0.931; 0.917; 0.966; 0.906 and $p = 0.199$; 0.115; 0.772; 0.072 respectively). Categorical data such as gender, presence of course specifiers,

hospitalization or suicide attempts did not meet multinomial distribution in any of the groups. Two-step cluster analysis revealed that there were two different naturally occurring groups. Silhouette measure of cohesion and separation was 0.4, which denotes that the cluster quality was fair. The ratio of largest to smallest cluster was 2.1 (cluster 1, $n = 147$, 67.7%; cluster 2, $n = 70$, 32.3%). Among all the parameters included in the analysis, four most important variables on general clustering formation were the severity of depressive episodes, melancholic features, presence of hospitalization and suicide attempts. Higher severity of depressive episodes, the presence of more melancholic features and higher numbers of hospitalization and suicide attempts were represented in cluster 2 (the importance values of variables were 1, 0.67, 0.48 and 0.27, respectively) (Table 1 and Fig. 2a).

A cross tabulation of pre-defined DSM-IV diagnosis by group membership assignment, produced using two-step cluster analysis, showed significant differences between the above mentioned variables ($\chi^2 = 8.199$, $df = 3$, $p < 0.042$). While a significantly high proportion of rUD patients ($n = 50$, 62.5%) were assigned to cluster 1, sUD patients ($n = 47$, 77.0%), BP-I ($n = 55$, 94.8%) and BP-II patients ($n = 15$, 83.3%) were all represented together in cluster 2. Recomposition of the groups according to first analysis is shown in (Fig. 3).

We ran a second analysis using a different set of parameters. The main reason for this was to test whether the use of a single severity parameter (severity of past episodes) rather than all of the other severity related parameters would change the rank of parameters influencing the clustering. In this model, the presence of hospitalization, suicide attempts and psychotic features were excluded from analysis. Two-step cluster analysis revealed two different naturally occurring groups and a silhouette measure of cohesion and separation of 0.4. This time, the ratio of largest to smallest cluster was 1.58 (cluster 1, $n = 133$, 63.1%; cluster 2, $n = 84$, 38.7%). In this second analysis, the importance value of earlier illness onset moved up to third place after the severity of depressive episodes and higher rate of melancholia; the importance values of the variables were 1, 0.34 and 0.12 respectively (Fig. 2b). Cluster formation according to pre-defined DSM-IV diagnosis did not change greatly when the results of this second analysis were applied; BP-I ($n = 45$, 77.6%), II ($n = 11$, 61.1%) and sUD ($n = 47$, 77.0%) patients still clustered together, although this time at slightly different rates than the first analysis.

4. Discussion

The main finding of this study is that clinical features and course of depressive episodes of patients with a history of treatment-induced mania differ from patients with recurrent depression and show similarities to patients with bipolar disorder.

4.1. Diagnostic and treatment-related considerations

Among the 80 patients who were referred to the study for experiencing antidepressant-induced mania, 76% ($n = 61$) were included in the study for not having DSM-IV bipolar disorder. This rate falls within the previously reported rate for the misdiagnosis of bipolar patients as unipolar depression

