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Cognitive Functions in Euthymic Bipolar Patients and Lithium

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<http://dx.doi.org/10.5772/55126>

1. Introduction

Based on Kraepelin's works we had for many years been distinguishing between manic-depressive illness (bipolar disorder) and dementia praecox (schizophrenia) based on the assumption that bipolar patients tended to experience full remission, whereas the schizophrenic did not. Since the late 1990s, the evidence has been accumulated that the recovery in bipolar disorder is not complete [1]. Persistent psychosocial difficulties and cognitive deficits are common in patients with the bipolar disorder even in euthymic or asymptomatic states [2, 3]. After two decades of scientific work the nature of the cognitive impairments is still the focus of research and debate. The extent and pattern of cognitive impairment in euthymic patients remain uncertain [4]. A meta-analysis of the studies revealed widespread cognitive deficits in patients with schizophrenia and affective disorders in cognitive functioning, speed of information processing, encoding and retrieval, rule discovery, as well as response generation and response inhibition [5]. There is a growing need for clarification regarding the extent and clinical relevance of cognitive impairment in bipolar patients [6].

2. Subjects and methods

2.1. Subjects

Sixty euthymic bipolar patients (25 male, 35 female), aged 26–75 yr (mean±S.D.: 53±10 yr) attending the Outpatient Lithium Clinic at the Department of Psychiatry at the Poznan University of Medical Science were studied. Consensus diagnosis by two psychiatrists was made for each patient, according to DSM-IV criteria (Structured Clinical Interview for DSM-IV Axis I – SCID) [7]. The patients had been treated with lithium carbonate for at least 5 yr. On

the day of the study, all patients were euthymic, as defined by a score of <7 on the 17-item Hamilton Depression Rating Scale (HAM-D17) [8] and a score of <7 on the Young Mania Rating Scale (YMRS) [9]. Among the patients, 13 were excellent lithium responders, defined as having had no affective episodes on lithium monotherapy for the entire period of lithium administration [10]. Eighty-four healthy controls recruited from the local community were matched by age, gender and education level. The study was approved by the Ethics Committee at the Poznan University of Medical Science. Patients and volunteers gave their written informed consent after hearing a complete description of the study.

2.2. Cognitive assessment- methods

Patients and controls underwent an extensive neuropsychological assessment that included an evaluation of attention, working memory, verbal and visual episodic memory, verbal fluency and executive functions. Neuropsychological testing lasted approximately 2 h. Subjects completed the tests in a fixed order with a break half-way through. The Trail Making Test (TMT) [11], Stroop Colour-Word Interference test [12, 13], verbal fluency tests, as well as selected tests from the Cambridge Automated Neuropsychological Test Battery (CANTAB; CeNeS Ltd, Cambridge, UK) [14-17], were employed.

2.2.1. Cognitive tests: Paper-and-pencil tests

The Trail Making Test (TMT) consists of two parts. TMT requires subjects to connect 25 consecutively numbered circles, (part A) and 25 numbered and lettered circles by shifting between the two sets (part B) as quickly as possible, and is very sensitive to cerebral dysfunction. Part A of the test measures psychomotor speed. The results of part B reflect the ability to shift strategy and assess executive function and visuospatial working memory [18]. Time is recorded in seconds.

The Colour-Word Stroop Interference test (CWST). The first part of the test (part A)- Reading Colour Names in black (RNCb), measures verbal abilities and attention. The subject is asked to read as quickly as possible words (colour names) printed with black ink on a white card. The second part (part B): Naming the Colour of Word – different (NCWd) – measures verbal working memory and executive functions. The subject is asked to name the colour of each printed word. The colour of the printed word is different from the colour described by the word [12]. Scoring is based on time (seconds).

