

DIFFERENCES IN CLINICAL CHARACTERISTICS BETWEEN BIPOLAR PATIENTS WITH CURRENT PSYCHOTIC SYMPTOMS AND THOSE WHO HAVE NEVER BEEN PSYCHOTIC

Zsuzsanna Belteczki¹, Zoltan Rihmer^{2,3}, Julia Ujvari¹, Dorian A. Lamis⁴ & Peter Dome^{2,3}

¹Sántha Kálmán Psychiatric Hospital, Nagykálló, Hungary

²Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary

³National Institute for Psychiatry and Addictions, Budapest, Hungary

⁴Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, United States

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SUMMARY

Background: Psychotic symptoms are common in bipolar disorder (BD). Data suggest that BD patients with or without psychotic symptoms may differ from each other with regards to some clinical features of BD (e.g., age at onset, suicidality, psychiatric comorbidity, number of hospitalizations). However, the literature in this area is relatively scarce and not always conclusive. Therefore, the objective of the current study was to investigate whether the presence of psychotic symptoms is associated with clinical characteristics of patients with BD.

Subjects and methods: We enrolled 365 hospitalized patients who were diagnosed with BD according to the ICD-10 criteria. After we excluded 196 patients without current psychotic symptoms but psychotic mood episodes in their medical history, our final sample consisted of 169 patients (i.e., 89 BD patients presenting with current psychotic symptoms and 80 BD patients who were hospitalized in the same period, but who did not have psychotic symptoms either currently or during their previous hospitalizations). Clinically available data were collected, systematized and statistically processed according to the aims of the study.

Results: Early age of onset, bipolar-I diagnosis, comorbid personality disorder, number of hospitalizations and suicidality were significantly more common in the psychotic group compared to the never-psychotic group. On the contrary, sedative/hypnotics dependence was more frequent in the never-psychotic group.

Conclusions: Our results support the notion that the presence of psychotic symptoms in the context of BD may be associated with various other clinical features of this disease.

Key words: bipolar disorder - age at onset – suicidality – mania – depression - psychotic

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INTRODUCTION

Psychotic symptoms may be present in about 60% of patients with bipolar disorder (BD) at least once in their lifetime (Fountoulakis 2015, Keck et al. 2003). Within psychotic symptoms, delusions are more frequent than hallucinations (12-96% vs. 8-66%) in these patients (Fountoulakis 2015). In BD, depressive and manic episodes are associated with psychotic symptoms in 9-66% and 33-96%, respectively (Fountoulakis 2015). Others also reported that psychotic symptoms are more common in manic than in depressive episodes (Altamura et al. 2015, Caldieraro et al. 2017, Keck et al. 2003). Moreover, the rate of psychotic symptoms in mixed episodes is more frequent than in depression and similar to that of mania (approximately 40%) (Fountoulakis 2015). Psychotic symptoms in BD can either be mood-congruent or mood-incongruent, and they may occur in the context of any kinds of mood episodes (Azorin et al. 2006, Fountoulakis 2015, Grande et al. 2016, Tohen et al. 1992). The co-occurrence of mood-congruent and incongruent psychotic symptoms is also not rare (Fennig et al. 1996). Intriguingly, 17% of BD patients have Schneiderian first-rank symptoms – previously believed to occur exclusively in schizophrenia – at least once in

their lifetime (Fountoulakis 2015, Keck et al. 2003). It is also important to note that several – but not all (e.g. Goldberg & Harrow 2004) – findings have indicated that psychotic mood episodes tend to be repeated during the course of BD (i.e., if a patient has a mood episode with psychotic features during the course of BD, he/she is at an increased risk of also becoming psychotic during the subsequent episodes) (Black et al. 1988, Coryell et al. 2001, Fountoulakis 2015, Fountoulakis et al. 2017, Ostergaard et al. 2013). Although psychotic symptoms are frequent in BD, their presence often leads to the misdiagnosis of BD as schizophrenia, which may result in the inadequate treatment of BD (Altamura et al. 2015, Fountoulakis 2015). Psychotic features are more common in BD-I than in BD-II and in bipolar than in unipolar major depression (Brugue et al. 2008, Caldieraro et al. 2017, Fountoulakis 2015, Goodwin & Jamison 2007, Serretti et al. 2002, Vieta et al. 1997). There are at least two reasons which may explain why psychotic symptoms are more frequent in BD-I than in BD-II: 1) in BD-II, psychosis can be present only in the context of depressive episodes but not in the context of hypomania (since according to the 4th and 5th edition of the DSM, if psychotic symptoms are present during the period of elevated/expansive/irritated mood the episode

should be denoted as manic); 2) in contrast to BD-I, episodes of psychotic depression are extremely rare in patients with BD-II (APA 1994, 2013, Mazzarini et al. 2010, Parker 2016, Vieta et al. 1997). A possible biochemical explanation for this phenomenon may be the decreased activity of dopamine beta-hydroxylase in BD-I (compared to BD-II), demonstrated more than 30 years ago (Rihmer et al. 1984).

