Archives of Psychiatry and Psychotherapy, 2009; 2: 69–78

RESEARCH

q1Bipolar spectrum features in drug resistant unipolar depression patients : TRES-DEP pilot study

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Summary

Aim. The aim this pilot study of the all-Polish multicenter TRES-DEP (Treatment Resistant Depression) project was the detection and analysis of bipolar spectrum features in drug-resistant (DR) patients with unipolar depression in comparison with patients who responded to standard antidepressant treatment and remitted (non-drug-resistant-non-DR).

Method. Fifty DR patients (group 1) and 50 non-DR patients (group 2), aged 18-65 years, fulfilling ICD-10 / DSM-IV criteria for depressive episode or recurrent depressive disorder, were included in the study. The presence of bipolar spectrum (BS) was detected by the Mood Disorder Questionnaire (MDQ) and the Hypomania Checklist Scale (HCL-32).

Results. There were statistically significantly more patients fulfilling BS criteria as assessed with MDQ or HCL-32 in group 1 than in group 2 (44% vs 12%, $p < 0.001$ and 62% vs 34%, $p < 0.005$ respectively). Significantly more DR patients, compared to non-DR patients, considered their last remission as partial (88% vs 52%, $p = 0.001$). Non-DR patients had a history of fewer depressive episodes (5.1 ± 3.8 vs 8.5 ± 5.0; $p = 0.001$) and reported a longer time since the last hospitalization (41.9 ± 17.1 vs 14.8 ± 26.5 months, $p< 0.005$). More DR patients fulfilling MDQ BS criteria (MDQ(+)) compared to DR patients without bipolar spectrum considered the last remission as partial or reported lack of remission (100% vs 21%; $p < 0.05$) or reported treatment nonadherence (41 vs 18%, $p = 0.055$). More MDQ(+) DR patients had occurrences of suicide attempts (41% vs 18%, $p = 0.055$) and a mean number of suicide attempts was higher in this group (0.86 ± 1.28 vs 0.25 ± 0.59; $p < 0.05$).

Conclusion. The results of the study suggest that misdiagnosed and inadequately treated bipolarity may be one of the main reasons for non-response in the treatment of depression with antidepressant drugs.

bipolar disorder / drug-resistant depression, bipolar spectrum / Mood Disorder Questionnaire / Hypomania Check List-32

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This research has not been aided by any grant.

INTRODUCTION

A growing body of evidence suggests that undiagnosed and therefore inadequately treated bipolarity may be one of the most important causes of drug resistance in depression diagnosed as unipolar. The results of the Polish multicenter DEP-BI study showed that a significant majority of patients treated for either a depressive episode or recurrent depressive disorder present different forms of bipolar dis-

order (BD) [1, 2]. Such patients were more often drug resistant. [3]. Other trials have also revealed bipolar features in drug-resistant depressive patients [4, 5, 6, 7]. The need for further and more detailed research into this problem was the basis for the multicenter all-Polish Treatment Resistant Depression Project (TRES-DEP). The main aim of TRES-DEP was analysis of the bipolar features in a group of drug resistant patients with unipolar depression in comparison to depressive patients who responded to standard antidepressant treatment and remitted. The demographic and clinical characteristics of the drug-resistant patient group was also described.

The following paper presents the pilot results of the TRES-DEP project.

MATERIAL AND METHODS

Fifty drug-resistant (group 1) and 50 non-drug-resistant (group 2, control group) patients, aged 18-65 years fulfilling ICD-10 / DSM-IV criteria for depressive episode or recurrent depressive disorder were included in the study. The main exclusion criteria were: treatment with mood stabilizers, the diagnosis of substance misuse, dementia, and the diagnosis of severe neurological or somatic disease. Patients who scored > 18 points on the Hamilton Depression Rating Scale were also not included in the study in order avoid the risk of false negative results in bipolar detection tools due to severe depressive state. Patients were interviewed using clinical and sociodemographic questionnaires. The severity of depressive symptoms was measured by the 17-item Hamilton Depression Rating Scale (HDRS-17) [8, 9, 10]. Bipolar features were detected using the Mood Disorder Questionnaire (MDQ, by Hirschfeld et al) [11, 12] as well as the Hypomania Check-List (HCL-32, by Angst et al) [13].

