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Association of different cognitive domains with lifetime history of psychosis and reported antipsychotic-treatment adverse events in bipolar disorders

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Summary

Aim of the study. The present work aimed to assess the association between cognitive functions, the lifetime occurrence of psychotic symptoms, and reported adverse effects of antipsychotic treatments in patients with bipolar disorders.

Methods. In the present work, 44 bipolar disorder inpatients hospitalized in the Affective Disorders Unit of the Institute of Psychiatry and Neurology in Warsaw, were investigated. All of them met the criteria of remission and were prepared for release from the hospital unit. Twenty-two patients were hospitalized in the manic stage of the illness, and 22 were in the depressive stage of illness. Both groups were assessed using adequate psychiatric rating scales (HDRS or YMRS and CAMRS) and neuropsychological tests (WCST, TMT, Stroop Test and Verbal Fluency Test).

Results. Patients who had a prior history of psychotic symptoms had poorer verbal functioning in comparison to subjects without such a history. However, individuals hospitalized in the manic state of disease, and who reported more adverse events after antipsychotic medication during the whole course of illness, had worse results in some parameters of executive function measurements in the WCST test, namely occurring in a greater percentage of nonperseverative errors and a lower number of completed categories.

Discussion. Generally the results confirm findings according to which, patients with the history of psychosis performe worse on neurocognitive tasks. However, the nature of dysfunctions found, generates questions about its relations with the experience of psychosis and antipsychotic treatment. Conclusion: Different aspects of cognitive dysfunctions may be related to the experience of psychosis and antipsychotic treatment in patients with bipolar disorders.

psychotic symptoms / executive functions / verbal functions / bipolar disorders

INTRODUCTION

Numerous studies have confirmed that cognitive decline is observed in individuals with bipolar disorders, not only during the acute phases of illness (manic or depressive episodes), but also in euthymia [1, 2, 3, 4, 5, 6]. In the whole population of bipolar disorder patients, about one- third of them experiences at least one psychotic episode during their lifetimes. It is considered that the history of psychosis has a great impact on a patient's cognitive functioning. According to most of researchers, cognitive dysfunctions in bipolar patients with the experience of psychosis, are particularly related to a greater impairment of working memory and executive

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functions associated with activation of the prefrontal cortex. It results in worse cognitive flexibility, particularly in the ability to change behavior according to environmental circumstances during cognitively demanding situations.

The impact of pharmacological treatment is relevant among the many different factors that influence on the cognitive functioning of bipolar patients [7]. Although cognitive dysfunctions are observed even in unmedicated bipolar individuals, different types of pharmacological treatment may lead to additional cognitive impairment [8]. Not only benzodiazepines taken occasionally or antidepressants given during depressive phases, but also normothymic treatments (except for lithium, that seems to have no o slight negative impact on cognition) may influence on psychomotor slowing and impairment of attention and memory [9, 10]. The most robust cognitive deficits, particularly impairment of working memory and executive functions, are considered to be associated with antipsychotic pharmacological treatments [11, 12].

Cognitive dysfunction in bipolar patients is considered to have a similar pattern as in schizophrenic individuals, although it is not as intense [13]. However, it is not certain, whether these deficits are illness-related (taking into account possible neurodevelopmental abnormalities and neurodegenerative course of disease alike in schizophrenia processes) and to what extent might be caused by antipsychotic treatment.

In the present work, using a neuropsychological test battery, we investigated the cognitive functions of 44 bipolar disorder patients. The aim of this research was to assess the strength of the associations between cognitive functions and the lifetime occurrence of psychotic symptoms, as well as the reported adverse effects of antipsychotic treatment in the bipolar disorder patients.

PATIENTS AND METHODS

Researched group

The present study was conducted in the Institute of Psychiatry and Neurology in Warsaw. The procedures were approved by the Bioethical Committee of the Institute of Psychiatry and Neurology and were in accordance with the Helsinki Declaration of 1975. All investigated patients were treated in the Affective Disorders Unit of the 2nd Departament of Psychiatry. The researched cohort consisted of 44 BD inpatients (20 males, 24 females), aged 20-81. Twenty-two of the patients (11 males, 11 females) were hospitalized in the manic phase of the disease and 22 individuals (9 males, 13 females) were in the depressive episode of illness. The basic characteristics of the two groups are shown in Tab. 1.