Although some studies have been conducted so far with the aim of assessing the association between psychotic features and other clinical aspects of bipolar disorder (e.g., age at onset, suicidality, number of hospitalizations, type of BD (i.e. BD-I vs BD-II), psychiatric comorbidity), the results of these studies are not always consistent (e.g. Bjorklund et al. 2017, Caetano et al. 2006, Caldieraro et al. 2017, Hua et al. 2011, Keck et al. 2003, Mazzarini et al. 2010, Ostergaard et al. 2013, Ozyildirim et al. 2010). For example, findings are contradictory regarding the association between psychotic symptoms and early disease onset, frequency of psychiatric comorbidity, suicidality or family history of psychiatric disorders (see the discussion of these issues in the Results section). The objective of our study was to further understand the association between psychotic symptoms and various aspects of BD.

SUBJECTS AND METHODS

The assessment took place between 1 January 2015 and 30 September 2016 in the active psychiatric departments of the Sántha Kálmán Psychiatric Hospital, Nagykovács, Hungary. Patients (n=365) were diagnosed with BD based on the ICD-10 criteria during this period and included in the study. Patients with schizoaffective disorder were excluded. Clinically available data were collected and systematized according to the target of our study. Based on the psychotic symptoms detected during their hospitalization (in the period mentioned above), and also psychotic symptoms in their medical history, we categorized bipolar patients into two groups consisting of currently psychotic or never-psychotic (control) patients. To this end, we excluded those patients who were not psychotic currently but whose medical history included psychotic episode(s).

During the investigation of hospital records, we gathered data concerning, for instance, age at onset, family history, psychotic symptoms, number of hospitalizations, psychiatric comorbidities and suicidal behaviour. Finally, we compared – with regards to the above listed aspects – the currently psychotic and the never-psychotic groups.

For the comparison of categorical variables and non-normally distributed continuous variables, Chi-square (or Fisher's exact) tests and Mann-Whitney U test were used, respectively. Normality of distribution was verified by the Kolmogorov-Smirnov test. Differences were considered significant at $p < 0.05$. Chi-square and Fisher's exact tests were conducted with the online calculators at <http://www.socscistatistics.com/tests/chisquare/Default2.aspx>

and <http://www.socscistatistics.com/tests/fisher/Default2.aspx>, respectively. Other calculations were performed using SPSS 24 software (IBM, USA).

The study protocol was approved by the local ethical committee.

RESULTS AND DISCUSSION

Eighty-nine patients (i.e., 24% of 365 patients enrolled) exhibited psychotic symptoms during the study period and – accordingly – comprised the “psychotic group” (Table 1). Throughout the study duration, we did not notice psychotic features for the remaining 276 patients; however, after examining the previous case-reports of these subjects, we determined that only 80 patients (22% of 365 patients enrolled) had never experienced psychotic symptoms. Accordingly, the “never-psychotic” group consisted of these 80 patients (Table 1).

Age and gender

The average ages of patients in the psychotic and never-psychotic groups are presented in Table 1. According to the results of Mann-Whitney U test, there was no significant difference between groups with respect to age. In the psychotic group, the average age of males and females were 52.5 and 54.9 years, respectively; whereas, in the never-psychotic group, the average age of males was 50.0, that of females was 57.1 years.

In the total sample of patients with BD a female predominance (66%) was found. According to the literature, the female-male proportion in BD-I is 1:1; however there is a slight female predominance in BD-II (Grande et al. 2016, Rihmer and Angst 2009). Since the contributions of patients with BD-I or -II were almost equal to the total sample (52% vs. 48%, respectively) it is not surprising that our total sample consists of more females than males. We have not found a significant difference in the male/female proportion between the psychotic and the never-psychotic groups (Table 1.). This is in line with previous results by others (Caldieraro et al. 2017, Hua et al. 2011, Keck et al. 2003, Mazzarini et al. 2010, Ozyildirim et al. 2010, Rende et al. 2006).

