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Symptomatic differences and symptoms stability in unipolar and bipolar depression. Medical charts review in 99 inpatient

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Summary

Aim. Misdiagnosis of bipolar disorder may result in a non-optimal treatment, higher service costs and increase in the patient's suffering and risk of suicidal behavior. Lack of clinically approved and suitable for widely use biomarkers of BD led clinicians to focus on clinical course and symptomatology of depression in BD. The aim of this study was the retrospective evaluation of symptomatic differences and symptoms stability between MDD and BD patients during three subsequent depressive episodes in the inpatient setting.

Methods. Retrospective chart review of 99 patients with diagnosis of MDD and BD during three subsequent depressive episodes. Chi-squared test and logistic regression was used to analyze the symptomatic profile. Cohen's kappa value used to estimate symptoms stability.

Results. Statistical differences were observed in the case of 7 out of 22 depressive symptoms. Somatization (pain and non-pain complains), psychomotor agitation and pathological guilt were more frequent in MDD patients. Anhedonia, attention deficit, and suicidal ideation were more frequent in BD group. In MDD group relatively highest symptom stability was observed for somatization, middle insomnia, early wakening, and attention deficit. In BD group relatively highest symptom stability was observed for delusions, somatization (pain and non-pain complains), initial and middle insomnia, memory disturbance, psychomotor retardation, and pathological guilt.

Conclusions. The observed symptomatic differences may be an additional factor of MDD/DB differential diagnosis. Lower than previously reported symptoms stability highlights the need to evaluate more than one depressive episode in differential diagnosis.

Key words: unipolar depression, bipolar depression, symptoms

Introduction

Depression is one of the leading causes of disability worldwide, and according to WHO, by 2020 it is expected to be the second largest contributor to the world's disease burden [1]. The 1-year prevalence of unipolar depression (major depressive disorder – MDD) was estimated to be 4.1 per 100 with the lifetime prevalence of 6.7 per 100 [2]. Authors of World Mental Health Survey Initiative reported on 1-year prevalence of bipolar disorder (BD) to be 1.5 per 100 with the lifetime prevalence of 2.4 per 100 [3], but this data seems to be underestimated. The distinction between MDD and BD is based on the prevalence of hypomania/mania in the clinical course of the illness. For majority of bipolar patients the first episode is a depressive episode [4] and the average time from the onset of symptoms to the proper diagnosis of bipolar disorder can be as long as ten years [5, 6]. In the group observed by Hirschfeld et al. [7] 69% of bipolar patients received a primary incorrect diagnosis, of which 60% were diagnosed as MDD. Misdiagnosis of bipolarity may result in an inappropriate pharmacological treatment and yield higher costs for healthcare providers [8, 9]. Therefore, there is an urgent need for studies on predictors of bipolarity in depressive individuals.

A number of clinical features and depressive symptoms were proposed to determine the risk of bipolarity in patients with an episode of depression. A higher global severity of symptoms was observed more frequently in BD [10, 11] as well as in MDD [12]. Several authors observed melancholic features, decreased energy, irritability, pathological guilt, worthlessness, fatigue, and anhedonia more frequently in BD [13–19]. Similarly like atypical [18, 20, 21] and psychotic symptoms [11, 15, 17,22, 23]. Anxiety symptoms were observed more often in MDD [17, 24, 25]. Suicidal ideation was reported as more frequent in BD [12, 18, 26, 27], and more frequent in BD I in comparison to BD II individuals [27]. Inconsistent data concerns psychomotor agitation/retardation [10, 18, 28–31]; anger attacks and dysphoria [28, 32]; attention deficit [12, 18, 19, 33]; sleep disorders [12, 27, 34]; and appetite disturbance [19, 26, 35, 36]. Results of the Polish DEP-BI study [37] revealed that in the population of over 800 patients suffering from MDD and BD, in the BD group episodes with hypersomnia, increased appetite, psychotic features and treatment-resistance occurred more frequent that in the MDD group. The authors did not observe differences in prevalence of psychomotor agitation, attention deficit or panic attacks [38].