Verbal fluency tests. Phonologic verbal fluency was studied by asking subjects to generate as many words as possible that begin with each of the letters F, A and S, in consecutive 1-min time periods (FAS Test, from the Controlled Oral Word Association Test) [19]. Semantic verbal fluency was measured with the Category Instant Generation Test, by naming as many items as possible in a given category (animals, vegetables and fruits) within the same time limit. Scores were the sum of all acceptable words produced in the three trials. The Polish version of the FAS test was used. This test was used for the assessment of verbal fluency, which is also a sensitive measure of executive functions, as it requires the subject to generate his/her own strategy.

2.2.2. Cognitive tests: Selected tests from the Cambridge automated neuropsychological test battery

Rapid Visual Information Processing (RVP) - a test of visual sustained attention, which is sensitive to dysfunction in the parietal and frontal lobe areas of the brain and is also a sensitive measure of general performance. RVP A' is the signal detection measure of target sensitivity regardless of error tendency (range 0.00 to 1.00; bad to good). This metric is a measure of how good the subject is at detecting target sequences. RVP Mean latency measures the mean time taken to respond and is reported in milliseconds. Response latency in the RVP task is a good indicator of sustained attention function [20].

Stockings of Cambridge (SOC) is a visuospatial planning test based on the Tower of London task [21]. This is a spatial planning test which gives a measure of frontal lobe function. The subject is shown two displays containing three coloured balls. The displays are presented in such a way that they can easily be perceived as stacks of coloured balls held in stockings or socks suspended from a beam. This arrangement makes the 3-D concepts involved apparent to the subject, and fits with the verbal instructions. The subject must use the balls in the lower display to copy the pattern shown in the upper display. The balls may be moved one at a time by touching the required ball, then touching the position to which it should be moved. The time taken to complete the pattern and the number of moves required are taken as measures of the subject's planning ability.

Spatial Span (SSP) - a visuospatial analogue of the Digit Span test assessing working memory capacity. White squares are shown, some of which briefly change colour in a variable sequence. The subject must then touch the boxes which changed colours in the same order that they were displayed by the computer (for clinical mode) or in the reverse order (for reverse mode). The number of boxes increases from 2 at the start of the test to 9 at the end, and the sequence and colour are varied through the test. After an incorrect attempt at choosing the boxes in sequence, the next trial remains at the same difficulty level. The Spatial Span is calculated at the highest level at which the subject successfully remembers at least one sequence of boxes.

Spatial Working Memory (SWM) - is a test of the subject's ability to retain spatial information and to manipulate remembered items in the working memory, which measures the working memory for spatial stimuli and requires the subject to use mnemonic information to work towards a goal. Subjects are required to search through boxes that appear on the screen with the aim of finding the 'blue tokens' hidden inside. The key instruction is that once a token had been taken out of a box, that box would not be used again to hide a token. After two practice trials with two boxes, there were four test trials with each of two, three, four, six and eight boxes. Returning to an 'empty' box already opened and a token removed on a previous search constituted a 'forgetting' or 'Between Search' error (BSE). A Strategy score was calculated from subject's performance on the six and eight box levels, to reflect how often a searching sequence was initiated from the same box during a given trial. Higher Strategy scores represent lower use of strategy (i.e. many sequences beginning with a different box in a given trial), and lower scores represent efficient use of strategy (i.e. many sequences starting with the same box in a given trial).

2.2.2.1. Statistical analyses

Statistical analyses were carried out with Statistica version 10.0 for Windows. To evaluate normality of distribution of the variables, the Shapiro–Wilk test was applied. As most of the investigated variables were not normally distributed, non-parametric tests were employed. Between-group differences in the demographic characteristics and neuropsychological tests were assessed by the Mann–Whitney test (two-groups comparisons) and Kruskal-Wallis ANOVA (multiple comparisons). All the results were expressed as the mean and standard deviation (S.D.). Statistical significance was set at $p<0.05$ for all analyses.

3. Results

Demographic characteristics are presented in table 1.