Bipolar-I/II distribution

Research has demonstrated that psychotic symptoms occur two to three times as frequently in BD-I as compared to BD-II (Brugue et al. 2008, Caldieraro et al. 2017, Goodwin & Jamison 2007, Serretti et al. 2002, Vieta et al. 1997). Consistent with previous findings, in our sample of patients with psychotic symptoms, the proportion of BD-I patients was higher than of BD-II patients (62% vs. 38%, respectively) and, in reverse, in the never-psychotic group the proportion of BD-I patients was lower than of BD-II patients (41% and 59%, respectively) (the difference in the proportions of subjects with BD-I or BD-II between the psychotic and never-psychotic groups was significant; $p < 0.01$) (Table 1.).

Table 1. Comparison of Clinical Characteristics in the psychotic and never-psychotic groups

	Psychotic group N (%)	Never-psychotic group N (%)	Total N (%)
Number of patients	89 (53%)	80 (47%)	169 (100%)
Female ^a	60 (67%)	52 (65%)	112 (66%)
Average age (and range) in years ^b	54.1 (27-75)	54.6 (23-85)	54.3 (23-85)
BD-I ^c	55 (62%)	33 (41%)	88 (52%)
BD-II ^c	34 (38%)	47(59%)	81 (48%)
Positive family history ^d	23 (26%)*	17 (21%)**	40 (24%)
Early onset (under 20 years) ^e	31 (35%)	6 (8%)	37 (22%)
Current episode of mania ^f	24 (27%)	12 (15%)	36 (21%)
Current episode of depression ^f	39 (44%)	22 (28%)	61 (36%)
Current mixed episode ^f	26 (29%)	46 (58%)	72 (43%)
Previous or current suicide attempt ^g	30 (34%)	11 (14%)	41 (24%)
Comorbid psychiatric disorders			
Personality disorder ^h	13 (15%)	4 (5%)	17 (10%)
Anxiety disorder ⁱ	13 (15%)	10 (13%)	23 (14%)
Alcohol-dependence ^j	18 (20%)	19 (24%)	37 (22%)
Sedative/hypnotics dependence ^k	0 (0%)	6 (8%)	6 (4%)
Illicit drug dependence ^l	0 (0%)	1 (1%)	1 (0.6%)
Number of hospitalizations (mean; range) ^m	11.9 (1-40)	8.3 (1-32)	10.2 (1-40)

All comparisons were made between psychotic and never-psychotic groups: ^a - $\chi^2=0.11$, $df=1$, $p=0.74$;

^b - Mann-Whitney $U=3726.5$, $p=0.6$; ^c - $\chi^2=7.13$, $df=1$, $p<0.01$; ^d - $\chi^2=0.49$, $df=1$, $p=0.48$; ^e - $\chi^2=18.40$; $df=1$, $p<0.0001$;

^f - $\chi^2=13.85$, $df=2$, $p<0.001$; ^g - $\chi^2=9.13$, $df=1$, $p<0.01$; ^h - $\chi^2=4.3$, $df=1$, $p=0.04$; ⁱ - $\chi^2=0.16$, $df=1$, $p=0.69$; ^j - $\chi^2=0.31$, $df=1$, $p=0.58$;

^k - Fisher's exact=0.01, $df=1$, $p<0.05$; ^l - Fisher's exact=0.47, $df=1$, $p>0.05$; ^m - Mann-Whitney $U= 2625.5$, $p=0.003$.

* In respect of affective disorders (bipolar, major depressive and schizoaffective disorders). Remark: 5 patients were found to have a family history of schizophrenia. ** In respect of affective disorders (bipolar, major depressive and schizoaffective disorder). Remark: in the non-psychotic group, there was no schizophrenia present in the family history.

Family history of affective disorders

Familial accumulation is one of the highest in bipolar affective disorder among all of the psychiatric diseases (BD is 8-10-times more frequent in the first-degree relatives of BD patients than in the members of general population) (Goodwin & Jamison 2007, Morley et al. 2004). Research suggests that about 7% of first degree-relatives of BD patients have also BD (Kelsoe 2003). It has also been established that unipolar major depressive disorder (MDD) is more frequent (about 2-3-times) in relatives of patients with BD than in members of the general population (Morley et al. 2004).

In accordance with the above data, we found a positive family history (within first-degree-relatives) for affective disorders (BD, MDD and schizoaffective disorder) in 24% of our total group of BD patients. Given that we have not restricted family history to BD (i.e., we have also considered family members with schizoaffective disorder and MDD), it is not surprising that the figure we found is somewhat higher than what has been reported previously only for BD among first-degree relatives.