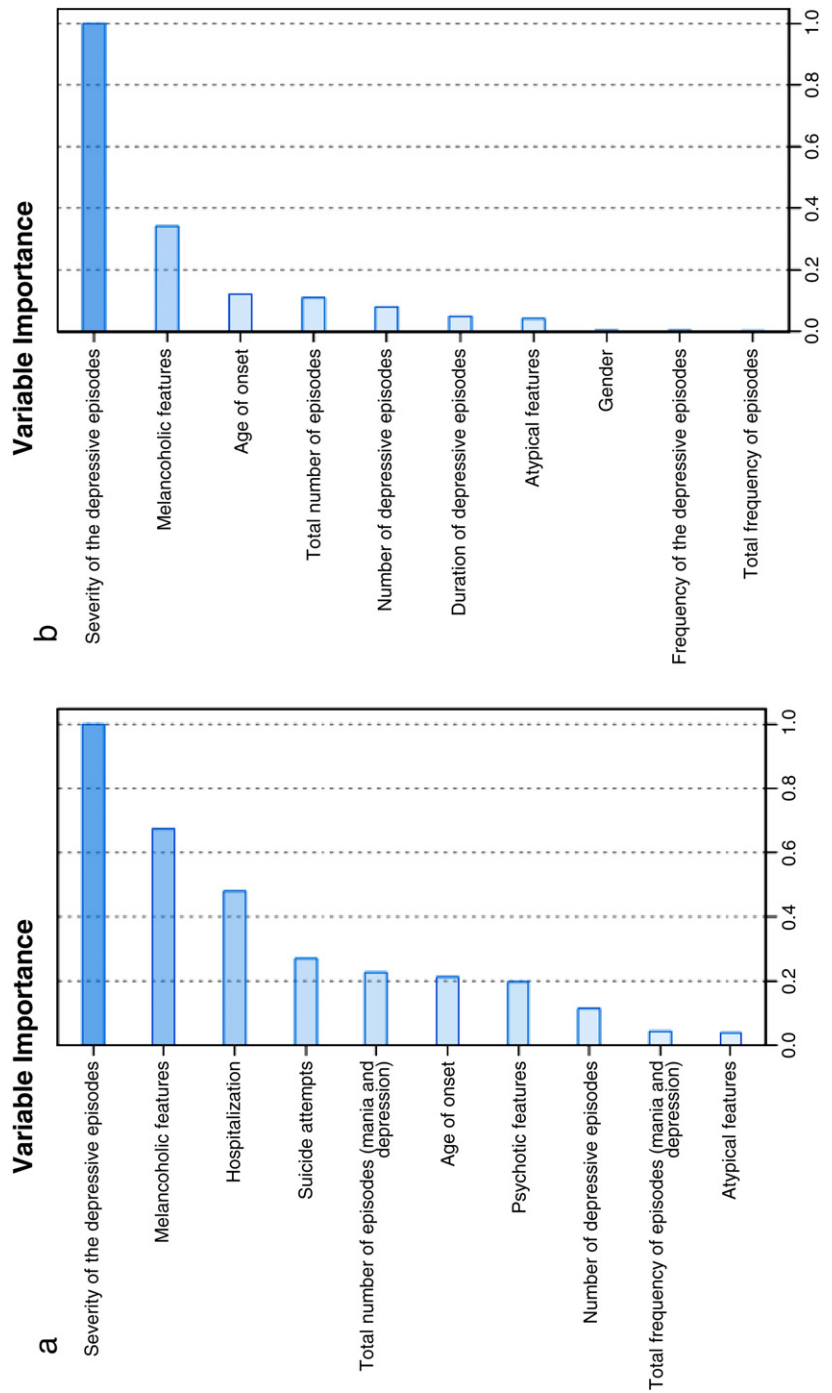


Fig. 2. a–b. Importance of the variables in clustering process.

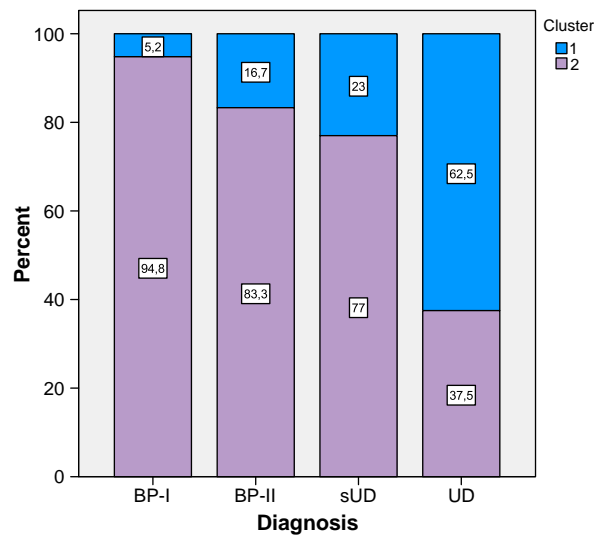


Fig. 3. Association between pre-defined DSM-IV diagnoses and clusters. BP-I (bipolar type I); BP-II (bipolar type II); sUD (treatment induced mania = switchers); and rUD (recurrent depression).