Drug-resistance was defined as a lack of significant clinical improvement after at least two treatment trials with antidepressants applied through a suitable period of time (min. 4 weeks) and in suitable doses [14, 15]. Group 2 (gr. 2, N = 50) consisted of patients who did not show drug-resistance in previous depressive episodes and who achieved symptomatic and clinical remission during the last or current depressive episode (< 7 points in HDRS17).

Presence of the bipolar spectrum detected by MDQ was defined as at least 7 positive ("yes") answers in the first part of the MDQ including 13 questions concerning manic / hypomanic symptoms plus the occurrence of at least two of them in the same period of the patient's life as well as any moderate or serious problems which these symptoms cause for the patient [11, 12]. The HCL-32 bipolar spectrum criterion used in the study was 14 or more positive answers ("yes") [13].

The statistical analysis of the quantitative data was examined with descriptive statistics (median, mean, standard deviation) and boxplots. If the normality and equality of variance assumptions were present (Shapiro-Wilk test), a t-test was performed. If the assumptions were not met, a non-parametric test was used (Mann Whitney U test or Wilcoxon rank-sum test). The chi^2 test was performed for the analysis of qualitative differences between groups. A p value of < 0.05 was considered statistically significant [16, 17, 18].

RESULTS

1. Sociodemographic characteristics

The mean age (± SD) in the drug resistant group was significantly higher than in control group. There were no significant differences in the male/female ratio between group 1 (1/4) and group 2 (6/19), (Chi^2 test) in addition to there being no other statistically significant differences between the groups according to sociodemographic parameters /variables such as: marital state, number of children, education level, or occupational status (Tab. 1).

2. Clinical characteristics (disease course, current depression episode)

Taking into account the course of the disease, patients in group 1 were ill for an average of 10.7 ± 7.7 years, while patients in group 2 for 8.5 ± 6.7 of years but the difference was statis-

tically not significant. The age at the onset of the illness in both groups wasn't significantly different. Moreover, in both groups the number of patients with early onset of disease (before 25) was similar (Tab. 2).

The average number of previous episodes of depression was significantly larger in the treatment resistant than in the control group. There were no statistically significant differences between groups with respect to the number of hospitalized individuals (as reported during interview) and the average number of hospitalizations. However, the time since the last hospitalization was significantly longer in the group of non drug-resistant patients in comparison to the drug-resistant patient group. Patients from group 1 more frequently estimated their last remission as incomplete. There were no significant differences between groups in different aspects of compliance, i.e. unauthorized discontinuation of treatment or modification of doses. The groups did not differ statistically in the number of suicide attempts or ideations in the history as well as in comorbidity with somatic illness (Tab. 2).

Patients from group 2 more frequently reported a lack of family history of mental disorders than treatment-resistant patients (group 1). Family history of depression, schizophrenia, anxiety disorders, suicides, and BD did not differentiate between the groups. BD occurrence in the family was reported by only one person in group 1 and one in group 2. However, a family burden of alcohol abuse was statistically more frequent in the drug-resistant patient group than in the control group (Tab. 2).

The duration of the current depressive episode was statistically longer in the treatment –resistant group (group 1) than in the group 2 (Tab. 3).

There were no significant differences between groups in frequency of occurrence of suicidal thoughts and suicidal tendencies during the course of the episodes (Tab. 3).

