Cognitive Functions of Bipolar Disorder Patients in Remission on Monotherapy: A Follow-Up Study

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Summary

Objective: Multiple sectional studies indicate that the cognitive functions of bipolar disorder (BD) patients in remission are damaged. These studies also suggest that cognitive functions get worse over time. Although the results are inconsistent, there are limited follow-up studies that reveal any contradictory results. Interestingly, there have been major difficulties in the interpretation related to this subject. In particular, scarcity of longitudinal studies and not eliminating the role of multidrug side effects on cognitive functions are just a few. Due to these aforementioned limitations, the longitudinal course of cognitive functions and their sectional differences were investigated in BD patients that underwent remission with monotherapy in this study.

Methods: In this study, the cognitive functions (premorbid IQ, attention, executive functions, memory, visual-spatial skills, and psychomotor speed) of BD patients (n=27) in remission and on monotherapy for at least 1 month were assessed at baseline and at an 18 (6-77) month follow-up period and compared to healthy controls (n=35).

Results: The BD group's performance was worse than those of the control group on tests that evaluated attention, executive functions including concept formation, mental flexibility, response inhibition, set shifting, and reasoning, verbal memory, and psychomotor speed. On the other hand, the BD group showed no significant differences at baseline and follow-up examinations.

Conclusion: All cognitive functions of BD patients on monotherapy remained stable during the follow-up. This suggests that this group might be a sub-group of BD with good prognosis, and monotherapy may not be harmful on cognitive functions. On the other hand, it needs longer time to detect cognitive dysfunctions.

Key words: Bipolar disorder, neurocognition, euthymia, monotherapy, prospective design

INTRODUCTION

Meta-analysis studies evaluating cognitive functions of bipolar disorder (BD) patients in remission indicate that there are cognitive impairments during the remission period in BD (Robinson and Ferrier 2006, Robinson et al 2006, Torres et al 2007, Arts et al 2008, Bora et al 2009, Bourne et al 2013). According to meta-analysis findings, impairments can be found in vocabulary memory, attention, and executive functions during the remission period (Bourne et al 2013). Despite increasing knowledge, data about this field are based on cross-sectional studies (Şentürk et al 2007, Mann Wrabel et al 2011). Follow-up studies are needed to investigate the relationship between BD and cognitive impairments. However, follow-up studies that examine the association with BD and cognitive impairments are merely scarce in numbers (Balanza-Martinez et al 2005, Mur et al 2008, Depp et al 2008, Tabarés-Seisdedos et al 2008, Martino et al 2009, Bonnin et al 2010, Bearden et al 2010, Chaves et al

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2011, Lewandowski et al 2013, Torres et al 2014, Yazıhan et al 2015).

Interestingly, two follow-up studies compared the cognitive functions of BD patients with schizophrenia patients and the healthy controls (Depp et al 2008, Tabarés-Seisdedos et al 2008) and showed that the control group scored better than the BD patients. Conversely, Depp and his colleagues (2008) showed no difference in cognitive functions between the patient and control groups. In another study (Tabarés-Seisdedos et al. 2008), the BD patient group had a better ratio for cognitive function than the schizophrenia group. Longitudinal evaluation in those studies revealed improvement of the cognitive functions for the BD group (Depp et al 2008, Tabarés-Seisdedos et al 2008). In the study carried out by Lewandowski and colleagues (2008), it was revealed that the cognitive functions of patients diagnosed with schizophrenia, schizoaffective disorder, and BD with psychotic characteristics were impaired in all of the diagnosis groups. This was observed even though there was improvement on clinical symptoms and no improvement in many areas of the cognitive function.

According to the results of the study of Balanza-Martinez and colleagues (2005), the cognitive functions of patients with BD did not show any change in time. In the study by Mur and colleagues (2008), the BD group was more impaired in comparison with the control group and this impairment showed continuity over time for executive functions, attention, and process speed.