Difficulties to establish the symptomatic profile in BD and MDD may be related to methodological differences including incoherent criteria of bipolarity or a high rate of conversion from unipolar to bipolar diagnosis. Major depressive disorder is the most common misdiagnosis in bipolar disorder patients [7, 39, 40]. Conversion rate from MDD into BD was estimated in previous reports as approximately 1% annually [41], and the mean delay in the Polish population form the firsts symptoms to the proper diagnosis may be as long as 9.3 years [40]. Qualification of younger individuals into

the group of MDD poses a high risk of disfiguring of the real symptomatic differences between depression in BD and MDD. This is associated with a high risk of conversion of diagnosis into bipolar disorder, schizophrenia spectrum disorder or personality disorders. Similarly, qualification of older depressive individuals into MDD and BD groups poses a risk of including patients in whom symptoms may be due to the presence of early dementia. Another difficulty is related to uncertain stability of the symptoms during the consecutive depressive episodes [42, 43].

Most of the research concerning symptomatology of depression in BD and MDD patients is based on evaluation of single depressive episode. Minority include more than two episodes [33, 42–44]. For example, Perlis et al. [12] examined prospective data from a cohort of 3,750 individuals with bipolar I or II disorder participating in *the Systematic Treatment Enhancement Program for Bipolar Disorder* study, which experienced at least two depressive episodes during two years of follow-up. A total of 583 subjects experienced two episodes, 149 of those subjects experiencing a third one. Moderate temporal stability of dimensional structure of symptoms was observed. Greatest evidence of stability was observed for neurovegetative features, suicidality, and pathological guilt/rumination, while loss of interest and fatigue were not consistent across episodes. Authors emphasize significant stability of suicidal ideation across adjacent depressive episodes. Psychotic symptoms, though presented only in low number of patients, showed a relatively stability as well. The research carried out up to now are insufficient to answer the question on stability of symptoms and differences between BD and MDD groups of patients. As it has been showed in the previous results, diagnostic stability is greater for contiguous episodes than for noncontiguous episodes [33].

Aim

The aim of this study was the retrospective evaluation of symptomatic differences and stability of symptoms in 99 patients with MDD and BD, during three subsequent depressive episodes, including the attempt to determinate the pattern of specific symptoms during the subsequent episodes (hypothesis I) and analysis of the MDD/BD symptomatic differences in prevalence of specific symptoms (hypothesis II).

Material and methods

Data

Data analysis concerned the individuals hospitalized at least three times with separate depressive episodes. Detailed medical chart analysis enrolled 297 charts of 99 subjects (BD $n = 70$; MDD $n = 29$), aged 35–60 during the first analyzed depressive episode. 22 symptoms of depression were retrospectively evaluated based on medi-

cal charts (including medical and nursing documentation and attached psychometric tools and diagnostic scales). All subjects fulfilled major criteria for depression and were diagnosed with depression in MDD or BD according to ICD-10. On the basis of the literature review, the author's inventory of depressive symptoms was created in a form enabling comparison of data with previous research results [18, 40–45]. Psychotic symptoms in the form of delusions have been reported during hospitalization. Symptoms of somatization were divided into symptoms of pain somatization (pain without an obvious somatic cause) and symptoms of painless somatization (for example, feelings of chest pressure, neck pressure, head pressure, tingling or numbness). Irritability/dysphoria was treated as a symptom both when described by the investigator and in the form of patient complaints. Daily fluctuations (including morning deterioration) of symptoms and psychomotor agitation or slowdown were recorded based on the assessment of the treating physician. Presence of other symptoms, including, but not limited to sleep and appetite disorders, weight loss before hospitalization, memory disorders, attention deficit, deterioration of physical fitness, sense of anhedonia, indifference, guilt, suicidal thoughts – were assessed on the basis of entries in the documentation based on complaints of the respondents during the interviews with the respondents. Weight loss during hospitalization was assumed to be at least 1 kilogram in the first four weeks of hospitalization. Research protocol has been accepted by Bioethics Committee of Institute of Psychiatry and Neurology in Warsaw.

Subjects analysis (step I) concerned the individuals hospitalized in the Department of Affective Disorders of the Institute of Psychiatry and Neurology (IPIN) between 2000 and 2010, due to unipolar depression (n = 385) or bipolar disorder (n = 485). The further analysis (step II) concerned individuals hospitalized at least three times because of separate depressive episodes who had symptomatic remission in the periods between hospitalizations (MDD n = 121; BD n = 216). Subjects were excluded from the review if the diagnosis was changed at the end of the trial to other than bipolar disorder or unipolar depression. To the detailed (step III) medical chart analysis we enrolled 297 charts of 99 subjects (BD n = 70; MDD n = 29) aged 35–60 during the first analyzed depressive episode. The analysis of the clinical course and symptomatology of depression were based retrospectively on: (1) referral from the outpatient clinic; (2) emergency department psychiatric evaluation on admission; (3) copy of the previous medical charts; (4) evaluation of the present psychiatric condition by the attending psychiatrist on admission; (5) evaluation of the psychiatric condition by the consultants; (6) nursing documentation; (7) attached psychometric tools and scales; (8) resume of the hospitalization. Due to the naturalistic nature of the study, remission was defined as the entries in the medical records (during anamnesis and/or during subsequent mental health examinations) of asymptomatic periods preceding the analyzed episode, or disappearance of depressive symptoms during the analyzed episode.