Table 1. Selected sociodemographic data in groups 1 and 2

	Gr.1 n = 50	Gr.2 n = 50	Gr.1 vs Gr.2 p
			t-Test
Age	**49.0± 7.5**	**45.4 ± 9.6**	**0.037**
Number of children	1.7 ± 1.2	1.4 ± 1.1	NS
			Chi^2-Test
Sex	M n = 10 (20%) F n = 40 (80%)	M n = 12 (24%) F n = 38 (76%)	NS
Marital status	Yes n = 37 (74%) No n = 13 (26%)	Yes n = 0 (60%) No n = 20 (40%)	NS
Education level	primary 14% vocational 10% secondary 48% higher 28%	primary 10% vocational 20% secondary 42% higher 28%	NS NS NS NS
Working	n = 18 (36%)	n = 20 (40%)	NS
Pension	n = 25 (50%)	n = 2 0 (40%)	NS

3. Occurrence of bipolar features in studied groups

In the drug-resistant patient group (group 1), the MDQ bipolar spectrum criteria were fulfilled by significantly more individuals than in the non-drug-resistant group (group 2) . Among the drug-resistant patients, too, more individuals fulfilled the bipolar features criteria by the HCL-32 in comparison to the drug-resistant patients. Similarly, applying the criteria of both tests simultaneously, the number of patients with bipolar spectrum features was significantly greater in group 1 than in group 2. (Tab. 4)

Table 2. Selected clinical data regarding the course of the illness in groups 1 an 2

	Gr 1 n = 50	Gr 2 n = 50	Gr 1 vs Gr 2 p
			t-Test
Time since the beginning of illness (years)	10.7 ± 7.7	8.5 ± 6.7	NS
Age at onset of illness	38.4 ± 8.5	36.9 ± 10.0	NS
Number of episodes	**8.5 ± 5.0**	**5.1 ± 3.8**	**0.001**
Number of hospitalizations	2.3 ± 2.8	1.5 ± 1.6	NS
Months since the last hospitalization	**14.8 ± 26.5**	**41.9 ± 71.1**	**0.003**
Number of suicide attempts	0.52 ± 1.0	0.46 ± 1.0	NS
			Chi^2-test
Suicide attempts in the past	n = 14 (28%)	n = 13 (26%)	NS
Last remission	**Full 12% (n = 6) Incomplete 88% (n = 44)**	**Full 48% (n = 24) Incomplete 52% (n = 26)**	**0.001**
Irregularity of treatment	n = 14 (28%)	n = 12 (24%)	NS
Family history of depression	n = 18 (36%)	n = 12 (24%)	NS
Family history of alcoholism	**n = 12 (24%)**	**n = 4 (8%)**	**0.029**
Negative family history of mental disorders	**n = 17 (34%)**	**n = 31 (62%)**	**< 0.050**

Table 3. Selected clinical data regarding the current depression episode in groups 1 and 2 of the illness in groups 1 an 2

	Gr 1 n = 50	Gr 2 N = 50	Gr 1 vs Gr 2 p
			t-Test
Duration of episode (in weeks)	**13 ± 8.7**	**7.6 ± 3.3**	**0.001**
Number of treatments	**2.34 ± 0.6**	**1.0 ± 0**	**0.001**
			Chi^2-Test
Presence of suicidal thoughts	n = 29 (58%)	n = 22 (42%)	NS
Presence of suicidal tendencies	n = 10 (20%)	n = 6 (12%)	NS

Table 4. Bipolar features – number of people fulfilling bipolar MDQ or HCL-32 criteria in groups 1 and 2. (MDQ (+)/HCL (+) – subgroups of patients, whose results in MDQ and HCL respectively indicated presence of bipolar features. MH (+) – subgroup of patients, fulfilling both – the MDQ and HCL bipolar spectrum criteria

	Gr 1 n = 50	Gr.2 n = 50	Gr. 1 vs Gr. 2 p Chi^2-Test
MDQ (+) MDQ (-)	**n = 22 (44%) n = 28 (56%)**	**n = 6 (12%) n = 44 (88%)**	**< 0.001**
HCL (+) HCL (-)	**n = 31 (62%) n = 19 (38%)**	**n = 17 (34%) n = 33 (66%)**	**0.005**
MH (+) MH (-)	**n = 19 (38%) n = 31 (62%)**	**n = 5 (10%) n = 45 (90%)**	**= 0.001**

