Cognitive Functioning in Euthymic Bipolar Patients on Monotherapy with Novel Antipsychotics or Mood Stabilizers

Duygudurum Düzenleyici veya Atipik Antipsikotik ile Monoterapide Olan Ötimik Bipolar Bozukluk Hastalarının Bilişsel İşlevleri

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ABSTRACT

Introduction: Bipolar disorder is associated with cognitive dysfunction in several domains. Medication effect is a potential confounder that can only be statistically controlled in many studies. The cognitive profile in bipolar disorder during remission on maintenance antipsychotics or mood stabilizers medication has not been compared before.

Methods: We compared the cognitive profile of bipolar disorder patients euthymic for 2 month or more on monotherapy with novel antipsychotics (AP) (n=16), lithium carbonate (Li) (n=25) or valproic acid (VPA; n=26). Forty-two individuals were assessed as controls. The cognitive battery included Wechsler Adult Intelligence Scale-Revised (WAIS-R) subtests, the Wechsler Memory Scale (WMS), and Wisconsin Card Sorting Test (WCST).

Results: All three patient groups compared to controls performed poorly on the working memory and verbal memory tasks (F=3.59, df=3, p=0.02 for WAIS-R Arithmetic and F=123.64, df=3, p<0.01 for WMS Logical Memory). The differences remained significant after controlling for age. Across patients, the only significant difference was between the Li and AP groups in terms of working memory. The Li group performed better (F=3.59, df=2, p=0.02) and the difference survived correction for age and clinical features.

Conclusions: The findings of this study suggest that working memory impairment in bipolar patients on monotherapy with atypical AP, whereas verbal memory impairment might be related to bipolar disorder itself. Working memory might be a state marker, whereas verbal memory could be a trait marker of bipolar disorder. Atypical AP might have an adverse effect on cognition in bipolar disorder. These findings cannot be generalized to all bipolar patients, particularly the poor responders to monotherapy.

Keywords: Bipolar disorder, euthymia, lithium, valproic acid, atypical antipsychotic

ÖZ

Amaç: Bipolar bozuklukta bilişsel işlev bozukluğu görülmektedir. Farmakoterapinin bilişsel işlevler üzerindeki karıştırıcı etkisi birçok çalışmada istatistiksel olarak kontrol edilmeye çalışılmıştır. Ötimik dönemde bipolar bozukluğu olan ve atipik antipsikotik veya duygudurum düzenleyicilerle tekli ilaçla izlemde olan hastaların bilişsel işlevleri daha önceki çalışmalarda karşılaştırılmamıştır.

Yöntem: DSM-IV TR Bipolar Bozukluk tanısı konmuş olan ve tekli Li (n=25), VA (n=26) ya da İKAP (n=16) ile tedavide olan üç ötimik hasta grubu ve 42 sağlıklı kontrol grubu karşılaştırılmıştır. Wechsler Yetişkinler için Zeka (WAIS-R) alttestleri, Wechsler Bellek Skalası (WMS) ve Wisconsin Kart Tarama Testi (WCST) kullanılan bilişsel ölçekler arasında yer almaktadır.

Bulgular: Her üç hasta grubu kontrol grubuna oranla işlem belleği ve sözel bellek testlerinde kötü performans göstermiştir (WAIS-R Aritmetik için F=3,59, df=3 p=0,02; ve WMS Mantıksal Bellek için F=123,64, df=3, p<0,01). Bu farklılık yaşın etkisinin düzeltilmesinden sonra da devam etmiştir. Hasta grupları karşılaştırıldığında Li grubunda işlem belleği performansı İKAP grubundakinden daha yüksek bulunmuştur. Yaş ve klinik özellikler eşdeğişken olarak değerlendirildiğnde, her iki grup arasındaki fark anlamlı kalmıştır (F=3,59, df=2, p=0,02).