Table 1. Basic characteristics of patients with bipolar disorders hospitalized with symptoms of mania/hypomania (n=22) or depression (n=22). Mean values ± SD.

	BD patients after manic episode (n=22)	BD patients after depressive episode (n=22)
Age	45 ± (20-81)	57 ± (32-82)
Years of education	16 ± (11-20)	17 ± (10-20)
Number of hospitalizations	7 ± (1- 41)	4 ± (1-12)
Duration of current episode (weeks)	7 ± (3-20)	12 ± (4-36)
YMRS CAMRS –average	5 ± (0-17) 7 ± (0-29)	-
Hamilton Depression Scale	-	8 ± (1-19)

Only patients with total or partial remission according to the diagnosis of the leading psychiatrist prior to the planned patient's release from the hospital unit, were included into this study. All investigated subjects gave their written informed consent that was received following their familiarization with the written information given to the patient regarding the objectives and

methods of the study, including the possibility to withdraw their consent at any time of research procedure. The clinical investigation consisted of assessment of the patients using standard psychiatric rating scales and a questionnaire regarding their clinical and psychosocial data. The clinical assessment, was conducted by a specialist psychiatrist who was not involved in the treatment process of the investigated patients. Neuropsychological assessments were performed by a specialist in clinical psychology, following the interview with the psychiatrist. After the patients were finished participating in the research, they had an opportunity to obtain information concerning the current condition of their cognitive functions, as well as guidelines for cognitive training. Patients with severe neurological and/or significant somatic diseases, that would make data interpretation more difficult, addiction to alcohol or other psychoactive substances and individuals who refused their consent, were excluded from the study.

Most patients from both groups were currently in polytheraphy. In the first group of patients (n=22) hospitalized with a diagnosed manic (n=13) or hypomanic (n=9) state of BD, most of them (n=18) were currently on a second-generation antipsychotic treatment (one patient was treated with a typical neuroleptic) with an additional one (n=8) or two (n=10) mood stabilizers. Three patients were treated with two mood stabilizers but no antipsychotic drug. Onlyone patient was in monotherapy with one mood stabilizer. Before the current treatment, most patients (n=16) were treated with antipsychotics, mood stabilizers and antidepressants. Three patients had never taken antidepressants, and two had not been treated with an antipsychotic treatment before. Twelve patients declared that they were taking medications on a regular basis, while 10 on an irregular basis.

In the second group of patients, hospitalized in a depressive state of BD (n=22), all of them were currently being treated with antidepressants. Most of these subjects (n=15) were also on second-generation antipsychotic treatments (only three patients were taking a typical antipsychotic), with the exception of one individual, additionally were taking one (n=12) or two (n=2) mood stabilizers. Six patients were being treated with antidepressants and one mood stabilizer without an antipsychotic treatment, and one patient was in monotherapy with an antidepressant. Before the current treatment, 13 patients were taking all the mentioned types of drugs (antipsychotics, antidepressants and mood stabilizers), while 8 of them were taking mood stabilizers and antidepressants and one was in monotherapy with only an antidepressant. Fourteen patients declared that they were taking their medications on a regular basis, while 8 took medications on an irregular basis.

The patients' histories of psychotic symptoms and reported adverse effects of antipsychotic treatments over the entire course of the disease

In the first group (n=22) hospitalized with diagnosed manic (n=13) or hypomanic (n=9) state of BD, 9 patients had a history of psychotic symptoms over the entire course of the disease and, two of them had experienced auditory hallucinations in the past. All of these individuals had reported side effects caused by antipsychotics experienced during the entire course of the disease. The most frequent symptoms were increased body mass, somnolence and sedation after taking olanzapine (in 4 patients); increased body mass after taking risperidone or pernazine, (n=2), with the remaining symptoms including menstruation disorders and the Parkinson's syndrome observed after typical antipsychotic treatments.

In the second group of patients hospitalized in depressive state of BD (n=22), a history of psychotic symptoms over the entire course of the disease was reported by 4 individuals. Six patients suffered from side effects caused by antipsychotics. Four patients reported somnolence and increased body mass after olanzapine, 1 subject experienced EPS after risperidone, 1 patient had low blood pressure after risperidone and 1 subject had difficulties with concentration after quetiapine treatment.

ASSESSMENT

Psychopathological symptom evaluation:

1. The YMRS (Young Mania Rating Scale) [14] and the CAMRS (Clinical Adult Mania Rating Scale) were used for the assessment of the cur-

rent symptoms of mania in the group of patients hospitalized in manic/hypomanic episodes.