4. Bipolar features – characteristics of answers in MDQ and HCL

The next step was the analysis of answers to the individual questions in the MDQ and HCL questionnaires. In the first 13-question part of the MDQ, drug-resistant patients (gr. 1) answered "yes" onto following questions (Q) statistically significantly more frequently in comparison to the non drug-resistant group (gr. 2) : Q1 : "…you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble ? ($p = 0.002$, Chi^2 test), Q3 : "...you felt much more self-confident than usual?" ($p = 0.002$, Chi^2 test), Q5 : "...you were much more talkative or spoke much faster than usual?" ($p = 0.025$; Chi^2 test)", Q8 : "...you had much more energy than usual?" ($p = 0.008$; Chi^2 test), Q9 : "...you were much more active or did many more things than usual?" ($p = 0.001$, Chi^2 test), Q11: "...you were much more interested in sex than usual ?" ($p = 0.010$; Chi^2 test).

In the HCL-32, among 32 questions from the mania/hypomania symptoms list, statistically significantly more answered "yes" in group 1 in comparison to group 2 on three questions : Q5 : "I am more sociable (make more phone calls, go out more)" ($p = 0.009$, Chi^2 test), Q16 : "I am more interested in sex, and/or have increased sexual desire" ($p = 0.005$, Chi^2 test), Q21 : "I am more easily distracted" ($p = 0.020$, Chi^2 test).

5. Clinical and demographic characteristics of patients with drug-resistant depression

There were no statistically significant differences regarding age, sex, marital state, number of children, education level, and occupational status between drug-resistant patients fulfilling and not-fulfilling the bipolar spectrum criteria by MDQ or HCL-32 (Tab. 5 and 6).

Table 5. Bipolar features according to MDQ criteria – selected sociodemographic data regarding the course of treatment in the group of patients with drug-resistant depression (group 1)

		MDQ(+)	MDQ(-)	MDQ(+) vs MDQ(-) p
				t-Test
Age		49.0 ± 7.2	49.0 ± 7.8	NS
Number of children		1.9 ± 1.3	1.5 ± 1.2	NS
				Chi^2-Test
Sex	M	n = 6 (27.3%)	n = 4 (14.3%)	NS
	F	n = 16 (72.7%)	n = 24 (85.7%)	NS
Marital status		n = 16 (72.7%)	n = 21 (75.0%)	NS
Education level	primary	n = 5 (22.7%)	n = 2 (7.1%)	NS
	vocational	n = 2 (9.1%)	n = 3 (10.7%)	NS
	secondary	n = 9 (40.9%)	n = 15 (53.6%)	NS
	higher	n = 6 (27.3%)	n = 8 (28.6%)	NS
Working		n = 9 (40.9%)	n = 9 (32.1%)	NS
Pension		n = 9 (40.9%)	n = 16 (57.1%)	NS

There were also no statistically significant differences in a range of such factors characterizing course of the illness as: age at the onset of disease, average number of episodes and hospitalizations, average time since the last hospitalization (Tab. 7 and 8).

Similarly, family history of depression, alcohol abuse, bipolar disorder, schizophrenia, anxiety disorders, suicides and coexistence of somatic diseases did not differentiate drug-resistant patients presenting or not presenting bipolar spectrum features (Tab. 7 and 8).

Moreover, there were no differences in selected clinical data regarding the current depression episode i.e.: duration of episode, number of administrated treatments, presence of suicidal thoughts or tendencies (Tab. 9 and 10).

It should be emphasized that drug-resistant patients fulfilling the MDQ bipolar features criteria estimated their last remission as incomplete and reported non-compliance reflected by irregularities in treatment and dosing non-adherence significantly more often than non-bipolar spectrum patients. Moreover, in drug-resistant bipolar spectrum patients in comparison with patients not fulfilling the MDQ criteria, there was a statistically significant greater number of suicide attempters and a greater average number of suicide attempts (Tab. 7).

Table 6. Bipolar features according to HCL criteria – selected sociodemographic data regarding the course of treatment in the group of patients with drug-resistant depression (group 1).