Tartışma: Bu çalışma bulguları bipolar bozukluğu olan hastalarda işlem belleğindeki bozulmanın atipik antipsikotiklerle ilişkili olabileceğini, sözel bellekteki bozulmanın ise bipolar bozukluğa özgü bir sorun olabileceğini telkin etmektedir. Bu bulgulara göre işlem belleği 'state marker' olarak değerlendirilebilirken sözel bellek 'trait marker' olarak değerlendirilebilir. Atipik antipsikotiklerin bipolar bozukluğu olan hastalarda bilişsel işlevleri üzerinde olumsuz etkileri olabilir. Bu çalışma bulguları özellikle tedavi yanıtı kötü olan bipolar bozukluklu hastalar başta olmak üzere tüm hasta grubuna genellenemez.

Anahtar kelimeler: Bipolar bozukluk, ötimi, lityum, valproik asid, atipik antipsikotik

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INTRODUCTION

Cognitive dysfunction has been one of the main research topics in bipolar disorder during the last decade. Several meta-analyses have focused on cognitive impairment in bipolar disorder in the euthymic period to investigate the magnitude and reasons for cognitive dysfunction (1,2,3). In a recent meta-analysis, Bourne et al. reported that there have been dysfunctions in euthymic patients, namely on executive functions, memory, and attention (3). However, a review by Mann-Wrobel et al. (2) suggested that there was no differential impairment in verbal memory and executive function. A meta-analysis by Robinson et al. (4) concluded that executive functions and verbal memory are the primarily affected cognitive functions, whereas attention, psychomotor speed, and immediate memory are considerably less affected in euthymic patients. However, conclusions of these meta-analyses are relatively different from each other in terms of the affected domains of cognition, effects sizes, and causes of cognitive dysfunctions in bipolar disorder, although aims and databases of the studies were similar.

The reason for cognitive dysfunction in bipolar disorder is unclear, since there are probably many factors effecting cognition in bipolar disorder. Mood symptoms and concurrent medication use are considered the main confounders in the studies on this topic (5,6).

Robinson and Ferrier (6) reviewed studies investigating the relationship between cognitive deficits and illness variables, which are one of the main confounders. Authors reported that characteristics of illness, particularly the number of episodes and hospital admissions and the duration of illness is related to cognitive dysfunction in patients with bipolar disorder

The effect of pharmacotherapy on cognitive functions is still uncertain due to limited number of studies. Moreover, the widespread use of polypharmacy in bipolar disorder (7,8,9) makes it difficult to understand the impact of individual pharmacological components on cognition. Videira Dias et al. (9) focused on the impact of pharmacotherapy on cognition in a recent systematic review. Authors suggested that lithium might have negative effects on psychomotor speed and verbal memory, and valproate was associated with attention and memory. In addition, there was a mild negative effect of atypical antipsychotics on cognitive functions in bipolar disorder. It is reported that there is a need for new studies to establish the effect of atypical antipsychotics on cognition, both in monotherapy and in association with other medications, specifically in this illness. In a study, Torrent et al. (10) focused on effect of atypical antipsychotics on cognition in euthymic bipolar patients and reported that there is possibly a negative effect of pharmacotherapy on cognition in euthymic bipolar patients.

To our knowledge, there are three studies comparing the extent and pattern of cognitive functions between bipolar patients on monotherapy with either lithium or valproate (11,12,13). Goswami et al. (11) compared patients on lithium and valproate and drug-free patients and control subjects. The three treatment groups showed poor performance on executive functions compared to controls. Gualteri and Johnson (12) reported that valproic acid had the most neurotoxicity compared to other anticonvulsants, whereas lithium effects on neurocognition were intermediate. Senturk et al. (13) suggested that impaired verbal memory was detected in euthymic bipolar patients comparing healthy controls. By contrast, no study has compared the effect of antipsyhotics and mood stabilizers on cognition in eutyhmic bipolar patients.

Aims of the Study

The aim of this study was to assess whether the antipsyhotics and mood stabilizers lithium and valproate had different effects on cognition in bipolar disorder. We investigated the performance of euthymic patients on monotherapy with the antipsychotics or mood stabilizers on two cognitive domains, namely memory and executive functions. We hypothesized that there would be a difference on memory and executive functions in euthymic bipolar patients on monotherapy with antipsychotics or mood stabilizers lithium or valproate. The findings of this study would add to the current knowledge with regard to a state marker of bipolar disorder or iatrogenic effects of treatments in bipolar disorder or both.