Subjects

The whole sample consisted of 72 women (72.7%) and 27 men (27.3%), the unipolar group included 23 (79.3%) women and 6 men (20.7%), while the bipolar group included 49 women (70.0%) and 21 men (30.0%). Mean age of the subjects during the first analyzed depressive episode was 49.40 years (range 35–60). In the unipolar group – 50.76 (range: 38–59); in the bipolar group – 48.91 (range: 35–60). There were no statistically significant differences between the groups. The mean time-frame in which the analyzed episodes occurred (from the date of the first hospitalization to the end of the third hospitalization) in the MDD group was 47.33 months (SD = 25.44, in the range of 15–105 months), and in the BD group – 45.25 months (SD = 27.58, in the range of 12–113 months). The mean age of seeking medical treatment (defined as first contact with general practitioner or psychiatrist because of symptoms of depression) for the whole sample was 36.05 (range: 16–57). We observed a younger age of seeking medical treatment in the bipolar group than in the unipolar group (34.59 vs. 39.59; p = 0.006). The average lifetime number of psychiatric hospitalizations (at the time when the analysis was conducted) was 9.1 (SD = 7.6), higher in the bipolar group – 9.8 (SD = 8.19) vs. unipolar group – 7.41 (SD = 5.74). The average lifetime number of depressive episodes was also higher in the bipolar group – 9.44 (SD = 6.3) vs. 6.24 (SD = 2.92). The average lifetime number of hypomanic and manic episodes in the BD group was 4.81 (SD = 4.69, in the range of 1–25).

Statistical analysis

For the comparison of symptoms differences between BD and MDD patients, the Chi-squared test and logistic regression were used. In the logit model, in the first stage, univariate analysis was performed at the significance level of 0.1. Then, the factors, for which the p-value was less than 0.1, were included in to the logit model. Final model was matched by the backward stepwise manner for the exclusion level of 0.1. For symptoms stability during the subsequent depressive episodes, to keep comparability with previous reports, we calculated Cohen's weighted kappa. Analysis of variance (ANOVA) was used for variables of age of onset and age at the time of the first analyzed depressive episode. Threshold of p = 0.05 was used to indicate a statistically significant difference.

Results

Prevalence of depressive symptoms

In the MDD group, a psychomotor retardation and worthlessness were the most prevalent symptoms during the first analyzed depressive episode. A high prevalence was observed for attention deficit. During the second depressive episode,

a high rate of prevalence was observed for psychomotor retardation and agitation, middle insomnia, appetite loss, worthlessness, and pathological guilt. During the third depressive episode: a psychomotor retardation, psychomotor agitation, initial insomnia, appetite loss, attention deficit, worsening of physical fitness, anhedonia, and worthlessness.

In the BD group, the most prevalent symptom in each depressive episode was a psychomotor retardation. A high rate of prevalence was observed for: initial insomnia, middle insomnia, appetite loss, attention deficit, anhedonia, and worthlessness – in the first analyzed episode; initial insomnia, appetite loss, attention deficit, anhedonia – in the second analyzed episode; initial insomnia, middle insomnia, appetite loss, attention deficit, anhedonia, and worthlessness – in the third analyzed episode. Data are summarized in Table 1.

Table 1. **Prevalence of depressive symptoms among unipolar (MDD) and bipolar (BD) patients during three subsequent depressive episodes. Pearson's Chi-squared test**