Data obtained from sectional studies led us to believe that the cognitive function impairments increase over time. Nevertheless, the main procedural handicap to reach these results was the sectional nature of the studies. Furthermore, results from the follow-up studies did not support this opinion. The results obtained from limited number of follow-up studies were not consistent and indicate that patients with BD show cognitive function impairment compared to healthy controls. Furthermore, this impairment remained stable over time. In addition to this, Torres and colleagues (2014) documented that newly diagnosed BD patients consistently showed worse performance in many cognitive functions compared to healthy controls. However, the process time and executive functions showed improvement over time. It has been documented that those who do not have alcohol or substance abuse history and whose antipsychotic treatment was terminated develop better on cognitive function tests (Torres et al 2014). On the other hand, there has been follow-up studies showing that cognitive functions were not affected from clinical and pharmacotherapeutical factors (Mur et al 2008, Depp et al 2008, Lewandowski et al 2013). A relatively updated meta-analysis whereby sectional studies were reviewed suggested that euthymic BD patients have an association with cognitive impairment and clinical and pharmacotherapeutical factors. However, the impairment in cognitive functions cannot be fully explained by those factors (Bourne et al 2013).

The reason for the differences in follow-up study results may be related to the inclusion of non-euthymic patients (Depp et al 2008, Tabares-Seisdedos et al 2008, Lewandowski et al 2013) and patients that were followed up with polypharmacy protocols (Depp et al 2008, Tabares-Seisdedos et al 2008, Lewandowski et al 2013, Torres et al 2014). Hence, the failure of controlling clinical features and treatment models (specifically the confusing effects of multi drug treatments) that could be influential in the BD - cognitive function relation may be involved. Martino and colleagues (2009) indicated that the effects of pharmacotherapy on the cognitive functions could not be excluded. This was a limitation of their study without giving the information of the treatment they used on the cases. In another study (Bonnin et al 2010), it was demonstrated that polypharmacy was one of the base limitations of the study, which was limited with mood stabilizers as well as antidepressants, antipsychotics, and anxiolytics. Mur and colleagues (2008) only examined patients using lithium. Chaves and colleagues (2011) focused on the relationship between change of mood symptoms and cognitive functions and reported that depressive symptoms were related to verbal fluency. Similarly, a study that focused on correlating mood symptoms and cognitive functions observed 9 male patients' cognitive functions during their manic and euthymic period and demonstrated that in the manic period, attention and learning was relatively impaired in comparison to the euthymic period (Yazıhan and colleagues 2015). Studies researching the relationship between mood symptoms and cognitive functions (Chaves et al 2011, Yazıhan et al 2015) were follow-up studies. However, they did not present information related to the change of the cognitive functions for euthymic patients over time.

In the light of this information from the literature, the purpose of this study was to compare the cognitive functions of healthy controls and patients with BD in remission, and to examine the cognitive functions of BD patients prospectively. In this study, we hypothesized that the cognitive functions of BD remission patients followed with monotherapy would be worse than healthy controls and cognitive function impairment would increase over time.

METHOD

Sampling

Sampling consisted of patients of BD patients (BD I group, n=24 and BD II group, n=3) in remission for more than one month, which used a single mood stabilizer (MS) or an atypical antipsychotic (AP) treatment (n=27). and These were compared to healthy people that did not have neurological or psychiatric diseases.

As part of this project, we were able to contact patients (n=55) of whom we kept in contact with from from previous studies (Şentürk ve ark 2007, Cankorur Şentürk ve ark 2016). However, only 11 patients could be included due to reasons such as patients on a manic or depressive period (n=9), logistical problems (n=16), or patients not wanting to get involved in the study (n=11). The other patients included on the study (n=16) are follow-up patients from two different university hospitals. The author who evaluated the subjects (H.D.) traveled to the centers where the patients were located and made the first and follow-up evaluations on two different timelines. Pharmacotherapy used was as follows: Lithium carbonate (n=9), sodium valproate (n=10), lamotrigine (n=1), olanzapine (n=3), quetiapine (n=3), and risperidone (n=1). The control group was selected from one center and consisted of healthy people that applied and worked there on a volunteer basis.