	Bipolar patients n=60	ER n=13	nonER n=47	Controls n=84
Age (years)	52.6 (10.2)	51.3 (12.1)	52.9 (9.8)	50.6 (14.7)
Gender - Male: Female*	25: 35	7:6	18:29	25:59
Education (years)	13.7 (3.5)	15.1 (2.4)	13.3 (3.7)	13.2 (2.4)
Duration of illness	22.2 (10.8)	21.0 (11.2)	22.6 (10.9)	-
Duration of prophylactic lithium treatment	12.7 (8.9)	12.1 (8.4)	12.9 (9.2)	-
No. of recurrences	13.3 (8.1)	7.2 (5.4)	15.3 (7.9)	-
Intensity of depressive symptoms (HDRS)	2.6 (1.8)	2.3 (0.8)	2.6 (2.0)	0.8 (1.5) ^{1,2,3}
Intensity of manic symptoms (YMRS)	0.6 (0.9)	0.1 (0.4)	0.7 (1.0)	0.3 (0.7)

* chi-square test

¹ – $p<0.01$ Mann-Whitney test, difference between bipolar patients and controls

² – $p<0.05$ ANOVA difference between ER and controls

³ – $p<0.01$ ANOVA difference between nonER and controls

Table 1. Demographic and clinical characteristic of euthymic bipolar patients and healthy controls. ER - Excellent lithium responders; nonER- non – excellent responders; HAMD - Hamilton Depression Rating Scale; YMRS - Young Mania Rating Scale (values are expressed as mean, standard deviation is shown in brackets).

No differences in age, gender distribution as well as education level between bipolar patients and healthy controls were detected. No difference between excellent responders (ER) and non-excellent responders (nonER) were detected either. Bipolar patients were euthymic but scored significantly worse on Hamilton's depression scale. Both ER and nonER had higher depression scores than the controls. In the bipolar group, 35 patients were treated with lithium as monotherapy, 13 – lithium in combination with carbamazepine, 4 – lithium+valproate, 8 – lithium+ atypical neuroleptic.

3.1. Assessment of attention, working memory and executive functions

To evaluate working memory planning and executive functions SSP, SWM, SOC from CANTAB Battery and the so-called "paper and pencil test": fluency tests (semantic and phonemic), CWST part B, TMT A and B, were used. To assess sustained attention RVP (CANTAB), and part A from CWST were employed. In table 2 the results of the neuropsychological evaluation of bipolar patients treated with lithium and healthy controls are presented. The bipolar group consists of two subgroups: excellent lithium responders and the remaining patients (non- excellent lithium responders).

Subjects with bipolar disorder scored significantly worse than controls on the tests assessing working memory, executive functioning and planning. The longest sequence successfully recalled (SSP Span length) was significantly shorter in the patients group than the controls. SSP total error number was higher in the BD group than in the controls, but the difference was not statistically significant. On the Spatial Working Memory (SWM) test results are presented in two measures: strategy and between errors. Patient scored worse on both of them. On the SOC results were displayed as three dimensions: SOC Mean initial thinking time (5 moves) giving an indication of the time taken to plan the problem solution, SOC Mean subsequent thinking time (5 moves) as well as SOC Problems solved in a minimum number of moves recording the number of occasions upon which the subject has successfully completed a test problem in the minimum possible number of moves. Bipolar patients had significantly worse results in both initial and subsequent thinking times. The controls performed better on fluency tests (verbal and phonemic), and TMT both parts. On the CWST B measuring verbal working memory and executive functions, bipolar patients had significantly worse results than the control subjects. On the sustained attention tests patients also scored significantly worse. Results of RVP A' - the signal detection (a measure of how good the subject is at detecting target sequences) as well RVP Mean latency (a measure of the mean time taken to respond) were significantly worse in the patients groups. After dividing lithium-treated patients into ELRs and non-ELRs the differences in cognitive functions between subgroups were observed. The results of excellent lithium responders were similar to those of healthy controls, whereas non-ELRs scored significantly worse on SSP Span length, SWM between errors and strategy, SOC initial thinking time, as well as sustained attention test. The only measure in which ELR scored worse than the controls was RVP mean latency. The results of ELRs were better than the scores of the controls on SSP span length and SOC problems solved in a minimum number of moves, but the difference did not reach statistical significance.