In the group of psychotic subjects, positive family history for affective disorders among first-degree relatives was found in 23 (i.e., 26%) patients (in about half of these psychotic patients ($n=12$); however, the number

of first-degree relatives (i.e., sibling, child, parent) suffered from affective disorders was ≥ 2). In addition to familial history of affective disorders, 3 out of these 23 patients reported a history of schizophrenia in the family. Furthermore, there were 2 psychotic BD patients who had a positive family history for schizophrenia, but not for affective disorders. This finding is consistent with the well documented partially common genetic basis of BD and schizophrenia (Cardno & Owen 2014, Craddock & Sklar 2013, Goodwin & Jamison 2007).

Seventeen patients (21%) in the never-psychotic group had a positive family history in terms of affective disorders; whereas, in the cases of 3 out of these 17 patients (18%), the number of affected first-degree relatives was ≥ 2 . Schizophrenia did not occur among the first-degree relatives of members of the never-psychotic group.

Previous results on the association between psychotic symptoms in the context of BD and family history of affective disorders are inconsistent. Accordingly, some studies found that family members of non-psychotic BD subjects are more frequently affected by affective (Keck et al. 2003, Mazzarini et al. 2010, Ozyildirim et al. 2010) or by any psychiatric disorders (Mazzarini et al. 2010) than family members of psychotic BD patients. Other studies have reported that the presence (vs. the absence) of psychosis in BD is not associated with the

family history of depression or bipolar disorder (Caldieraro et al. 2017, Hua et al. 2011). Finally, results of one study indicated that MDD and mania more frequently occurred in the family members of those BD subjects with a lifetime history of psychosis (Rende et al. 2006). In our study, there was not a significant difference between the two groups (i.e., the psychotic and the never-psychotic) regarding positive family history of affective disorders in first degree-relatives ($p=0.48$).

Age of onset

Results of some, but not all (e.g. Benazzi 2000, Mazzarini et al. 2010, Ozyildirim et al. 2010, Perlis et al. 2004), investigations with various designs suggest that early disease onset in BD is associated with the presence of psychotic symptoms during the disease course (Azorin et al. 2013, Baldessarini et al. 2010, Caldieraro et al. 2017, Colom & Vieta 2009, Hua et al. 2011, Schurhoff et al. 2000, Suominen et al. 2007).

In our total sample, early disease onset, defined as the onset of BD at 20 years of age or younger, were found in 22% of patients. Of patients with psychotic symptoms, 35% had an early onset form of BD; whereas, the corresponding figure was only 7.5% in the group of never-psychotic patients; this difference proved to be highly significant ($p<0.0001$).

Psychotic symptoms during manic, depressive and mixed episodes

Prior research suggests that psychotic symptoms are more frequent during the manic than the depressive phases of BD (see discussed in the "Introduction" section). At the same time, in our sample, 67% and 64% of patients with manic and depressive episodes exhibited psychotic symptoms, respectively. This difference did not reach statistical significance (chi-square=0.07; $p=0.79$). A possible explanation of the higher than expected rate of psychotic symptoms among patients with depressive episode may be that only hospitalized patients were enrolled into our study. Accordingly, it can be assumed that in our sample there were patients with more severe depressed state than in those studies where non-hospitalized subjects were also enrolled. Studies have found that the rate of psychotic symptoms in mixed episodes can be as high than in mania (Fountoulakis 2015). In spite of this, in our sample, the rate of psychotic symptoms were found to be the lowest – out of the three episode types - in the mixed episode type (36%).

Psychiatric comorbidity

Psychiatric comorbidity is quite common (65-75%) in patients with BD (APA 2013, Asaad et al. 2014, Fountoulakis 2015, Goodwin & Jamison 2007, Grande et al. 2016). In our total sample, 63 patients (37%) had

at least one comorbid psychiatric condition. Accordingly, in our sample, the rate of comorbidity was somewhat lower than the figures often cited in the literature. There may be two reasons for this difference: 1) we collected data only on the occurrence of anxiety, personality and substance use disorders, but not on the occurrence of other types of psychiatric disorders (e.g., ADHD); 2) our data on comorbidity were derived from hospital documentations and not from structured clinical interviews.

Results on the association between psychotic features in patients with BD and the presence/frequency of psychiatric comorbidity are ambiguous, given that some studies (e.g. Asaad et al. 2014, Caldieraro et al. 2017, Hua et al. 2011, Rende et al. 2006) reported higher psychiatric comorbidity in psychotic BD (vs. non-psychotic BD), while others (e.g. Keck et al. 2003, Mazzarini et al. 2010) did not. With the exception of personality disorders, which were more common in the psychotic group, and sedative/hypnotics dependence, which were more common in the never-psychotic group ($p<0.05$ in both cases), we did not find significant differences in the frequencies of comorbidities between the two groups.