People who had electroconvulsive therapy (ECT) in the last year, treatment with antipsychotics within the last three months, history of alcohol or substance use, used medication or had any diseases that may affect cognitive functions (such as dementia or mental retardation), and/or had a psychiatric diagnosis (except anxiety disorder) were not included in this study. Ethical Board Permission was granted from the University of Ankara Faculty of Medicine Evaluation Committee for Non-invasive Clinical Researches.

Socio-demographic and Clinical Evaluation Tools

The socio-demographic information, clinical features, course of the diseases, and use of medication history were evaluated with the Socio-demographic Information Form. Diagnoses on axis I DSM-IV were made with The Structured Clinical Interview for DSM-IV Axis I Disorders, SCID-I (Çorapçıoğlu et al 1999).

In our study, the evaluation of residual mood symptoms for patients in remission was assessed with the Hamilton Depression Rating Scale (HAM-D) (Williams 1978, Akdemir et al 2001) and the Young Mania Rating Scale (YMRS) (Young et al 1978, Karadağ et al 2002). The patient was accepted as in remission once he or she scored lower than 7 on both scales. Patients that were defined as in remission were evaluated again one month later. Those that fulfilled the inclusion criteria were included in the study. Patients that had the first evaluations and had seizures during the study or were shown to have multi-drug usage were excluded from the study. During the follow-up evaluation, the times of remission were obtained from the patients or hospital records. Other psychiatric symptoms that could affect cognitive functions were evaluated with the Hamilton Anxiety Scale (HAM-A) (Hamilton 1959, Yazıcı et al 1998) and the Brief Psychiatric Evaluation Scale (BPES) (Overall and Gorham 1962, Soykan 1990). Because of the high probability for the treatment to cause tardiness on motor functions, The Unified Parkinson Disease Evaluation Scale – Motor Subscale (UPDES-M) was used in order to control their potential impact on the cognitive function (Post et al 2005).

Neuropsychological Assessment

Premorbid IQ

An information subtest of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Weschler 1981, Atkinson et al 1989) was used in order to evaluate the Premorbid IQ. The reason the WAIS-R was chosen to evaluate the IQ rather than the Verbal subtest was because the Verbal subtest scores did not reflect the premorbid cognitive functions on patient groups with cognitive impairment (Russel et al 2000).

Attention

The evaluation of attention was carried out with the WAIS-R Digit Span subtest (Weschler 1981, Atkinson et al 1989).

Executive Functions

Concept Formation and Mental Flexibility

Concept formation was evaluated with Wisconsin Card Sorting Test (WCST) Completed Categories (Heaton 1981) and WAIS-R Similarities subtests (Weschler 1981, Atkinson et al 1989). As for the evaluation of mental flexibility, the WCEST Perseverative Errors (Heaton 1981) subtest was used.

Reaction Inhibition

The Stroop Color-Word Interference Test (SCWT) (Golden 1978) was used to evaluate reaction inhibition. This test, which reveals the ease of changing the perceptional setup towards variable desires and under aliasing, showed abnormal behavior and suppression of common behavioral pattern (Spreen and Strauss 1998). The form was used in this study and was adapted by Karakaş and colleagues (1999), the TBAG form.

Set Shifting

Set shifting abilities were evaluated with the Trail-Making Test (TMT) (Reitan and Wolfson 1985). The test consisted of two parts TMT-A and TMT-B, respectively. While part A was dependent on attention, visual scanning, and motor speed (Spreen and Strauss 1998), part B was the indicator of set shifting abilities (Libon et al 1994). The set shifting ability in this study was calculated using the B-A scores, which were predicated on the completion time difference of two sections and removed the motor component effect.

Reasoning

The WAIS-R Picture Arrangement subtest was used to evaluate reasoning skills (Weschler 1981, Atkinson et al 1989).