	Bipolar patients	ER	nonER	Controls
Working memory and planning, executive functions				
SSP Span length	5.0 (1.1)	5.8 (1.1)	4.7 (0.9) ³	5.4 (1.2) ^{1,4}
SWM Between errors	46.8 (19.7)	40.4 (14.9)	48.6 (20.6)	36.5 (18.7) ^{2,4}
SWM Strategy	37.3 (4.3)	36.5 (3.7)	37.6 (4.5)	35.2 (4.8) ^{1,4}
SOC Mean initial thinking time (5 moves)	11376.6 (11785.4)	9580.5 (8738.2)	11873.43 (12532.6)	6853.5 (5823.2) ^{2,4}
SOC Mean subsequent thinking time (5 moves)	3649.0 (2453.2)	3484.4 (3128.5)	3694.51 (2270.7)	3057.4 (2955.0) ²
SOC Problems solved in a minimum number of moves	7.6 (1.6)	8.1 (1.7)	7.5 (1.6)	7.4 (1.6)
Semantic fluency (No of words)	40,8(9.0)	44,6(8.9)	39,7(10.0)	47,6(10,0) ²
Phonemic fluency (No of words)	28,5(8.8)	33,3(9.3)	27,2(12.9)	35,6(12.9) ²
CWST B (time [sec])	78,7(26.3)	38,2(17.5)	46.0(10.9)	62,9(20,3) ²
TMT A (time [sec])	44,3(17.3)	89,2(39.0)	119,7(42.7)	36,1(10,9) ²
TMT B (time [sec])	113,2(46.80)	65,5(19.4)	82,9(20.3)	81,3(42,7) ²
Sustained attention				
RVP A'	0.83 (0.05)	0.86 (0.05)	0.83 (0.05)	0.88 (0.05) ^{2,4}
RVP Mean latency	604.7 (139.6)	577.6 (164.5)	612.2 (132.9)	482.9 (124.8) ^{2,3,4}
RVP B''	0.89 (0.21)	0.88 (0.16)	0.89 (0.23)	0.88 (0.28)
CWST A (time [sec])	28,2(5.8)	26,8(5.1)	28,6(9.4)	28,4(9.4)

¹ –difference between BD and controls p< 0.05 Mann-Whitney test

² - difference between BD and controls p<0.01 Mann-Whitney test

³ - difference between ER and controls (p<0.05) ANOVA

⁴ – difference between non-ER and controls (p<0.05) ANOVA

Table 2. Neuropsychological evaluation of bipolar patients and healthy controls treated with lithium and healthy controls (values are expressed as mean and standard deviation in brackets). Table presents results of CANTAB tests and paper-and-pencil tests results.

4. Discussion

4.1. Cognitive functions in bipolar patients

Not so long ago it was claimed that bipolar disorder is episodic, and the patient fully recovers between episodes, with no signs of affective, cognitive or psychosocial symptoms [2]. But patients in remission seem to be both affectively disturbed and cognitively impaired which may be a contributory factor to poor psychosocial outcome [2, 22-25]. During the last decade the results of numerous neurocognitive and neuroimaging studies in BD have been reported. They have revealed various dysfunctions in bipolar disorder present during affective episodes and have demonstrated that many neurocognitive deficits persist into periods of clinical remission or euthymia [16, 26]. Patients during affective episodes show significantly lower performance on several measures (tests) of attention, executive function, learning and verbal memory, and psychomotor speed [27-29].

Disturbances of executive functions, verbal and visual memory dysfunctions have been observed in depressive bipolar patients [23, 29-31]. Results of studies in manic patients are less consistent - although impairments in executive functions have been reported [23, 30-35]. Sweeney et al. [30] reported worse results of manic compared to depressive bipolar patients. Manic, but not depressed, patients made suboptimal decisions in Murphy's [35] computerized decision-making task.