Symptoms:	Episode I			Episode II			Episode III		
	MDD	BD	p	MDD	BD	p	MDD	BD	p
Delusions	13.80%	17.10%	0.680	6.90%	11.4%	0.496	13.80%	11.4%	0.743
Somatization, pain complains	44.80%	20.00%	0.012*	51.70%	31.4%	0.057	41.40%	20.0%	0.078
Somatization, non-pain complains	55.20%	35.7%	0.074	51.70%	32.9%	0.079	48.30%	21.4%	0.008*
Irritability/dysphoria	6.90%	22.9%	0.061	6.90%	21.4%	0.081	6.90%	18.6%	0.140
Morning worsening	37.90%	40.0%	0.848	44.80%	35.7%	0.396	20.70%	32.9%	0.226
Psychomotor agitation	41.40%	28.6%	0.215	69.00%	37.1%	0.004*	69.00%	47.1%	0.048*
Initial insomnia	58.60%	67.1%	0.420	58.60%	67.1%	0.420	69.00%	72.9%	0.696
Middle insomnia	51.70%	67.1%	0.149	62.10%	58.6%	0.747	51.70%	64.3%	0.244
Early morning wakening	51.70%	50.0%	0.876	27.60%	35.7%	0.435	31.00%	37.1%	0.563
Drowsiness	10.30%	14.3%	0.597	10.30%	7.1%	0.595	6.90%	11.4%	0.496
Appetite loss	58.60%	71.4%	0.215	65.50%	68.6%	0.767	65.50%	67.1%	0.876
Weight loss before admission	31.00%	35.7%	0.655	17.20%	14.3%	0.709	17.20%	28.6%	0.238
Weight loss during hospitalization	10.30%	22.9%	0.117	20.70%	17.1%	0.677	13.80%	20.0%	0.466
Attention deficit	65.50%	72.9%	0.465	48.30%	78.6%	0.003*	62.10%	72.9%	0.288
Memory disturbance	37.90%	34.3%	0.730	20.70%	21.4%	0.935	20.70%	21.4%	0.935
Psychomotor retardation	72.40%	78.6%	0.509	82.80%	81.4%	0.876	79.30%	84.3%	0.550
Worsening of physical fitness	55.20%	50.0%	0.639	51.70%	55.7%	0.717	62.10%	51.4%	0.333
Anhedonia	37.90%	68.6%	0.005*	51.70%	64.3%	0.244	44.80%	62.9%	0.099
Less interest	51.70%	60.0%	0.448	58.60%	64.3%	0.596	65.50%	58.6%	0.520
Pathological guilt	58.60%	41.4%	0.119	62.10%	38.6%	0.033*	44.80%	47.1%	0.834

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Worthlessness	72.40%	62.9%	0.362	72.40%	58.6%	0.195	65.50%	61.4%	0.775
Suicidal ideation	41.40%	52.9%	0.299	37.90%	38.6%	0.952	27.60%	52.9%	0.022*

* $p \leq 0.05$

Symptomatic differences between unipolar and bipolar depression

The logistic regression was performed for each episode separately (Table 2). Features of somatization (pain and non-pain complaints) during each episode differentiate BD/MDD subjects (OR: 0.3; 0.16; 0.32). As additional differential factors have been indicated: irritability/dysphoria (episode I, OR: 5.016; episode II, OR: 4.324), anhedonia (episode I, OR: 3.773), attention deficit (episode II, OR: 7.741), pathological guilt (episode II, OR: 0.34), and suicidal ideation (episode III, OR: 2.662).

Table 2. **Logistic regression of symptomatic differences MDD vs. BD**

Symptoms	b value	Standard deviation	Wald's statistic	p value	Odds ratio
Depressive episode I					
Somatization, pain complains	-1.189	0.52	5.260	0.02	0.3
Irritability/dysphoria	1.613	0.83	3.798	0.05	5.016
Anhedonia	1.328	0.49	7.315	0.01	3.773
Mean	0.32	0.39	0.66	0.42	1.38
Depressive episode II					
Somatization, pain complains	-1.812	0.63	8.249	0.004	0.16
Irritability/dysphoria	1.464	0.84	3.033	0.008	4.324
Attention deficit	2.047	0.64	10.212	0.001	7.741
Pathological guilt	-1.074	0.52	4.322	0.04	0.34
Mean	0.67	0.49	1.905	0.17	1.958
Depressive episode III					
Somatization, non-pain complains	-1.138	0.48	5.530	0.02	0.32
Suicidal ideation	0.98	0.49	3.942	0.005	2.662
Mean	0.88	0.35	6.442	0.01	2.406

Stability of depressive symptoms

For the value of the kappa compliance factor, the following compatibility (repeatability) ranges have been assumed according to Landis and Koch [46]: 0–0.2 low compliance; 0.21–0.4 satisfactory compliance; 0.41–0.6 moderate compliance; 0.61–0.8

high compliance; above 0.81 very high compliance. In the analyzed material, both in the MDD and BD group, satisfactory or moderate repeatability of symptoms dominated in subsequent episodes of depression. Thus, it was not possible to determine a constant pattern of depressive symptoms (expressed in high repeatability of specific symptoms) in the course of MDD and BD, during subsequent analyzed episodes.