Abstracting

The WAIS-R Comprehension subtest was used to evaluate abstracting (Weschler 1981, Atkinson et al 1989).

Memory

The WAIS-R Arithmetic subtest (Weschler 1981, Atkinson et al 1989) and Auditory Consonant Trigrams (ACT) test were used to evaluate the executive memory. In the ACT, performance was based on the capacity of short term memory, divided attention, attention allocation, and online information processing capacity (Anıl et al 2003). It has an important advantage because it has been found to be relatively independent from education. As for the evaluation of verbal memory the Wechsler Memory Scale - Revised (WMS-R), the Logical Memory subtest was used (Wechsler 1987). This test has been shown to be the most comprehensive regarding memory measurement and the most advanced in assessing psychometrics.

Other Cognitive Functions

Visuospatial Perception

Visuospatial Perception was evaluated with WAIS-R Block Design subtest (Weschler 1981, Atkinson et al 1989).

Psychomotor Speed

The WAIS-R Digit Symbol subtest was used to evaluate the psychomotor speed (Weschler 1981, Atkinson et al 1989).

The practices were carried out by a clinical psychologist with neuropsychological evaluation, education, and experience (H.D.). Evaluation of cognitive functions took approximately 2 hours and the evaluations were made in the morning. Neuropsychological tests were performed on every subject in the same order. No clinical specifications or medication name was given to the assessor. All cognitive function test points were reported as corrected points. The data of the first evaluation of the BD group was used to compare the BD group and the control group. Time between the first evaluation and the follow-up evaluation varied between 6 and 77 months with 18 months as the intermediate (6 months n=3, 7-11 months n=8, 2-4 years n=3, 4-7 years n=7).

Statistical Analysis

Statistical analysis was made with the SPSS 15.0 program. Data of the control group and the BD group was compared using the Independent Groups T-test. Paired Groups T-test was used to compare BD group's first data and follow-up study data. A p-value of less than 0.05 was accepted as the measure of significance for the analysis between groups.

RESULTS

Socio-demographic and Clinical Features of Bipolar Disorder and Control Groups

The bipolar and control groups were similar regarding age and education. Average age (min-max) in the BD group was 36.6±11.1 (18-63) and 37.8±9.4 (22-61) (p=0.64) in the control group. The average education time was 13.2±4.3 and 12.9±2.9 ages (p=0.80), and 56.7% of the BD group consisted of women while, the control group was 40% (p<0.01) (Table 1).

For their first evaluation, the HAM-D scores of the BD group had an average of 3.7±3.5 compared to the control group of 1.8±1.6. The mean depression scores of the control group was significantly lower (p<0.01). Similarly, the mean HAM-A scores were 7.0±4.0 in the BD group versus 1.6±1.7 in the control group. The mean anxiety scores of the control group was significantly lower than the BD group (p<0.01), and the mean YMRS scores were significantly lower in the control group (0.0±0.0) compared to the BD group (1.3±2.7) (p<0.01). (Table 1)

Comparison of Cognitive Functions of Bipolar Disorder and Control Groups

Premorbid IQ

The WAIS-R scores of the BD and control groups were 11.4±3.4 and 11.5±2.3, respectively and showed no significant difference (p=0.83) (Table 2).

Attention

The WAIS-R Digit Span subtest performance of the BD group was found more impaired than the control group (6.7±2.4 and 8.7±2.6 respectively, p=0.01) (Table 2).

Executive functions

Concept Formation and Mental Flexibility

While no significant difference was found in the WAIS-R Similarities subtest scores (9.7±3.3 and 10.0±2.0, respectively, p=0.75), the scores of the BD group on WCST Completed Categories and WCST Perseverative Errors subtest were more impaired than the control group. The Completed Categories scores were lower (5.3±1.4 and 6.0±0.2, respectively, p<0.01) and the Perseverative Errors scores were higher (13.5±12.4 and 7.3±2.8 respectively, p<0.01) (Table 2).