(Calabrese et al., 2006; Chun and Dunner, 2004; Clarke et al., 2008; Hirschfeld et al., 2005; Muzina et al., 2007; Olfson et al., 2005). The finding that pre-switching depressive episodes of these patients showed similar characteristics to the depressive episodes of bipolar patients supports the proposal that antidepressant-induced switching may represent an acceleration of the natural course of bipolar disorder, as suggested by Akiskal et al. (Akiskal et al., 2000; Akiskal and Pinto, 1999; Ghaemi et al., 2001; Joseph et al., 2009; Wehr and Goodwin, 1987). The same authors conceptualize a high sensitivity of “pharmacological hypomania”. We used a stringent definition of switching, based on the literature (Altshuler et al., 1995; Goldberg and Truman, 2003; Salvatore et al., 2010) and included only treatment-induced manic episodes that matched with the full DSM-IV-TR criteria for a manic episode (American Psychiatric Association, 2001).

The leading drug for manic switch in our study population was venlafaxine (approximately 20%), which is consistent with other studies (Boerlin et al., 1998; Goldberg and Truman, 2003; Koszewska and Rybakowski, 2009; Leverich et al., 2006; Muzina et al., 2007; Nemeroff et al., 2008; Post et al., 2006; Vieta et al., 2002). However, evidence for the more unsafe antidepressants remains limited. The rate of venlafaxine use in these patients may be related to the severity of depressive episodes, and therefore to the need for a potent antidepressant with dual neurotransmitter effect. Studies demonstrate relatively lower risk of mania for SSRIs (Amsterdam et al., 1998; Joseph et al., 2009; Nemeroff et al., 2008; Peet, 1994; Schaffer et al., 2006). Overall SSRI use in the switchers reached 35% in our group. It is not possible to draw any conclusions with regard to the role of SSRIs in our switch group because the finding may be related to the antidepressant preference bias in our clinic, as also evidenced by the high rate of SSRI use (75%) in the rUD group.

4.2. Demographic considerations

We showed that the mean age of illness onset in sUD patients was between BP-I and rUD groups, but it did not differ

significantly from either BP-I or BP-II groups. Although there is no consensus on early or late illness onset in bipolar disorder (Baldessarini et al., 2010; Colom and Vieta, 2009; Hamshere et al., 2009), some studies reported that switchers were older than those with unipolar depression at intake (Carlson et al., 2007; Serretti et al., 2003; Tamada et al., 2004), but one study (Truman et al., 2007) showed the opposite association, similar to our sUD patients, who were significantly younger than BP-II patients at the time of study enrollment. The evidence suggests that there is a negative correlation between age and risk for antidepressant-induced mania (Martin et al., 2004). The close follow-up of this relatively young population is important to decide on treatment modalities for maximizing the use of mood stabilizers (Ghaemi et al., 2001; Thase and Sachs, 2000) and for their lifelong protection from social, occupational or cognitive impairments (Maskill et al., 2010; Rosa et al., 2010; Solé et al., 2011).

Although female domination of the groups is consistent with previous studies (Angst et al., 2003; Benazzi, 2000; Kessing et al., 2008; Leibenluft, 2000; Perugi et al., 2000; Schaffer et al., 2010; Weissman et al., 1996), the proportion of female participants differed significantly only between the rUD and BP-I groups. There is no consensus on the gender liability for switching. Some studies (Altshuler et al., 1995; Angst, 1985; Koszewska and Rybakowski, 2009), but not all (Henry et al., 2001) link the phenomenon of switching with female gender. The predominance of female patients in our study could be explained by a tendency for females to appear in greater proportions in the depressive pole (Altshuler et al., 2010) or by possible referral bias and/or greater treatment-seeking behavior among women (Duax et al., 2007).