Results of neuroimaging scans show structural and functional brain abnormalities in mood disorders in such regions as: basal ganglia frontal lobes, the locus caeruleus, subcortical white matters, hippocampus, amygdala, temporal lobes, as well as subtle structural deficits in the dorsal raphe [28, 36]. Cognitive dysfunctions were observed in affective acute bipolar patients (attention deficits, flexibility deficits, verbal fluency impairment, memory disturbances) [13, 31, 32, 35] have been reported also during periods of remission [37, 38], independently from residual affective symptoms [1, 16]. Sustained cognitive deficits could be a marker of disease or bipolar traits, it could be a prognostic factor as well [37]. Still, there is ambiguity about those issues [23, 39]. Research results are inconsistent [39], in small groups, diagnosis of bipolar is not precise, and information about treatment is not provided [23].

Recent reports have suggested the presence of persistent cognitive impairments in patients diagnosed with BD even after prolonged euthymic phases [16, 26, 40-48]. Review by Torres et al. [4] revealed widespread cognitive deficits in tests assessing attention, speed of information processing, memory and executive dysfunctions in remitted bipolars versus controls. There was no difference in premorbid intelligence and vocabulary. Some dysfunctions in remitted patients [49] are similar to those observed in patients in acute phase. Cognitive deficits are regarded by several authors as trait-markers or their background (genetic, developmental or associated with illness progression) remains to be evaluated [4]. The studies in euthymic patients are to answer questions concerning the state-dependent (reflecting mood changes) and stable character of cognitive deficits [2, 26, 40, 41, 50, 51].

Disturbances of executive functions, working memory and planning. The results of our study confirmed the reports on disturbances of executive functions in remitted bipolar

patients [42-48; 52-54]. Several authors do not show executive dysfunctions [55, 56] or show mild degree dysfunctions [4]. These discrepancies probably result from various definitions of executive function, which lead to the use of different tests and methods as well as problems with clear explanation of the nature of cognitive dysfunction(s). Disturbances of cognitive flexibility and inhibitory control were the most important findings, auditory memory and verbal fluency were more impaired. Intellectual functioning was intact. A recent review of the literature [57] shows deficits in working memory and some aspects of executive functions (inhibitory control).

Larson [58] et al. evaluated two specific aspects of executive functioning: inhibitory control, and spatial delayed working memory. Manic and euthymic patient groups performed similarly in the spatial delayed working memory test. On the inhibitory test manic and euthymic patients committed significantly more perseverative errors than healthy participants. These results indicated that patients had relatively normal working memory abilities, but had a deficit in behavioral self-regulation, which was evident across mood states. In our bipolar remitted group spatial working memory (SWM) was disturbed compared to the control group, and subjects performed worse when it came to updating the working memory continually but strategy planning was less disturbed.

Goswami et al. [59] have measured neurocognitive functions in bipolar disorder and tried to find links to residual mood symptoms, soft neurological signs and psychosocial impairment. They tested attention, memory and executive function in euthymic patients with bipolar disorder and controls. Psychosocial functioning, soft neurological signs and residual mood symptoms were assessed. Tests results on executive function and verbal memory (but not attention) were significantly poorer in bipolar patients. Residual (sub-syndromal) mood symptoms were connected with small cognitive effects, predominantly on verbal memory. Some patients showed a marked social disability which correlated strongly with soft neurological signs but weakly with executive dysfunction, which was linked to the number of episodes. Cognitive dysfunction, social dysfunction and soft signs may represent trait deficits of bipolar illness. Both in the present study and in other authors' results remitted bipolar patients have verbal and nonverbal memory disturbances [4] compared to healthy controls. Those results are consistent through various data [49], a wide spectrum of executive dysfunctions, memory and attention was detected in remitted bipolars [25]. The results of our study are consistent with those of Sole et al. [60] who reported that bipolar patients showed a significantly lower performance on several measures of attention, learning and verbal memory, and executive function compared with healthy controls. Worse performance on TMT is especially important in light of the finding of Sole et al. [60] that the one measure related to executive function (Trail Making Test, part B) was the variable that best predicted psychosocial functioning of bipolar patients. In a two year follow up study in euthymic bipolar patients on lithium executive function and processing speed were affected, and such deficits were maintained over time. Those results show that executive dysfunction is the main long-term neuropsychological deficit of bipolar disorder [61]. After controlling for the effect of subsyndromal depressive symptoms [62] impairment of verbal memory and executive dysfunctions were noticed and this cognitive impairment seems to be related to a worse clinical course and