2. The HDRS (Hamilton Depression Rating Scale) was used in assessing the current depressive symptoms in individuals hospitalized in depressive episodes [15].

Neuropsychological assessment:

1. A computer version by Heaton et al., of the WCST (Wisconsin Card Sorting Test) was used for the assessment of working memory and executive functions [16].

2. The Trial Making Test was used for assessing psychomotor speed (part A) and visuospatial working memory/set shifting (part B) [17].

3. The Stroop Test was used for evaluating verbal processing speed (part A) and verbal working memory/ inhibition (part B) [18].

4. The Verbal Fluency Test (Letter FAS and Category Test) was used to assess the ability for generating words in a 60-second time window.

Statistical analysis

The statistical analyses were performed with the statistical package STATISTICA Version 8. Due to the small sample size, and because none of the variables tested with the Shapiro-Wilk Test did met the condition of a normal distribution, non-parametric tests were used. The mean values and standard deviations were calculated for quantitative traits. R-Spearman correlations were used for examining the significant associations between independent variables and the results of the neuropsychological tests. An ANOVA Kruskal-Wallis Test for independent groups and a U Mann-Whitney non-parametric tests were used for the comparison of groups of patients with and without a history of psychotic symptoms as well as with and without reported adverse effects of antipsychotic medications were counted to verify statistically significant differences between the groups. This work was powered statistically only to be treated as a preliminary study. A Bonferroni correction was taken into account.

RESULTS

Neuropsychological tests results

Table 2. Significant (p< 0.05) R-Spearman correlations between psychosocial data, clinical data and the performance on neuropsychological tests in bipolar disorder patients after a manic (n = 22) or depressive (n = 22) episode.

Spearman correlation	BD patients after manic episode (n = 22)			BD patients after depressive episode (n = 22)		
Neuropsychological tests	Age	Age of onset	Education	Age	Age of onset	Education
WCST % PE WCST % N-PE WCST CC WCST % CLR WCST 1st cat	ns 0.51 ns -0.52 ns	ns 0.50 ns -0.57 ns	ns ns ns ns ns	0.65 ns -0.73 -0.59 ns	ns 0.74 -0.58 -0.59 ns	ns ns 0.55 ns 0.52
TMT A TMT B	0.53 ns	ns ns	ns ns	0.55 0.80	0.66 0.82	Ns ns
Stroop A Stroop B Stroop B errors	ns ns ns	ns ns ns	ns ns ns	0.50 0.53 ns	0.42 0.68 ns	Ns ns -0.44
VF category test - correct words - perseverations VF letter test - correct words - perseverations - intrusions	 ns ns ns 0.45 ns	 ns ns ns ns ns	 ns ns ns ns ns	 -0.55 ns -0.60 ns 0.56	 -0.56 ns -0.45 ns ns	 ns ns ns ns ns

There were no significant differences in the performance on neuropsychological tests between "manic" patients compared to "depressed" individuals (tab. 1). Significant correlation between cognitive test performance and age were found in both groups of patients. Elderly individuals had more perseverative errors, a lower number of correct completed categories and a lower percentage of conceptual-level responses on the WCST, that indicates on an age-associated worsening of cognitive flexibility, conceptual formation and effectiveness of thinking. Elderly patients also had showed worse performance on the TMT A and B, indicating at poorer psychomotor speed and visuospatial working memory, and had worse results on the Verbal Fluency Test (less correctly generated words and more intrusions in the letter part of this test).

In both groups, a later onset age of illness was associated with a lower percentage of conceptual-level responses in the WCST and worse results in the TMT A and B.

Later-onset patients from the "depressive" group generated significantly fewer words in the Verbal Fluency Test. In the same group of patients after depressive episode, a greater number of years of education was correlated with a higher number of completed categories in the WCST and also a better functioning of verbal working memory (better performance on the Stroop Test).

In the "manic" group, a higher intensity of manic symptoms as measured by the YMRS and CAMRS, correlated with better results (i.e. shorter performance times) on the Stroop A test (R=-0.43; $p<0.05$). In the "depressed" group of patients, there were no significant correlations between their scores of the HDRS scale and their neuropsychological test results.