		HCL(+)	HCL(-)	HCL(+) vs HCL(-) p
				t-Test
Age		48.4 ± 8.5	50.0 ± 5.4	NS
Number of children		1.8 ± 1.4	1.3 ± 1.0	NS
				Chi^2-Test
Sex	M	n = 6 (19.4%)	n = 4 (21.1%)	NS
	F	n = 25 (80.6%)	n = 15 (78.9%)	NS
Marital status		n = 23 (74.2%)	n = 14 (73.7%)	NS
Education level	primary	n = 5 (16.1%)	n = 2 (10.5%)	NS
	vocational	n = 3 (9.7%)	n = 2 (10.5%)	NS
	secondary	n = 14 (45.2%)	n = 10 (52.6%)	NS
	higher	n = 9 (29.0%)	n = 5 (26.3%)	NS
Working		n = 12 (38.7%)	n = 6 (31.6%)	NS
Pension		n = 15 (48.4%)	n = 10 (52.6%)	NS

Table 7. Selected clinical data regarding the course of the illness in drug resistant patients (group 1) fulfilling (MDQ(+)) or not fulfilling (MDQ(-)) MDQ bipolar spectrum criteria

	MDQ(+) n = 22	MDQ(-) n = 28	MDQ(+) vs MDQ(-) p-value
			t-Test
Time since the beginning of illness (years)	9.9 ± 7.6	11.2 ± 9.8	NS
Age at onset of illness	39.1 ± 9.4	37.8 ± 7.9	NS
Number of episodes	8.0 ± 4.4	6.0 ± 4.6	NS
Number of hospitalizations	2.0 ± 2.4	2.5 ± 3.1	NS
Months since the last hospitalization	13.2 ± 19.2	15.4 ± 31.0	NS
Number of suicide attempts	**0.86 ± 1.28**	**0.25 ± 0.59**	**0.029**
			Chi^2-Test
Last remission	**Full n = 0 (0%) Incomplete n = 22 (100%)**	**Full (n = 6) 21% Incomplete n = 22 (79%)**	**0.021**
Irregularities of treatment	**n = 9 (41%)**	**n = (18%)**	**(0.055)**
Suicide attempts in the past	n = 9 (41%)	n = 5 (18%)	(0.055)
Family history of depression	n = 9 (41%)	n = 9 (32%)	NS
Family history of alcoholism	n = 6 (27%)	n = 6 (21%)	NS
Negative family history of mental disorders	n = 9 (41%)	n = 13 (46%)	NS

Table 8. Selected clinical data regarding the course of the illness in drug resistant patients (group 1) fulfilling (HCL (+)) or not fulfilling (HCL(-)) HCL-32 bipolar spectrum criteria

	HCL(+) n = 31	HCL(-) n = 19	HCL(+) vs HCL(-) p-value
			Test-t
Time since the beginning of illness (years)	10.9 ± 8.7	10.2 ± 6.0	NS
Age at onset of illness	37.5 ± 9.4	39.8 ± 6.9	NS
Number of episodes	6.8 ± 4.2	6.4 ± 5.0	NS
Number of hospitalizations	2.2 ± 2.4	2.6 ± 3.4	NS
Months since the last hospitalization	15.2 ± 21.7	14.1 ± 34.2	NS
Number of suicide attempts	0.71 ± 1.16	0.21 ± 0.54	NS
			Test Chi^2
Last remission	Full n = 2 (6%) Partial n = 29 (94%)	Full n = 4 (21%) Partial n = 15 (79%)	NS
Irregularities of treatment	n = 10 (32%)	n = 4 (21%)	NS
Suicide attempts in the past	n = 11 (36%)	n = 3 (16%)	NS
Family history of depression	n = 13 (42%)	n = 5 (26%)	NS
Family history of alcoholism	n = 7 (23%)	n = 5 (26%)	NS
Negative family history of mental disorders	n = 12 (39%)	n = 10 (53%)	NS

Table 9. Selected clinical data regarding the current depression episode in drug resistant patients (group 1) fulfilling (MDQ (+)) or not fulfilling MDQ (MDQ(-)) bipolar spectrum criteria