Reaction Inhibition

Reaction inhibition, which is measured by lower Correction number in the SCWT, was found to be better in the control group. (Correction number in the BD group 0.8±0.8, the control group 0.3±0.6, p<0.01) (Table 2).

Table 1. Socio-demographic and Clinical Features of Bipolar Disorder and Control Groups

Variables	Bipolar Disorder (n=27)				Control (n=35)	Control and BB baseline comparison T-test	
	Baseline	Follow-up	T test				
	Mean (SD)	Mean (SD)	t	P	Mean (SD)	t	P
Age	36.6 (11.1)	39.1 (11.8)	-6.061	0.01	37.8 (9.4)	-0.473	0.64
Education (year)	13.2 (4.3)	13.2 (4.3)			12.9 (2.9)	0.258	0.80
Illness duration (month)	141.0 (138.2)	167.9 (141.6)	-4.676	0.01			
Number of hospitalization	1.1 (0.9)	1.3 (1.2)	-1.295	0.21			
Age of illness origin	23.4 (8.3)	23.4 (8.3)					
Number of depression episodes	3.7 (4.6)	3.7 (4.7)	-0.170	0.87			
Number of manic episodes	1.4 (1.4)	1.5 (1.7)	-0.698	0.49			
Number of hypomanic episodes	2.2 (4.6)	2.5 (4.7)	-1.558	0.14			
HAM-D	3.7 (3.5)	4.0 (3.4)	-0.331	0.74	1.8 (1.6)	2.921	0.01
HAM-A	7.0 (4.0)	8.0 (4.0)	-1.129	0.28	1.6 (1.7)	6.827	0.01
YMRS	1.3 (2.7)	1.6 (2.1)	-0.685	0.50	0.0 (0.0)	2.756	0.01
BPES	3.9 (5.0)	5.4 (3.5)	-1.381	0.18			
UPDES-M	2.6 (2.3)	3.9 (3.7)	-1.824	0.08			

HAM-D: Hamilton Depression Rating Scale, HAM-A: Hamilton Anxiety Rating Scale, YMRS: Young Mania Rating Scale BPES: Brief Psychiatric Evaluation Scale, UPDES-M: Unified Parkinson Disease Evaluation Scale – Motor Subscale

Set Shifting

According to TMT B-A scores, the set shifting skills were lower in the BD group (44.6±29.9 in the BD group and 27.7±7.5 in the control group, p<0.01) (Table 2).

Reasoning

The WAIS-R Picture Arrangement subtest scores were significantly higher in the control group compared to the BD group (9.4±2.1 and 6.4±2.6 respectively, p<0.01) (Table 2).

Abstracting

No difference was found in the WAIS-R Comprehension subtest scores of the BD and control groups (11.9±2.4 and 11.7±2.4 respectively, p=0.82) (Table 2).

Memory

Executive Memory

No significant difference was found in the WAIS-R Arithmetic subtest and ACT scores of the BD and control groups (WAIS-R Arithmetic subtest scores for BD group 9.1±3.6 and for the control group 10.3±3.8, p=0.18; ACT scores for BD group 46.6±8.5 and for the control group 48.5±6.5, p=0.38) (Table 2).

Verbal Memory

The WMS-R logical memory total score average was significantly lower than the control group (10±3.4 and 17.3±4.9 respectively, p<0.01) (Table 2).

Other Cognitive Functions

Visuospatial Perception

No significant difference was found in the WAIS-R Block Design subtest scores between the BD and control groups (8.7±3.1 and 8.9±2.7 respectively, p=0.75) (Table 2).

Psychomotor speed

The WAIS-R Digit Symbol subtest scores were significantly lower in the BD group than the control group (7.9±2.7 and 9.9±2.9 respectively, p<0.01) (Table 2).