In the MDD group, highest symptom stability was observed for somatization (non-pain complains), middle insomnia, early wakening, attention deficit, anhedonia, pathological guilt, and worthlessness (Table 3). In the BD group, highest symptom stability was observed for delusions, somatization (pain and non-pain complains), initial and middle insomnia, memory disturbance, psychomotor retardation, and pathological guilt. Analysis revealed Cohen's kappa measure lower than 0.6 in all cases. (Table 4).

Table 3. **Stability of symptoms during three subsequent depressive episodes in the MDD group. Cohen's kappa value**

Symptoms	Prevalence			Stability episode I vs. II		Stability episode I vs. III		Stability episode II vs. III	
	Episode I	Episode II	Episode III phase	kappa	p	kappa	p	kappa	p
Delusions	13.80%	6.90%	13.80%	-0.101	0.558	0.130	0.484	0.266	0.124
Somatization, pain complains	44.80%	51.70%	41.40%	0.175	0.340	0.368	0.047	0.246	0.176
Somatization, non-pain complains	55.20%	51.70%	48.30%	0.516	0.005	0.450	0.014	0.380	0.040
Irritability/dysphoria	6.90%	6.90%	6.90%	-0.074	0.690	-0.074	0.690	0.463	0.013
Morning worsening	37.90%	44.80%	20.70%	-0.273	0.137	0.277	0.103	0.046	0.775
Psychomotor agitation	41.40%	69.00%	69.00%	0.223	0.160	0.094	0.555	0.356	0.056
Initial insomnia	58.60%	58.60%	69.00%	0.289	0.119	0.336	0.064	0.336	0.064
Middle insomnia	51.70%	62.10%	51.70%	0.513	0.005	0.171	0.356	0.513	0.005
Early morning wakening	51.70%	27.60%	31.00%	0.253	0.122	0.455	0.007	0.418	0.024
Drowsiness	10.30%	10.30%	6.90%	0.628	0.001	0.346	0.056	0.346	0.056
Appetite loss	58.60%	65.50%	65.50%	-0.020	0.913	0.271	0.140	0.389	0.036
Weight loss before admission	31.00%	17.20%	17.20%	0.082	0.634	0.082	0.634	0.033	0.858
Weight loss during hospitalization	10.30%	20.70%	13.80%	0.112	0.342	0.237	0.046	0.057	0.634
Attention deficit	65.50%	48.30%	62.10%	0.249	0.153	0.627	0.001	0.453	0.011

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Memory disturbance	37.90%	20.70%	20.70%	0.277	0.103	0.277	0.103	0.159	0.391
Psychomotor retardation	72.40%	82.80%	79.30%	0.316	0.075	0.252	0.168	-0.008	0.967
Worsening of physical fitness	55.20%	51.70%	62.10%	0.377	0.042	0.151	0.411	0.374	0.039
Anhedonia	37.90%	51.70%	44.80%	0.590	0.001	0.151	0.411	0.313	0.089
Loss of interest	51.70%	58.60%	65.50%	0.306	0.096	0.442	0.013	0.417	0.023
Pathological guilt	58.60%	62.10%	44.80%	0.496	0.007	0.187	0.296	0.529	0.002
Worthlessness	72.40%	72.40%	65.50%	0.827	0.000	0.519	0.005	0.680	0.000
Suicidal ideation	41.40%	37.90%	27.60%	0.352	0.057	0.402	0.023	0.304	0.092

Kappa value between 0.4 and 0.6 is marked in light grey; Kappa value > 0.6 is marked in dark grey

Table 4. **Stability of symptoms during three subsequent depressive episodes in the BD group. Cohen's kappa value**