METHODS

Subjects

This is the extension of our previous study comparing the cognitive profile of bipolar disorder type I patients in remission with lithium or valproate monotherapy (13). To explore the cognitive profile in Bipolar I Disorder under atypical antipsychotic monotherapy and compare with the lithium and valproate groups, we included 67 patients diagnosed with bipolar disorder type I as per Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV who had been euthymic for 1 month or more and on monotherapy with either lithium (n=25) or valproate (n=26) or antipsychotics (n=16). Subjects in the atypical antipsychotics group were on quetiapine (n=9), olanzapine (n=7), and risperidone (n=1). Patients diagnosed with DSM-IV bipolar disorder type I who had been euthymic for 1 month or more and on monotherapy with lithium or valproate were included. The exclusion criteria were having a history of electroconvulsive therapy during the last year, depot antipsychotic use within the last 3 months, benzodiazepine use in the preceding week, mental retardation, head trauma, alcohol and substance use disorder, or any other central nervous system (CNS) disorder.

The lithium and valproate mean doses were 1014 mg/day and 1250 mg/day, respectively, at the time of clinical and neuropsychological assessment. Mean serum levels were 0.65 mEq/L for lithium and 70.57 mg/mL for valproate. Quetiapine (n=9), olanzapine (n=7), and risperidone (n=1) mean doses were 600, 12.5, and 4 mg/day, respectively.

Forty-two control subjects were included through newspaper advertisements. These subjects were screened for family history of psychiatric disorders; none of their parents had bipolar disorders. Written informed consent was obtained from all patients and control subjects. The study was approved by the Institutional Review Board in Ankara University School of Medicine. Some volunteers of this study also participated in another study that compared cognitive profile of euthymic bipolar patients on monotherapy with lithium or valproate (13).

Information on the illness characteristics were gathered from life charts, patient interview, and hospital medical records. The euthymic state was defined as low scores (<10) on the Hamilton Depression Rating Scale (HAMD) (14) and (<7) on the Young Mania Rating Scale (YMRS) (15).

Assessment Tools

Structured Clinical Interview for DSM-IV Axis I Disorders was applied to all subjects. The HAMD, YMRS, and Brief Psychiatric Rating Scale (BPRS) were used to assess mood severity and other clinical symptoms (14,15,16). Unified Parkinson's disease Rating Scale-Motor Examination (UPDRS-ME) was also conducted to assess slowing due to Parkinsonism, which might also influence cognitive functions (17). Patients were interviewed and assessed by two psychiatrists trained and experienced in the use of the scales that were applied. Consensus ratings were used in the statistical analyses.

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Cognitive assessment: Executive functions, mental flexibility, and categories completed were assessed using perseverative errors and categories completed on the WCST (18). Logical Memory Subscale of the Wechsler Memory Scale (WMS) was used to assess immediate verbal memory. The Wechsler Adult Intelligence Scale-Revised (WAIS-R) Information subtest was used as an approximation of premorbid cognition (19,20). The Vocabulary subtest was not used for this purpose, since Vocabulary scores may not reflect premorbid cognition in patient populations whose cognition is likely to be impaired (21). However, standard reading tests of premorbid cognition would depend less on the individual's level of knowledge in phonemic languages. The Digit Symbol Substitution, Arithmetic, and Block Design subtests of the WAIS-R were used to provide measures of psychomotor speed, working memory, and visuospatial abilities (22). These functions as measured using the WAIS-R subtests are considered more sensitive to illness effects or any CNS insult (21). A trained psychologist who was blinded to the medication applied neuropsychological assessments, and all tests were performed in the morning hours.

Statistical Analysis
Groups were compared in terms of age, education, premorbid IQ, and clinical features in a multivariate analysis of variance model (MANOVA).