In the group of patients hospitalized with manic episode, we found significant R-Spearman correlations between the number of depressive episodes experienced during the entire course a patient's illness and worse performance on the neuropsychological tests: a lower number of completed categories on the WCST (R=-0.46, $p<0.05$), a higher number of cards needed to complete the 1st category on the WCST (R=0.47, $p<0.05$), worse results on the TMT B (R=0.45, $p<0.05$) and a lower number of words in the category part of the Verbal Fluency Test (R=-0.66, $p<0.05$).

There were no significant results from the neurophysiological tests related to the type of current treatment for a patient and the fact whether a phase-switch occurred after antidepressant treatments.

The history of psychotic symptoms and neuropsychological test performance

As shown in Tab. 3, the history of psychotic symptoms, taking into account the course of the disease, was significantly related to patient's cognitive functioning. In the "manic" group individuals who had ever experienced psychotic symptoms, generated significantly fewer words in the Verbal Fluency Test ($p<0.05$) as compared to patients without such a history. In the "depressive" group subjects with a history of psychotic symptoms needed more time to complete the Stroop A Test ($p<0.03$), which is an indicative of worse verbal processing, than individuals without a history of psychosis.

Table 3. The results of neuropsychological tests performance in patients with and without the history of psychotic symptoms. Mean values ± SD.

	BD patients after manic episode		BD patients after depressive episode	
Neuropsychological test	With psychotic symptoms (n = 9)	Without psychotic symptoms (n =13)	With psychotic symptoms (n = 4)	Without psychotic symptoms (n = 18)
VFT letter test - correct words	27± (24-31)**	35 ± (26-38) **	ns	ns
Stroop A	ns	ns	25 ± (21.5-32) *	24.5 ± (21-28) *

Differences between patients with and without psychotic symptoms significant *p<0.03 and **p<0.05, U-Mann Whitney Test.

Adverse effects of antipsychotics and neuropsychological test performance

The U Mann-Whitney test showed statistically significant differences ($p < 0.01$) between groups of patients with and without reported adverse effects of antipsychotic treatment over the entire course of their disease. These results were statistically significant only in the group of patients hospitalized during manic/hypomanic episodes. Individuals who reported more adverse events after antipsychotics in the whole course of illness, at present had more nonperseverative errors in the WCST and completed fewercategories in the WCST (Tab. 4).

Table 4. The results of neuropsychological tests performance in patients with and without reported adverse effects from antipsychotics during the whole course of illness. Mean values ± SD.

	BP patients after manic episode		BP patients after depressive episode	
Neuropsychological test	With adverse effects (n = 9)	Without adverse effects (n =13)	With adverse effects (n = 4)	Without adverse effects (n =18)
WCST % nonperseverative errors	8 ± (7-11)	20 ± (15-24)	ns	ns
WCST completed categories	6 ± (6-6)	3 ± (1-5)	ns	ns

Differences between patients with and without adverse effects significant $p<0.01$
U-Mann Whitney test.

DISCUSSION

The main finding of this study was the association between lifetime psychotic symptom occurrence and the present impairment of verbal functions, but not executive functions.

The fact that patients with a history of psychotic symptoms performed worse on neurocognitive tasks, is in general accordance with the previous studies, though. The majority of authors confirm that, only a few of them have not found any correlations between lifetime psychotic symptoms' occurrence and poor current cognitive outcomes [19]. The studies confirming worse neurocognitive outcomes in psychotic bipolar patients indicate the presence of dysfunctions of working memory and executive functions that are associated with the activation of the prefrontal cortex [20]. A recent prospective study indicated that executive dysfunction is a core deficit observed even in clinically stable bipolar individuals [21]. Among the different aspects of executive dysfunctions, cognitive flexibility is considered to be one of the most important traits differentiating individuals with bipolar disorder who have or have not had a history of psychotic symptoms [22]. Recent research in children at risk for bipolar disorder shows that cognitive-flexibility disorders that are associated with abnormal activity of the ventrolateral prefrontal cortex, can represent a potential marker of bipolar disorder [23]. Our work did not confirm these findings, because different types of cognitive disorders occurred significant in differentiating patients with and without the occurrence of psychotic symptoms. Individuals of both the "manic" and "depressive" groups, who ever had experienced psychotic symptoms in the past had, at present, greater verbal dysfunction. Patients after mania/hypomania with the history of psychotic symptom occurrence generated significantly fewer words in the Verbal Fluency Test, whereas individuals after depressive episode who had experienced psychosis, had worse verbal processing speed.