Socio-demographic and Clinical Features of the Bipolar Disorder Group at Baseline and Follow-up evaluations

While the average age of the BD group was 36.6±11.1 in the first evaluation, the number was 39.1±11.8 in the follow-up. No difference was found in the evaluation for the HAM-D and HAM-A scores (3.7±3.5; 4.0±3.4 and 7.0±4.0; 8.0±4.0, respectively) (p=0.74; p=0.28). Similarly, the difference between the mean YMRS scores was non-significant (first evaluation 1.3±2.7; follow-up 1.6±2.1) (p=0.50). The mean BPES total scores did not show any significant difference between the baseline (3.9±5.0) and the follow-up (5.4±3.5) evaluations (p=0.18). Similarly, the mean UPDES-M scores did not show any significant difference between the baseline (2.6±2.3) and the follow-up (3.9±3.7) examinations (Table 1).

Table 2. Cognitive Functions of Bipolar Disorder and Control Groups

Cognitive functions	Bipolar Disorder (n=27)				Control (n=35)	Comparison control and bipolar patients baseline examination	
	Baseline Mean (SD)	Follow-up Mean (SD)	T-test T	P	Mean(SD)	T-test T	P
Premorbid IQ							
WAIS-R Information	11.4 (3.4)	10.9 (3.4)	1.317	0.20	11.5 (2.3)	0.218	0.83
Attention							
WAIS-R Digit Span	6.7 (2.4)	6.6 (1.6)	0.436	0.67	8.7 (2.6)	2.666	0.01
Executive Functions							
Concept Formation and Mental Flexibility							
WAIS-R Similarities	9.7 (3.3)	10 (3.6)	-0.361	0.73	10.0 (2.0)	0.324	0.77
WCST Completed Categories	5.2 (1.4)	5.2 (1.6)	0.198	0.84	6.0 (0.2)	2.982	0.01
WCST Perseverative Errors	13.5 (12.4)	15 (14.3)	-0.668	0.51	7.3 (2.8)	2.864	0.01
Response Inhibition							
SWCT	0.8 (0.8)	1.2 (0.8)	-1.514	0.15	0.3 (0.6)	2.945	0.01
Set Shifting							
TMT B-A	44.6 (29.9)	32.3 (18.9)	1.991	0.07	27.7 (7.5)	3.155	0.01
Reasoning							
WAIS-R Picture Arrangement	6.4 (2.6)	6.8 (2.5)	-1.500	0.17	9.4 (2.1)	-3.779	0.01
Abstracting							
WAIS-R Comprehension	11.9 (2.4)	11.6 (3.6)	0.297	0.77	11.7 (2.4)	0.218	0.83
Memory							
Working Memory							
WAIS-R Arithmetic	9 (3.6)	9.6 (2.8)	-1.209	0.24	10.3 (3.8)	-1.377	0.17
ACT	46.6 (8.5)	48.6 (8.7)	-1.351	0.20	48.5 (6.5)	-0.881	0.38
Verbal Memory							
WMS Logical Memory	10 (3.4)	10 (3.1)	-0.057	0.96	17.3 (4.9)	-6.517	0.01
Other Cognitive Functions							
Visuospatial Perception							
WAIS-R Block Design	8.7 (3.1)	9.4 (2.6)	-1.903	0.07	8.9 (2.7)	--0.323	0.75
Psychomotor Speed							
WAIS-R Digit Symbol	7.8 (2.7)	7.6 (2.8)	0.486	0.63	9.9 (2.9)	-2.838	0.01

WCST: Wisconsin Card Sorting Test, WAIS-R: Wechsler Adult Intelligence Scale - Revised, ACT: Auditory Consonant Trigrams, TMT: Trail Making Test, WMS: Wechsler Memory Scale. SCWT: Stroop Color-Word Interference Test.

Interestingly, the average time from the first episode was 141.0±138.2 months at the baseline evaluation and it increased (167.9±141.6 months) at the follow-up examination ($p<0.01$). No significant difference was found in the evaluations on the mean number that had mania, hypomania, and/or depression.

While the remission period on monotherapy was determined as a minimum of 1 month at the baseline evaluation, this range was determined from 6 months to 92 months in the follow up with18 months being the average value.