poor functional outcome. Executive dysfunctions are described as a central bipolar trait deficit and due to them bipolars' psychosocial problems are observed [63].

Attention deficits. The results of our study point to the deficits in attention tests. Patients scored worse on sustained attention measurement WCST part B and on RVP test from CANTAB battery. Euthymic bipolar patients have been reported to show persistent deficits in sustained attention tests [53]. Most research shows sustained attention deficits [41, 46], some tests did not show such disturbances [4]. Burdick [64] has not detected a direct relationship between attention deficits and depressive symptoms. Sustained attention deficits apparent during the euthymic period of bipolar disorder cannot be explained in terms of working memory impairment and represent a reduced inherent capacity rather than a changed response bias [16, 42, 44, 45, 53, 65, 66]. Sustained attention deficits are claimed to be a core deficit for bipolar disorder, but those deficits are not dependent on executive dysfunctions, including working memory. Attention deficits and information-processing speed are related to memory processing or other cognitive processes [2, 39, 47, 48]. Furthermore, the data support the view that deficits in verbal memory may be related to genetic factors. [65].

Memory deficits as result of hippocampal and medial temporal lobe dysfunctions could be a key cognitive problem in bipolar patients [67]. Malhi et al. [68] conducted a review of the literature to compare and contrast the neuropsychological profile of the 3 phases of bipolar disorder to identify potential state and trait deficits. They initially identified more than 100 articles and then excluded reviews and papers in which neuropsychological tests were not administered directly. This left 27 papers, which they further examined and the findings of which they tabulated and discussed. Cognitive and executive functioning deficits were found, including set-shifting, verbal fluency, planning, attention, and memory. In their opinion, those neuropsychological deficits found in bipolar depression, mania or hypomania, and euthymia provide important insights into the pathophysiology of bipolar disorder and may, in future studies, form the basis of clinically meaningful subtypes of bipolar disorder [68]. Deficits in sustaining attention may also help explain the difficulties in psychological and occupational functioning in bipolar disorder patients during remission.

4.2. Factors associated with cognitive deficits

Cognitive impairments result not only from affective disturbances (manic, depression phases) - they are also detectable during the phase free of affective symptoms (remission) Factors associated with cognitive dysfunction in bipolars might be the number of episodes [1, 38, 54], mainly the number of manic episodes [16, 41, 52, 54, 69, 70], chronicity [53, 54], residual affective symptoms, especially depressive ones [27, 38]. Clinical factors associated with cognitive impairment in bipolar patients are medicines such as mood stabilizers, antidepressants and neuroleptics. Drugs used in the treatment for somatic diseases might also influence the cognitive functioning of bipolar patients. The secondary cognitive deficits caused by treatment of bipolar disorder (lithium, antiepileptics, antidepressants, antipsychotics) are similar to the cognitive deficits associated with the disease [71]. Differentiation between cognitive dysfunctions related to the illness and those related to its treatment is difficult. Four studies showed that lithium had a negative effect on memory and speed of information

processing, often without subjective complaints or awareness of mental slowness [72, 73], lithium did not cause memory impairment or a change in self-assessment of memory functions [74]. In Engelsmann et al. observation survey mean memory test scores remained remarkably stable over the entire 6-year lithium therapy [75]. A comparison between two groups on lithium therapy: a long- and shorter term group (with means of 12.9 and 5.2 years, respectively) showed no significant differences between these groups on any of the memory tests [31]. Younger bipolars (below 55 yrs) had received lithium therapy for 1-5 years and showed no abnormalities on the Halstead-Reitan Neuropsychological Battery, so lithium therapy was not connected with cognitive impairment [76].