The broader meaning of verbal dysfunctions in bipolar disorders is generally not emphasized as much as in discussions of schizophrenia [24]. However, the latest studies by Meesters et al. [25] indicate that similar dysfunction profile is observed in older individuals diagnosed as bipolar I subjects as well as in remitted and non-remitted schizophrenic patients. The dysfunction profile includes not only executive dysfunction, butalso memory and verbal fluency deficits. Patients included into the Meesters' et al. study

were treated with antipsychotic medications, however, this was not an independent variable in the analyses of the neuropsychological tests. In our work, executive function disorders were significantly different between groups when taking into account the patients' histories of reported side effects of antipsychotic treatment. Subjects hospitalized after mania/hypomania, and who reported more adverse events after antipsychotic medication during the whole course of their disease, had, in the present study, greater executive function disorders that resulted in poorer conceptualization (fewer categories completed in the WCST) and more intense attention disorders (a greater percentage of nonperseverative errors). It could be hypothesized that the "frontal" dysfunctions observed in BD patients in the cited studies was not only associated with psychotic symptom occurrence itself, but might also be seen as an effect of the response for antipsychotic pharmacological treatment. One could also suppose that different aspects of executive dysfunction may be specific to each effect of antipsychotic treatment rather than deviations of the "core" executive impairment generally observed in bipolar disorder patients. In the present study, executive domains other than cognitive flexibility (as measured by the number of perseverative errors in the WCST) were more impaired in patients reporting adverse effects of antipsychotic treatment. Our results correspond with some findings of Torrent et al.[26] who examined the results of the neurocognitive tests of 119 bipolar individuals: 68 patients treated with antipsychotics and 16 unmedicated. The authors used a wide battery of neuropsychological tests and, confirmed cognitive decline in bipolar patients relative to healthy controls. They found that individuals who were not in a pharmacological treatment had significantly better cognitive outcomes, possibly indicating that cognitive dysfunction can be understood as a certain side effect of treatment response. However, the authors also considered that the group of unmedicated patients could have been a biased sample with better outcome. Compared to pharmacologically untreated individuals, patients on antipsychotic medication had worse results in semantic verbal fluency and verbal memory measures. That finding is consistent with our results indicating at verbal dysfunctions in patients with the history of psychotic symptoms, but not with executive dysfunctions differentiating patients with and without a history of adverse effects of antipsychotic treatment. Further prospective longitudinal studies should be conducted in order to explain whether and to what extent different types of cognitive dysfunctions are associated with psychotic symptom occurrence and when it should be understood as an evident effect of antipsychotic treatment.

Some significant age-related and educational-level-related between-patient differences in neuropsychological test performance, as well as the age of illness onset and sex-related differences (patients with a later age of onset and males performed worse on the Verbal Fluency Test) in the researched group, might be explained as simply the ageing of cognitive function [27]. However, worse neurocognitive outcomes were also related to the current intensity of the psychopathological symptoms in both manic/hypomanic patients as well as in depressive individuals. These data are consistent with the findings of other studies describing worse cognitive outcomes in BD patients who still had current depressive [28, 29, 30] or manic [31, 32, 33, 34] symptoms.

LIMITATIONS

The present work should be treated as a preliminary study that must be interpreted in light of its limitations. A relatively small sample of patients were investigated, with significant between-patient age bias. Some important data (such as the reporting of their history of psychotic symptoms and of the adverse effects of antipsychotic treatments) were just reported by the investigated subjects, and could not all of them were possible to be confirmed by the medical documentation. Although the individuals included into the study were considered to be remitted by leading highly qualified doctors and assessed by other an independent psychiatrist according to standard psychiatric rating scales, the patients' states of remission could vary between different individuals, due to the lack of a precise set of criteria for remission in bipolar individuals. Because the majority of patients were in polytherapy, the assessment of the influence of antipsychotic medication on cognition is very

limited. Lastly, because some of the investigated patients self-reported incomplete compliance, it is worth to indicate that this fact could additionally influence on the results.

CONCLUSION

In the present work, a lifetime history of psychosis in bipolar disorder patients was associated with verbal-function impairment. Working memory and executive function deficits, which in most studies are considered to be associated with the history of psychosis, were related to the adverse effects of antipsychotic treatments. The results suggest that psychotic symptom occurrence and the influence of antipsychotic treatments may be associated with the dysfunction of distinct cognitive domains.

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