Symptoms	Prevalence			Stability episode I vs. II		Stability episode I vs. III		Stability episode II vs. III	
	Episode I	Episode II	Episode III	kappa	p	kappa	p	kappa	p
Delusions	17.10%	11.4%	11.4%	0.305	0.009	0.305	0.009	0.435	0.000
Somatization, pain complains	20.00%	31.4%	20.0%	0.412	0.000	0.267	0.021	0.355	0.001
Somatization, non-pain complains	35.7%	32.9%	21.4%	0.430	0.000	0.317	0.005	0.218	0.057
Irritability/dysphoria	22.9%	21.4%	18.6%	0.213	0.074	0.263	0.027	0.376	0.002
Morning worsening	40.0%	35.7%	32.9%	0.364	0.002	0.110	0.350	0.303	0.011
Psychomotor agitation	28.6%	37.1%	47.1%	0.229	0.051	0.033	0.762	0.217	0.064
Initial insomnia	67.1%	67.1%	72.9%	0.288	0.016	0.458	0.000	0.322	0.006
Middle insomnia	67.1%	58.6%	64.3%	0.332	0.005	0.367	0.002	0.519	0.000
Early morning wakening	50.0%	35.7%	37.1%	0.086	0.454	0.114	0.322	0.229	0.055
Drowsiness	14.3%	7.1%	11.4%	0.042	0.705	0.236	0.046	0.241	0.037
Appetite loss	71.4%	68.6%	67.1%	0.117	0.329	0.163	0.171	0.378	0.002
Weight loss before admission	35.7%	14.3%	28.6%	0.103	0.309	-0.009	0.937	0.176	0.105
Weight loss during hospitalization	22.9%	17.1%	20.0%	0.298	0.061	-0.137	0.405	0.041	0.819
Attention deficit	72.9%	78.6%	72.9%	0.227	0.055	0.278	0.020	-0.006	0.963
Memory disturbance	34.3%	21.4%	21.4%	0.269	0.018	0.199	0.080	0.406	0.001
Psychomotor retardation	78.6%	81.4%	84.3%	0.465	0.000	0.248	0.034	0.397	0.001

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Worsening of physical fitness	50.0%	55.7%	51.4%	0.314	0.008	0.343	0.004	0.283	0.017
Anhedonia	68.6%	64.3%	62.9%	0.073	0.539	0.116	0.330	0.167	0.161
Loss of interest	60.0%	64.3%	58.6%	0.364	0.002	0.083	0.488	0.279	0.019
Pathological guilt	41.4%	38.6%	47.1%	0.286	0.016	0.308	0.010	0.537	0.000
Worthlessness	62.9%	58.6%	61.4%	0.193	0.105	0.180	0.131	0.346	0.004
Suicidal ideation	52.9%	38.6%	52.9%	0.098	0.395	0.140	0.241	0.154	0.180

Kappa value between 0.4 and 0.6 is marked in light grey

Discussion

The analysis of the course of the illness in the study group showed that the mean age for seeking for medical treatment due to the symptoms of depression was 36.05 (for BD 34.59, for MDD 39.59, respectively; $p = 0.006$). However, it cannot be excluded that the symptoms of mood disorders occurred significantly earlier, as indicated by data from the literature. The majority of authors claim that the first symptoms of the illness occur in patients with BD about 10 years earlier than in patients with MDD [36, 47, 48], and that the first symptoms of BD usually occur between 15 and 25 years of age [49]. Our results confirm previous observations in which the period from the onset of the first symptoms to the initiation of treatment for BD was estimated at 5–10 years [50]. Taking into account the clinical characteristics of the study group (three episodes over an average period of 4 years), the results we observed confirm data concerning the negative impact of late initiation of treatment on the course of BD, including the risk of hospitalization [51, 52].

The results of the statistical analysis of symptomatic differences between BD and MDD demonstrated that MDD was more associated with the features of somatization (pain and non-pain). This confirms earlier findings of, among others, Potter [24], Mitchell and Malhi [34], Perlis et al. [12]. The rate of prevalence of somatization symptoms was close to that reported by Bair et al. [53]. Somatization is often conceptualized as an expression of anxiety. Our results confirm indirectly the previously published reports [17, 24, 25] on a higher prevalence of anxiety in MDD. Symptoms of somatization may be a valid discriminator between MDD and BD. What is interesting, the prevalence of the features of somatization discriminated BD/MDD patients regardless of the illness duration, during each of the subsequent episodes. Prevalence of irritability/dysphoria was significantly higher in BD in our group – as in previous reports of Benazzi et al. [19] and Moreno et al. [27], but with a higher rate of the general prevalence. Observed differences concern all of the analyzed episodes, in the first two on the level of statistical significance. The discrepancy may be due to cultural differences in the classification of behavior as dysphoric. Our results suggest that irritability/dysphoria may be an

additional predictor of bipolarity – similar to Perlis et al. [32], what was not observed in the Polish DEP-BI study [37].