Cognitive function in long-term lithium-treated outpatients were investigated by Lund et al. [77] who tested memory, attention, speed, loss of effort, level of processing, productivity [77]. Results were within normal limits. But further analyses revealed that the performance of the lithium-treated patients indicated a relative lowering of the level of memory and perceptual processing when compared to the level of attention and productivity. Those results support opinion about lithium –influenced worsening in information processing. The effects of blind lithium discontinuation and resumption on measures of cognition, creativity, and fine motor performance in 46 lithium-maintained euthymic out-patients were investigated [72]. Scores on memory measures, tests of tapping speed, and associative productivity all improved significantly during the time off of lithium. The authors analyzed influence of six possible intervening variables: age, sex, lithium concentration in plasma, thyroid function, duration of lithium maintenance, and depressive symptoms. Further analysis suggested that lithium has a greater neuropsychological effect in younger, less-depressed patients having higher plasma lithium concentrations in plasma [72].

In our study lithium-treated patients as a group had poorer results on several tests measures compared to healthy controls, namely SSP span length, SWM between errors, SWM strategy, RVP A, RVP mean latency, and SOC mean initial thinking time as well as on TMT and Stroop test part B. The results of excellent lithium responders did not differ from those of healthy controls (except for one measure in RVP). These might support statement that lithium treatment is associated with a preservation of cognitive functions in ER group. According to literature review [78] neurostructural changes in BD would be hypothetically influenced by the neuroprotective/neurotrophic properties of lithium. These findings are interesting because the pathophysiology of BD involves structural and functional changes in cortical and limbic networks implicated in the regulation of mood and cognition. Reports on the impact of anticonvulsants on cognitive functions in bipolar patients are scarce. Some authors reported that plasma levels of anticonvulsants influence cognitive tests results and carbamazepine or valproinians may be responsible for attention deficits [79, 80]. Neuroleptics have been found to worsen psychomotor function and sustained attention, but higher cognitive functions are relatively unaffected [81]. Zubieta et al. [41] have found negative correlations between Wisconsin Card Sorting Test (WCST) performance and duration of neuroleptics exposition. The use of neuroleptics [82] as well as illness duration and family history were predictive factors for intelligence and memory in bipolar patients. Numerous authors believe that neuroleptics do not influence cognitive functions in bipolars. Cognitive deficits are related

probably to anticholinergics effects of drugs [31]. New neuroleptics (atypical) have positive impact on cognitive functions of schizophrenic patients [83], and probably new neuroleptics improve cognitive function especially in longtime treatment for manic patients [31].