4.3. Severity-related considerations and other course specifiers

The most severe depressive episodes cumulated equally in BP-I and sUD patients. Several studies suggest that early onset of bipolar disorder is associated with greater illness severity (Benazzi, 2009; Benazzi and Akiskal, 2008; Bowden, 2001;

Kessing et al., 2008; Mitchell et al., 2008; Mitchell and Malhi, 2004; Perlis et al., 2004; Schulze et al., 2002; Schurhoff et al., 2000; Vieta et al., 1997). Early onset has been linked with higher (Martinez-Aran et al., 2008; Schurhoff et al., 2000) and greater risk of suicidality in bipolar patients (Perlis et al., 2004; Schaffer et al., 2010). Although our switchers were not as young at onset as the BD-I patients, the equally severe episodes among the BD-I patients may point to a common pathogenesis in both conditions. The presence of psychotic features was found to be similar in sUD and BP-II patients in the current study. BP-I patients had the highest rates of psychotic features (53%). Taken together, these findings are in line with those of previous studies, where psychotic features were reported to be more likely in bipolar type I patients (Akiskal et al., 2000; Brugue et al., 2008; Goldberg and Harrow, 2001; Guze et al., 1975; Mitchell et al., 2001; Schneck et al., 2004), and in antidepressant-induced switchers (Serretti et al., 2003). In one of the limited number of studies that investigated psychotic symptoms in bipolar type II patients, the rate of psychotic features were found to be 19.5%, which is similar to our BP-II patients (Mazzarini et al., 2010). We found equally increased rates of suicide attempts in both BP-I and II patients compared to the sUD and rUD patients, which is in line with previous findings (Akiskal et al., 2001; Ben Ablu et al., 2006; Colom et al., 2006; Jamison, 2000; Moreno and Andrade, 2010; Novick et al., 2010; Perugi et al., 2000; Raja and Azzoni, 2004; Simon et al., 2007). The sUD patients and BP-II patients were alike in terms of the number of past hospitalizations, which supported the findings of previous studies (Ben Ablu et al., 2006; Schaffer et al., 2010; Serretti et al., 2003). The findings show that severity-related features of the diagnostic groups have major impacts on differential diagnosis of potential bipolar disorder.

We found equally higher rates of melancholic and atypical features in the sUD, BP-I and BP-II patients compared with the rUD group. These findings are in accordance with a broad range of literature referring to the presence of higher melancholic (Brugue et al., 2008; Ghaemi et al., 2001; Manning and Ahmed, 2002; Mitchell et al., 2001; Parker et al., 2000) and atypical features in bipolar disorder, especially in type II (Akiskal et al., 2001; Akiskal and Benazzi, 2005; Benazzi and Rihmer, 2000; Brugue et al., 2008; Perugi et al., 1998) than unipolar depression (Agosti and Stewart, 2001; Akiskal and Benazzi, 2005; Benazzi, 2000, 2006; Detre et al., 1972; Goodwin and Jamison, 1990; Mitchell et al., 2001; Moreno and Andrade, 2010; Serretti et al., 2002). Atypical symptoms are considered risk factors for relapse even in the presence of mood stabilizers (Pfennig et al., 2010). The clinical features of our BP-I, II and sUD groups comply with the concept that clinical admixture of melancholic, atypical and psychotic features can be considered as a “bipolar signature” (Mitchell et al., 2001; Mitchell and Malhi, 2004). Seasonality and postpartum characteristics were more frequently seen in sUD and BP-I patients, as shown previously (Akiskal et al., 2000; Bowden, 2005; Faedda et al., 1993; Freeman and Gelenberg, 2005; Freeman and Keck, 2001; Shin et al., 2005). We had only two patients with catatonic features, one in BP-I and another in the sUD group. Catatonia is rarely seen in bipolar disorder nowadays or it is often ignored and therefore under-diagnosed due to not using structured checklists (Colom and Vieta, 2009).