Lithium carbonate and sodium valproate blood levels were found within the therapeutic range at the baseline (0.7±0.1 and 73.7±8.1, respectively) and the follow-up (0.7±0.1 and 66.3±14.1, respectively) examinations. No significant statistical difference was found between the two evaluations ($p=0.59$, $p=0.42$, respectively).

Comparing Cognitive Functions of Bipolar Disorder Group at the Baseline and Follow-up Examinations

Premorbid IQ

The WAIS-R Information subtest score mean was not different at the baseline (11.4±3.4) and follow-up (10.9±3.4) evaluations ($p = 0.20$).

Attention

No significant difference was found between the baseline and follow-up evaluations on the WAIS-R Digit Span subtest (6.7±2.4 and 6.6±1.6 respectively, p=0.67).

Executive Functions

Concept Formation and Mental Flexibility

No significant difference was found for the WAIS-R Similarities subtests scores at baseline and follow-up evaluations (9.7±3.3 and 10±3.6, respectively) (p=0.73). Furthermore, no difference was found for the WCST Completed Categories mean scores (5.2±1.4 and 5.2±1.6) and WCEST Perseverative Errors mean scores (13.5±12.4 and 15±14.3) (p=0.84, p=0.51, respectively).

Reaction Inhibition

The mean correction number of the SWCT was 0.8±0.8 at baseline and 1.2±0.8 at the follow-up evaluations indicating that there was no change (p=0.15).

Set Shifting

The TMT B-A scores were calculated as the mean 44.6±29.9 at the baseline assessment and 32.3±18.9 at the follow-up assessment. No significant difference was found (p=0.07).

Reasoning

No significant difference was found for the WAIS-R Picture Arrangement subtest scores at baseline and follow-up examinations (6.4±2.6 and 6.8±2.5, respectively p=0.17).

Abstracting

No significant difference was found for the WAIS-R Comprehension subtest scores at baseline and follow-up evaluations (11.9±2.4 and 11.6±3.6, respectively, p=0.77).

Memory

Working Memory

No significant difference was found for the WAIS-R Arithmetic subtest and the ACT scores for the baseline and follow-up evaluations (WAIS-R Arithmetic subtest baseline 9±3.6 and follow-up evaluation 9.6±2.8, p=0.24; ACT baseline evaluation 46.6±8.5 and follow-up evaluation 48.6±8.7, p=0.20).

Verbal Memory

The WMS-R logical memory total score mean was 10±3.4 at baseline and 10±3.1 at follow-up evaluations with no statistical difference.

Other Cognitive Functions

Visuospatial Perception

The WAIS-R Block Design subtest scores were 8.7±3.1 at baseline evaluation and 9.4±2.6 at follow-up evaluation with no statistical difference (p=0.07).

Psychomotor Speed

No significant difference was found for the WAIS-R Digit Symbol subtest scores at baseline and follow-up evaluations (7.8±2.7 and 7.6±2.8, respectively p=0.63).

DISCUSSION

In this study, cognitive functions for BD patients in remission on monotherapy were compared with healthy controls and the cognitive functions of BD disorder patients was evaluated prospectively. The BD group showed worse cognitive function levels on the WCST Perseverative Errors and Completed Categories, TMT B-A, Stroop, WMS-R Logical Memory, WAIS-R Digit Span, WAIS-R Digit Symbol and WAIS-R Picture Arrangement tests when compared to healthy controls. On the other hand, there were no differences between the WAIS-R Arithmetic, Block Design, Comprehension, Similarities, and ACT test scores. The BD group's test scores did not change over time. The BD group showed worse levels of cognitive function in all tests regarding executive functions and some of the tests regarding memory, attention, and other cognitive functions. While these findings support part of our hypothesis, it does not support our assumption that cognitive dysfunction of the BD group worsens over time.