Complaints on cognitive functions deficit is common in depressive individuals. In the study group, complaints on anhedonia and attention deficit were observed more often in BD. In our group the prevalence rate was lower than in the previous reports [18, 27]. There were no clear differences regarding complaints on memory disturbance, which may occur due to the age restriction. While the prevalence of complaints about memory disorders was similar between the two groups in the course of three subsequent episodes, the prevalence of complaints about the attention deficit differed most clearly between patients with BD and patients with MDD in the second analyzed episode, where the proportion of these complaints in the MDD group was lower than in the other episodes. It cannot be ruled out that for MDD patients, the severity of attention distress correlates less with the duration of the illness and the number of episodes. As in previous reports [18, 26, 27], suicidal thoughts were more common in patients with BD during each of the analyzed episodes. The rate of suicidal ideation was surprisingly low, considering the fact that our group included inpatients. A possible explanation is a low reporting rate, even in the inpatient setting. There was a tendency towards decrease in the prevalence of suicidal thoughts in the MDD group (41.4% – episode I, 37.9% – episode II, 27.6% – episode III), which may indicate, among others, the effectiveness of therapeutic management. Such correlation was not observed in the BD group, where the occurrence of suicidal thoughts does not seem to correlate significantly with the number of episodes.

Pathological guilt was observed more frequently in MDD during episode I and II, while during the episode III in the BD group. The symptomatic analysis of our group did not confirm any significant differences in the prevalence of psychotic features (depressive delusions) [11, 15, 17, 20] or sleep or appetite disturbance, opposite to several reports. There were no clear-cut differences in the prevalence of features of melancholia, defined as a symptomatic complex of psychomotor disturbance, anhedonia, initial insomnia, morning worsening of symptoms, pathological guilt, and appetite loss.

To sum up, the results of the analyzed material indicate that pathological guilt and somatization symptoms, both painful and non-painful (more prevalent in MDD), as well as irritability/dysphoria, anhedonia, attention deficit, and suicidal thoughts (more prevalent in BD), may be helpful in MDD/BD differentiation. In the analyzed material, somatization symptoms most significantly differentiated patients with MDD from those with BD.

In both groups, BD and MDD, we observed satisfactory or moderate stability of symptoms. For example, in the BD group none of the analyzed symptoms showed higher kappa than > 0.61 (according to Landis and Koch [46]: 0.61–0.8 – high compliance). Our results partially confirm the previous observations. In group of 78 inpatients

with MDD, Quendo et al. [43] reported low symptoms stability across two subsequent depressive episodes. The most robust stability was noticed for anxiety and suicidal thoughts, while moderate stability was noticed for only few depressive symptoms. The authors concluded on instability of symptoms in recurrent major depression. Paykel et al. [45] among 28 depressive symptoms in MDD patients identified moderate stability of just few symptoms. In our group, the features of somatization, pathological guilt, sleep disturbance, and cognitive deficit (memory disturbance and attention deficit) demonstrated relatively highest stability. Somatization and pathological guilt were relatively stable in both MDD and BD patients.

Among sleeping disturbances most stable were initial and middle insomnia (in the BD group) and middle insomnia (in the MDD group). As the manner of the study was naturalistic, it is impossible to exclude influence of medications on the symptomatic profile of depression in both groups, especially tranquillizers and sleeping medications – what may have a significant impact especially on initial insomnia. Use of sleeping medication is common in clinical practice, therefore analysis of sleep pattern in the clinical setting in relation to phenomenology of depression may have a minor value.

Relatively high stability, higher than in other reports [45], was demonstrated for memory disturbance and attention deficit. In particular, prevalence of attention deficit was over 70% in all three subsequent episodes in the BD group. Higher rate of suicide ideation among bipolar patients is well known and proven [12, 27]. We did not observe high stability for suicidal ideations in BD, previously reported by Quendo et al. [43], Perlis et al. [12] and Williams et al. [54]. Prevalence of suicidal ideation decreased during subsequent episodes in the MDD group, but not in the BD group. Suicide ideation observed in bipolar patients in our group seems to occur independently of presence of suicidal ideation in the past (kappa value for subsequent episodes: 0.098, 0.140, 0.154).

Similar, high stability of neurovegetative symptoms in our group was not confirmed, contrary to Nierenberg et al. [42]. So-called 'atypical symptoms', such as psychomotor agitation and drowsiness, in our group were not more frequent in BD vs. MDD, and their stability across episodes was moderate. In the literature, there are reports which indicate that atypical symptoms occur more likely in the course of bipolar disorder vs. MDD, which was not confirmed in our report. Potential explanation may be related to clinical presentation of atypical depression, which is not often treated in hospital setting due to lower symptomatic severity and minor social impairment.