Cognitive scores were normally distributed in all groups except for the two WCST subtests. For the comparison of cognitive performance across the four groups, another MANOVA was performed using the individual test scores as the dependent variables and age as a covariate. Other variables which differed significantly across groups, namely, the duration of illness, age at onset, and YMRS and BPRS scores, were also included as covariates.

RESULTS
Sociodemographic and clinical features of the whole sample are summarized in Table 1. Age was significantly different across groups. There were no significant differences in terms of sex distribution, level of education, or premorbid cognition.

Sociodemographic and Clinical Variables of Lithium, Valproate, and Atypical Antipsychotic Treatment Groups
Patients on valproate treatment were younger than those on atypical antipsychotics and patients on lithium treatment groups; however, the difference between the three groups was not significant (F=1.53, df=2, p=0.23). The duration of education did not differ significantly between lithium, valproate, and antipsychotic groups (F=1.49, df=2, p=0.22).

The treatment groups were similar in terms of gender distribution (x^2=0.98, df=2, p=0.61); number of hospitalizations (F=0.71, p=0.50); number of depressive (F=0.56, p=0.57), manic (F=0.38, p=0.69), hypomania (F=1.12, p=0.33), and mixed (F=1.01, p=0.37) episodes; remission period (F=1.17, p=0.32); monotherapy period (F=0.82, p=0.45); comorbid physical (x^2=0.31, df=2, p=0.87) and psychiatric illnesses (x^2=5.37, df=2, p=0.07); psychiatric history in the family (x^2=0.47, df=2, p=0.79); and the estimated premorbid IQ (F=0.80, p=0.46). Most of the patients on lithium, valproate, and atypical antipsychotics had psychotic symptoms (80%, 65%, and 87%, respectively) in their previous episodes, and there was no statistical difference between the three treatment groups (x^2=2.73, df=2, p=0.26). Although duration of illness was longer (14.8±11.2 years) in the lithium treatment group compared to valproate (9.6±9.6 years) and atypical antipsychotic (8.9±8.3 years) groups, the difference was not

Table 1. Sociodemographic and clinical features of groups

	Li Mean (SD)	VPA Mean (SD)	AP Mean (SD)	Control Mean (SD)	MANOVA F	p
Age (years)	39.8 (11.3)	34.4 (15.0)	39.9 (8.2)	26.8 (5.2)	11.47	<0.01
Education (years completed)	12.8 (3.7)	12.6 (3.6)	12.0 (4.9)	11.0 (3.5)	1.49	0.22
Estimated premorbid cognition (WAIS-R Information subscore)	19.5 (6.0)	20.0 (5.1)	17.7 (6.7)	20.7 (4.3)	1.3	0.27
Age at onset (years)	22.4 (10.3)	24.9 (10.4)	30.3 (6.8)	-	3.32	0.04
Duration of illness (years)	14.8 (11.2)	9.6 (9.6)	8.9 (8.3)	-	2.39	0.10
Duration of remission (months)	2.6 (2.4)	2.1 (2.8)	1.4 (1.8)	-	1.17	0.32
Duration of current treatment (months)	14.2 (24.8)	11.9 (20.4)	5.7 (7.5)	-	0.82	0.45
Number of hospitalizations	1.1 (1.0)	1.1 (0.9)	1.5 (1.2)	-	0.71	0.50
Number of depressive episodes	3.2 (4.2)	2.5 (3.3)	2.0 (2.6)	-	0.56	0.57
Number of manic episodes	2.2 (1.6)	2.6 (2.6)	2.1 (1.1)	-	0.38	0.69
Number of hypomanic episodes	1.2 (2.3)	0.4 (1.1)	1.1 (2.7)	-	1.12	0.33
Number of mixed episodes	0.2 (0.5)	0.2 (0.7)	0.0 (0.0)	-	1.01	0.37
HAMD score	1.8 (1.7)	3.5 (4.5)	3.4(3.8)	-	1.89	0.16
YMRS score	0.6 (1.9)	2.2 (3.1)	0.9 (1.7)	-	2.86	0.07
BPRS score	1.8 (3.8)	5.8 (7.6)	3.6 (4.2)	-	3.10	0.05
UPDRS-ME score	3.1 (3.9)	4.4 (4.9)	2.0 (1.9)	-	1.79	0.18
	%	%	%		χ^2	dfp
History of psychotic symptoms	80	65	87	-	2.73	20.26