	MDQ(+)	MDQ(-)	MDQ(+) vs MDQ(-)
			t-Test
Duration of episode (in weeks)	11 ± 5.7	14.5 ± 10.2	NS
Number of treatments	2.18 ± 0.5	2.46 ± 0.7	NS
			Chi^2-Test
Presence of suicidal thoughts	n = 11 (50%)	n = 18 (64.3%)	NS
Presence of suicidal tendencies	n = 5 (22.7%)	n = 5 (17.9%)	NS

Table 10. Selected clinical data regarding the current depression episode in drug resistant patients (group 1) fulfilling (HCL(+)) or not fulfilling (HCL(-)) HCL-32 bipolar spectrum criteria

	MDQ(+)	MDQ(-)	MDQ(+) vs MDQ(-)
			t-Test
Duration of episode (in weeks)	11 ± 5.7	14.5 ± 10.2	NS
Number of treatments	2.18 ± 0.5	2.46 ± 0.7	NS
			Chi^2-Test
Presence of suicidal thoughts	n = 11 (50%)	n = 18 (64.3%)	NS
Presence of suicidal tendencies	n = 5 (22.7%)	n = 5 (17.9%)	NS

DISCUSSION

The group of drug-resistant patients, in comparison with non-drug-resistant patients, was characterized by a shorter time since the last hospitalization and a larger number of episodes, as well as a larger number of individuals who subjectively estimated their last remission to be incomplete. These data reflect the unfavourable pattern of the course of depressive disorder in the case of drug resistance.

In the group of drug-resistant patients, there were significantly more persons with a family history of different mental disorders (depression, alcoholism, schizophrenia, bipolar disorder, anxiety disorders). However, it should be pointed that in both groups, only 2% of patients reported cases of bipolar disorder in the family. Such an extremely low percentage suggests the underdiagnosis of BD. Attention should be paid to the statistically more frequent occurrence of alcohol abuse in the families of drug-resistant patients, which may be a confirmation of undiagnosed bipolarity. According to Sonne et al [19], alcohol abuse coexists with BD in about 33% of cases and maybe a factor suggesting incidence of bipolar spectrum in depressive disorder. It seems that use of the questions included in such tools as the MDQ or the HCL, not only for the examination of the patient, but also during a family interview may improve the detection of bipolarity among patients' relatives.

In the drug resistant group, in comparison to the non-drug-resistant group there were significantly more patients fulfilling MDQ and/or HCL-32 bipolar spectrum criteria. This suggests that a significant percentage of refractory depression is represented by misdiagnosed and therefore inadequately treated bipolar disorder. Such data are consistent with the results of previous investigations. Sharma at al [6] found the presence of BD (mainly type II) or features of broadly-defined bipolarity respectively in 59% and 80% of patients treated for drug-resistant depression. In another study, characterized by long-term follow-up (1-7 years), it was observed that a significant part of drug-resistant depression is associated with BD. The diagnosis was changed from unipolar affective disorder to bipolar disorder in 5 of 21 patients [7]. The results of the all-Polish, multicenter DEP-BI project showed that about 60% of the outpatients treated by psychiatrists for recurrent depression or depressive episode represent different forms of BD [1, 3]. Moreover, in a group of patients who fulfilled bipolarity criteria there were more cases of drug-resistance [3].

The differences between drug-resistant and non drug-resistant patients in frequency of answer to specific questions in the MDQ and HCL questionnaires shown in this pilot study also suggest that, in case of adding of a larger number of patients to the trial, it may be possible to choose such specific questions from the questionnaires used, which would be used during interviewing patients to increase the probability of recognition of bipolar features among drug-resistant patients. The varying, in terms of occurrence or lack of it, features of bipolarity in the group of drug-resistant patients, characterized by answers to questions from the MDQ and HCL questionnaires, may enable the separation of factors which, during the interview, may contribute to an improvement in diagnostic vigilance in the future.

Drug-resistant patients fulfilling the MDQ bipolar spectrum criteria, compared to the drug-resistant patients without bipolar spectrum, considered the last remission as partial or reported lack of remission, reported treatment nonadherence, had more frequent occurrences of suicide attempts as well as a greater number of suicide attempts. These results suggest that presence of bipolar spectrum may significantly and negatively affect the course and prognosis in drug-resistant depression.

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