The results of our study were similar with other follow-up results in the literature (Mur et al 2008, Depp et al 2008, Tabarés-Seisdedos et al 2008, Torres et al 2014). In addition, it makes a favorable contribution, which fills an informational void in regards to the change of cognitive functions for follow-up patients on monotherapy over time.

The differences of cognitive functions between the BD and control groups may be related to the sub-threshold mood symptoms. Although they were in a remission period, the mood symptoms were significantly higher than the control group. Similarly, the mood symptoms of the BD group were not different between at baseline and follow-up evaluations. This may explain why the cognitive functions could not be identified differently in the follow-up.

According to Mann-Wrabel and colleagues' (2011) meta-analysis, the relationship of the cognitive function disorder and high-level education was inversely proportional. As they state, bipolar disease starts early and with poor prognosis, incapacitates education. Therefore, the disease with good prognosis and less cognitive dysfunction is observed among the ones with the higher level of education. This study fits with Mann-Wrabel and colleagues' (2011) meta-analysis and the statement as the follow-up group has a high level education and cognitive functions were stable in time. According to the evidence of the study, we can determine that patients on follow-up with monotherapy have better prognosis and the cognitive functions are relatively preserved. Furthermore,

the continuance of the well-being in the long term of the patients can also indicate good prognosis for this patient group. When comparing the manic period and the recovery period in the follow-up study of Yazıhan and colleagues (2015), failure of attention, memory, and learning functions was informed. We can suggest that new episodes, especially severe manic episodes, create cognitive dysfunctions. Findings in our study support the idea that no new episodes/less episodes are influential on the preservation of the cognitive functions. Torres and colleagues (2014) informed that processing speed and executive functions show linear progress in time and better progress was achieved on patients with no alcohol/substance abuse history and with the ones who no longer have antipsychotic treatment. In our study, the stable condition of cognitive functions in long term may be related to the fact that no patients with alcohol/substance abuse were present or no poly-pharmacy was applied. Bora and colleagues (2016) proposed that cognitive function impairment on BD was different between the patient groups. This suggests that the existence of subgroups, including patients with poor cognitive functions, similar to the ones with good cognitive functions. The patients in our study with their long remission periods and clinical surveys, may represent a subgroup displaying good cognitive functions.

The strength of this study was the thorough evaluation of cognitive functions and controlling confounding elements that may affect the BD - cognitive function relationship such as clinical symptoms and polypharmacy. In addition, re-evaluation of the cognitive functions of the patients in the process was as strength. It showed a difference from other reports especially on the evaluation of anxiety symptoms. Sampling size was good in comparison to other studies, and the samples accepted on the international scale were used for evaluations. In literature, it has been reported that follow-up time between two evaluations was from 1 to 3 years (Mur et al 2008, Depp et al 2008, Tabarés-Seisdedos et al 2008, Lewandowski et al 2013, Torres et al 2014). The follow-up period in our study was 2.4 years and we believe that it is enlightening on the long term progression for cognitive function.

Because the sampling group consisted of monotherapy patients, we can say that the findings can be generalized to patients with this specification. While generalized to patient groups with good prognosis, we cannot make any speculation about patients with poor prognosis. One of the limitations of our study is that we did not have any follow-up data for the control group. Another limitation of the study is that the follow-up period was not the same for each patient. Again, although patients were on monotherapy, the cognitive function/medication interaction was not able to be controlled. The cognitive functions according to medication groups could not be compared due to the small sample size. Another limitation of the study was that the clinical information (episode periods and the treatment being carried on mono or polypharmacy) between the two evaluations was controversial. It can be presumed that the patients may have had attacks during the follow-up and may have used additional medication. In our study, the preservation of the present cognitive functions indicates that the BD group showed a relatively good clinical progression, which suggests that monotherapy can be sustained.

For subsequent studies, the investigation of cognitive functions for patients especially with different medications is needed. In addition, the relationship of accompanying subthreshold depression and anxiety symptoms with cognitive functions along with genetic and neuroimaging studies may further our understanding of the disease.

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