Suicide attempts

It is well-established that suicidal behaviour is common among patients with BD. Accordingly, up to 15% of BD patients take their own life, and about 50% of them make at least one suicide attempt in their lifetime. The suicide rate of (untreated) patients with BD is approximately 20–25 times higher than the corresponding rate of the general population (Grande et al. 2016, Rihmer & Dome 2016). In line with prior research, 24.3% of members in our total sample reported a suicide attempt (Table 1.). Several suicide risk factors have been identified in BP (see discussed in Gonda et al. 2012, Rihmer & Dome 2016). Results of some (Caetano et al. 2006, Caldieraro et al. 2017, Gonda et al. 2012; Rende et al. 2006, Rihmer and Dome 2016, Song et al. 2012), but not all (Black et al. 1988, Keck et al. 2003, Mazzarini et al. 2010, Seo et al. 2016), studies and literature reviews have indicated that one of these risk factors is the presence of psychotic symptoms in the context of a current or antecedent mood episode. Our results suggest that there is a difference between the two groups in this regard. Accordingly, in the psychotic group, 34% of BD patients had previously attempted suicide. This rate was significantly higher than in the never-psychotic group, where only 14% of BD patients had previous suicide attempts ($p<0.01$) (Table 1.).

Number of previous hospitalizations

Results of several studies suggest that the presence, compared to the absence of psychotic symptoms, during

mood episodes in the context of BD is associated with a higher number of hospitalizations (Bjorklund et al. 2017, Caetano et al. 2006, Hua et al. 2011, Mazzarini et al. 2010, Ozyildirim et al. 2010). At the same time, contradictory results may be found as well (e.g. Caldieraro et al. 2017).

Mean numbers of previous hospitalizations for our psychotic and never-psychotic groups are presented in Table 1. Results of Mann-Whitney U test demonstrated that the mean number of hospitalizations was significantly ($p=0.003$) higher in the psychotic compared to the never-psychotic group.

CONCLUSION

Although psychotic symptoms are frequently present in patients with BD (Fountoulakis 2015, Keck et al. 2003), their correlation with clinical features of BD is under-investigated and findings are not always conclusive. In order to further elucidate the association of psychotic symptoms with other features of BD, we compared two groups of BD patients; one consisted of subjects with current psychotic symptoms ($n=89$) while the other consisted subjects without current or previous psychotic mood episodes ($n=80$). As far as we know, this is the first such study from Hungary.

Our main findings are as follows: 1) the proportion of BD-I patients was higher than of BD-II patients in the psychotic group; whereas, the opposite was true for the never-psychotic group (the difference in the proportions of subjects with BD-I or BD-II between the psychotic and never-psychotic groups was significant; $p<0,01$); 2) sex ratios and the rates of positive family history for affective disorders were not significantly different between the two groups; 3) in the psychotic group (vs. the never-psychotic group), early age of onset was significantly more frequent; 4) personality disorders and sedative/hypnotics dependence were significantly more common in psychotic and never-psychotic groups, respectively; 5) rate of suicidality was significantly higher in psychotic than in the never-psychotic group; 6) number of hospitalizations was significantly higher in the psychotic compared to the never-psychotic group; 7) interestingly, in 5.6% of psychotic BD patients, schizophrenia was present among the family members; whereas, there was no schizophrenia among the first-degree relatives of never-psychotic patients.

Given that the study included a relatively small number of patients, and also the retrospective study design, the generalizability of our results is limited. Another possible limitation of our study that we excluded those 196 patients who did not have current psychotic symptoms, but who had psychotic symptoms in their medical history.

In conclusion, we have found that psychotic symptoms in the context of bipolar disorder are associated with several other aspects of BD. In general, our findings from Hungary are consistent with the results of studies from other countries.

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Conflict of interest:

Authors declare that the presented clinical epidemiological research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Contribution of individual authors:

Zsuzsanna Belteczki & Julia Ujvari: conducted patient enrollment, gathered clinical data and participated in the preparation of the manuscript;

Zoltan Rihmer & Peter Dome: designed the study, performed the statistical analysis and drafted the manuscript;

Dorian A. Lamis: DAL participated in the preparation of the manuscript.

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Correspondence:

Zsuzsanna Belteczki, MD
Santha Kalman Psychiatric Hospital
Szabadság ter 13, 4320, Nagykallo, Hungary
E-mail: belteczkizsuzsa@gmail.com