4.4. Course of illness

Depressive episodes were reported to be more numerous, lengthy and frequent in bipolar I patients than patients with unipolar and also bipolar II depression (Akiskal et al., 2000; Bowden, 2001; Cueller et al., 2005; Goodwin and Jamison, 1990, 2007; Mantere et al., 2008; Mitchell et al., 2001; Muzina et al., 2007; Perlis et al., 2006; Schaffer et al., 2010). We showed that sUD patients had the most frequent and longest depressive episodes. This finding may be explained by the mood destabilizing effect of using antidepressants (Akiskal et al., 2003; Ansari and Osser, 2010; El-Mallakh et al., 2008; El-Mallakh et al., 2010; Ghaemi et al., 2004; Licht et al., 2008) or by greater treatment-resistance in these patients (Ghaemi et al., 2004; Post et al., 2002). These findings point to a morbid course of switch process and a definite need for earlier detection and more aggressive and appropriate treatment of these patients.

4.5. Cluster analysis

This is the first study showing that sUD patients cluster together with BP-I and II patients and that rUD patients locate as a separate group. In our study, continuous variables were not normally distributed within the population, with the exception of the BP-II group. In addition, the categorical data did not meet multinomial distribution. However, according to Marija Norusis “the best results can be taken if continuous variables were normally distributed, or categorical variables have a multinomial distribution. This is seldom the case in practice. The clustering algorithm is thought to behave reasonably well when these assumptions are not met and it's perfectly acceptable for best performance” (SPSS 17.0 Guide to Data Analysis), (www.norusis.com/pdf/SPC_v13.pdf).

Two-step cluster analysis revealed that the main clinical features that would show impact on the differential diagnosis between potential bipolar depressive and true unipolar depressive episodes are the severity of the overall symptoms and also severity-related conditions such as hospitalization and suicide attempts. The larger cluster (67.7%) mostly contained severe depressive episodes in patients diagnosed with BP-I (74.1%); sUD (70.5%) and BP-II (61.1%). Among the course specifiers, melancholic features (BP-I 33.7%; sUD 36.5%) rather than psychotic (BP-I 72.1%; sUD 16.3%) and atypical features (BP-I 35.3%; sUD 47.1%) are strongly connected with the natural clustering of bipolar disorder and treatment-induced mania together. Younger age of illness onset may also play an important role in differentiating bipolar and unipolar depressive episodes, as the illness begins earlier than 21 years of age in 46.6% of the BP-I patients, as opposed to 13.8% of the patients in the rUD group.

4.6. Limitations

The current study has several limitations. Most notably, data regarding age of illness onset and number, duration or severity of the past episodes or lifetime course specifiers, were assessed retrospectively. However, the additional use of any available source of information about the patients, such as family members or medical records, helped minimizing

misinformation. The second limitation is the relatively small number of patients, especially in the BP-II groups. Nevertheless, we favored the sub-categorization of bipolar patients as BP-I and II to understand whether the sUD patients had a tendency for either of the bipolar subgroups, especially to the BP-IIs in terms of clinical profile. However, the exclusion of hypomanic switch due to the sensitivity and validation problems with its definition may also introduce a bias in disease severity, especially for BP-II patients. The third limitation was that we missed reverse polarity, focused only on first episode depressive bipolar patients. However the strength of our study is that all patients were evaluated by experienced psychiatrists with structured interviews at a university hospital. We included only well defined, treatment-induced manic episodes, leaving no doubt about the switching process. Mixed episodes were excluded from the sUD group as being a potential confounder.

4.7. Concluding remarks

Based on the findings of the present study, we suggest that attention should be paid to the severity and severity-related features of depressive episodes for potential bipolar illness, especially in patients with early age of illness onset, as suggested by several other groups. We recommend close-monitorization with antidepressant use in such patients and advise adding mood stabilizers to the treatment regimen.

Our findings strongly support the previous evidence that sUD patients are similar in nature to bipolar patients and should therefore be classified and treated as true bipolars. This viewpoint is an especially important consideration for the formation of DSM-5 and ICD-11.

Role of founding source

None.

Conflict of interest

None declared.

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