High dispersion of the results for melancholic features (anhedonia, morning worsening, early morning weakening, pathological guilt, psychomotor disturbance, appetite loss, and weight loss) preclude dependable conclusions. We have not been able to particularize any specific pattern of melancholic features. It is consistent with the results of Coryell et al. [33], who assessed stability of the depression subtype diagnosed during first episode in the group of 424 patients diagnosed with BD, MDD

or schizoafective disorder in 8-year follow-up. The highest stability was observed for psychotic subtype of depression, only moderate effect was observed for subtypes characterized by psychomotor disturbance and endogenous syndrome.

Stability of depressive delusions and irritability/dysphoria in our group was higher in BD than in MDD, which is consistent with previous results [12]. However, the occurrence of psychotic symptoms as compared to other symptoms was not characterized by significantly higher stability. This is in line with previous observations of Winokur et al. [44], who reported low repeatability of psychotic symptoms during subsequent episodes of depression.

The aim of the repeatability analysis was to determine a constant pattern of depressive symptoms (expressed in high repeatability of individual symptoms) in the course of MDD and BD during subsequent analyzed episodes. However, the satisfactory or moderate repeatability of most symptoms during the analyzed episodes suggests that the symptomatology of subsequent episodes of depression is highly heterogeneous. The observed differences concerned episodes which occurred on average time-frame of less than 4 years, so covered relatively short period when compared to the average duration of MDD or BD in the lifespan. We cannot exclude that a more fixed pattern of depressive symptoms in MDD/BD could be established by analyzing more episodes of depression. Similarly, the prospective nature of future research would make it possible to increase the relevance of observations. However, the results of our study call into question the validity of symptomatic MDD/BD differentiation attempts based on a single episode of depression.

Conclusions

1. Occurrence of pathological guilt and somatization symptoms, both painful and non-painful, as well as irritability/dysphoria, anhedonia, attention deficit, and suicidal thoughts may be helpful in MDD/BD differentiation.
2. In the analyzed material, somatization symptoms most significantly differentiated patients with MDD from those with BD. However, due to the satisfactory or moderate stability of depressive symptoms in the analyzed groups, this conclusion needs to be verified in subsequent samples.
3. In the analyzed material, both in the BD and MDD groups, prevailed satisfactory or moderate repeatability of symptoms in subsequent episodes of depression, which indicates the high heterogeneity of symptomatology of subsequent depressive episodes. Thus, it was not possible to determine a constant pattern of depressive symptoms (expressed in high repeatability of individual symptoms) in the course of MDD and BD during subsequent analyzed episodes.
4. Stability of depressive symptoms Lower than previously reported calls into question the validity of attempts to MDD/BD clinical differentiation on the basis of symptomatology of a single episode.

5. Further prospective research on large sample of BD/MDD patients are needed to define symptomatic differences and stability of symptoms in BD and MDD.

Limitations

Obvious limitation of our study is a retrospective design. Number of subsequent depressive episodes restricted to three may not give the clear pattern of symptoms stability. Lack of correlation of prevalence of depressive symptoms with general severity of depression is an additional limitation, which also results from a retrospective design of the study. Due to the same reason, it is impossible to exclude influence of medications on the symptomatic profile of depression in both groups, especially tranquillizers and sleeping medications.

The aim of our study was to determine the differences in the prevalence and repeatability of depressive symptoms. The obtained results, including those concerning the stability and prevalence of symptoms, in many dimensions do not coincide with the results obtained by other research teams, including those from prospective studies. However, it should be emphasized that due to the necessary long follow-up period required by prospective studies of this type, the availability of literature data is limited and the problem of repeatability of symptoms in subsequent depressive episodes is not fully recognized.

Due to the naturalistic, retrospective nature of the study and the characteristics of the study group (e.g., the age criterion applied, hospitalized patients, centre receiving drug-resistant patients referred from other hospitals), direct cause and effect reasoning and reference to the whole population is not possible. In particular, the prevalence and repeatability of symptoms that may be important in differentiating BD and MDD need to be confirmed. Thus, it is necessary to confirm the conclusions resulting from the presented analysis in subsequent, comprehensive prospective studies conducted on a larger group. Despite the obvious limitations of the study, we hope that the presented results will contribute to a deeper discussion on the symptomatology of depression.

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Disclosure of Interest

The authors report no conflicts of interest.

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