Data on antidepressants are also inconsistent. Literature review shows that antidepressants do not cause cognitive dysfunctions [84]. According to literature review by Knegtering et al. [85] amitriptyline, mianserin and trazodone impair attention and ability to concentrate in elderly, antidepressants with anticholinergic properties (nortriptyline, maprotiline, amitriptyline) might impair working memory. Higher plasma concentrations of nortriptyline correlate with greater cognitive impairment. Tests results about selective serotonin (5-hydroxytryptamine) reuptake inhibitors on cognitive performance in the elderly indicate no detrimental effect. Martinez et al. pointed out that mood stabilizers with antidepressant properties might influence cognitive function and social functioning [31]. Optimal treatment preferring second generation antipsychotics and avoiding drugs with anticholinergic effect, is essential. In Mencia and colleagues opinion prevention of iatrogenic effects of drugs should be now the main therapeutic intervention [71]. Treatment with atypical antipsychotics has been associated with improvement in cognitive tests in patients with schizophrenia, and the little data available in patients with bipolar disorder suggest the potential for similar benefits. MacQueen and Young [86] pointed to the need of further studies to determine if current treatments for bipolar disorder can prevent, delay, or even improve cognitive dysfunctions [86]. Bipolar patients have been treated for years with combination of mood stabilizers, antidepressants and antipsychotics and it is difficult to assess impact of such a combination on various cognitive functions. [28, 34]. Impaired executive functions in bipolars shown in tests might be the feature of bipolar disorder regardless the effects of medication [87]. The contributions of bipolar disorder trait – state cognitive impairment and medications is very complicated to distinguish as well as control [78]. Clinicians treating BD patients should take it into account in prescribing medications for long-term prophylaxis. Medication-related adverse cognitive effects should be taken into consideration. In order to reduce cognitive dysfunction, or at least avoid cognitive deterioration clinicians should use drugs with a favourable or neutral cognitive profile [78]. Cognitive outcome in patients with affective disorders appears to be associated with the number of affective episodes. In the study designed as a controlled cohort study [38] 118 unipolar patients, 28 bipolar patients and 58 controls were included and the analysis results was adjusted to the level of education and subclinical depressive and anxiety symptoms. Patients with recurrent episodes were significantly more impaired than patients with a single episode and more impaired than controls. Some research on bipolar showed negative correlations between number of depressive episodes and executive functions [16, 41, 42]. Verbal learning was correlated with number of depressive episodes [63] or not [42, 52]. Number of manic episodes was connected with worse results in verbal tests and worsening in executive functions tests [16, 41, 52, 54, 62, 63] and visual memory [88]. Systematic literature review by Robinson and Ferrier [25] showed relationship between cognitive dysfunction in bipolar disorder and worse prior course of illness, particularly the number of manic episodes, hospitalizations and length of illness. In their opinion cognitive impairment may be a trait vulnerability factor for bipolar disorder that is present before illness onset and worsens as the illness progresses. Residual affective symptoms might influence cognitive tests results [2, 16,

56, 89]. It is worth to underline that in previous studies usually euthymic patients meant patients free of affective symptoms who did not fulfilled criteria for affective episode. On the other hand 30% of Scott's [90] group of remitted bipolar had patients Beck's score was more than 10 points. In cognitive functions assessment in BD we should consider such factors as pharmacological treatment, course of illness, residual symptoms [2, 16], structural lesions of a neurodegenerative origin [91, 92], functional changes that are most likely genetic in origin [91-93]. There is a close relationship between cognitive impairment and poor treatment adherence, but the causal inferences of these findings are uncertain [94]. Poor treatment adherence may worsen the course of bipolar disorder and so indirectly worsen cognitive performance, or cognitive impairment may contribute to poor treatment adherence and reflect more severe illness.

5. Conclusion and future research

Data concerning cognitive functions in BD are still limited and inconsistent so that further research is necessary. It is worth to underline the growing evidence suggests that the presence of cognitive dysfunction in bipolar affective disorder is a core and enduring deficit of the illness. Impairment in the attention or executive control of action represents an important target for future research. Many clinicians have strongly indicated worse psychosocial functioning of bipolar patients [41, 95], which may be caused by cognitive impairment as neurocognitive deficits could result in psychological and social deficits. Evidence from neuroimaging, molecular genetic, pharmacological and animal studies related to the pathophysiology of bipolar disorder may provide clinicians with new treatment strategies. Neurocognitive impairment in bipolar disorder should be considered a potential therapeutic target, which means that research should focus on new drugs and psychological interventions, including neurocognitive rehabilitation to improve cognitive functions and the functional outcome of bipolar patients [96]. The Cognitive Remediation is defined as a behavioural training based intervention aimed at the improvement of cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization [97]. Several cognitive remediation programmes (CR) for patients with schizophrenia have already been developed. The potential benefits of CR in affective disorders may even exceed those of schizophrenia and such approaches hold significant promise for individuals with bipolar disorder [98].

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