AP: novel antipsychotics; BPRS: Brief Psychiatric Rating Scale; HAMD: Hamilton Depression Rating Scale; Li: lithium carbonate; SD: standard deviation; UPDRS-ME: United Parkinson Disease Rating Scale-Motor Examination; VPA: valproic acid; YMRS: Young Mania Rating Scale

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statistically significant (F=2.39, p=0.10). The only statistically significant difference on clinical variables was the age at illness onset (F=3.32, p=0.04), which was higher in the antipsychotic group (Table 1).

Hamilton Depression Rating Scale scores in lithium, valproate, and atypical antipsychotics groups were 1.8±1.7, 3.5±4.5, and 3.4±3.8, respectively, and the difference between three groups was not significant (F=1.89, p=0.16). YMRS scores were 0.6±1.9, 2.2±3.1, and 0.9±1.7 in lithium, valproate, and atypical antipsychotics groups, respectively. Regarding YMRS scores, the difference between the groups was also not significant (F=2.86, p=0.07). The mean BPRS scores of lithium, valproate, and atypical antipsychotics groups were 1.8±3.8, 5.8±7.6, and 3.6±4.2, respectively, and the difference between three groups was at the borderline (F=3.10, p=0.05). The mean UPDRS-ME scores of lithium, valproate, and atypical antipsychotics groups were 3.1±3.9, 4.4±4.9, and 2.0±1.9, respectively, and the difference between three groups was not significant (F=1.79, p=0.18).

Cognitive Functions of Patients and Comparison Subjects

The initial MANOVA was significant (F=8.26, df=18,276, p<0.01), with differences across groups in terms of working memory (F=3.36, df=3, p=0.02), psychomotor speed (F=6.74, df=3, p<0.01), and verbal memory (F=158.05, df=3 p<0.01), but not for visuospatial ability (F=2.52, df=3, p=0.06) or executive functions, namely, concept formation (WCST 4; F=2.45, df=3, p=0.07), or mental flexibility (WCST 6; F=2.37, df=3, p=0.08; Table 2).

The post-hoc analysis indicated poorer verbal memory (WMS) for all three patient groups compared to controls (control>lithium=valproate=antipsychotic) and better working memory performance in the lithium, valproate, and control groups compared to the antipsychotic group (lithium=control=valproate>antipsychotic). Visuospatial abilities and executive functions were not significantly different (Table 2).

All significant differences survived correction for age in the multivariate analysis of covariance model (MANCOVA; F=7.81, df=18, 273, p<0.01) analysis, with the exception of psychomotor speed (F=1.95, df=3, p=0.13). Univariate comparisons indicated the same pattern, with no significant difference for visuospatial ability (F=1.35, df=3, p=0.26), better working memory in the lithium group compared to the antipsychotic group (F=3.59, df=3, p=0.02) and worse verbal memory performance in all three patient groups compared to controls (F=123.64, df=3, p<0.01; Table 2).

Cognitive Functions of Lithium, Valproate, and Atypical Antipsychotic Groups

Executive functions were similar across the three groups as assessed by their concept formation abilities (Categories Completed) and mental flexibility (Preservative Errors) on the WCST (F=0.44, df=2, p=0.65 and F=0.87, df=2 p=0.42, respectively). Psychomotor speed, visuospatial abilities, and verbal memory performances were also similar (F=2.90, df=2, p=0.06 for the WAIS-R Digit Symbol Substitution; F=0.22, df=2, p=0.80 for the WAIS-R Block Design; and F=0.44, df=2, p=0.65 for the WMS Logical Memory scores, respectively). The main effect of the treatment group was significant for working memory (F=3.58, df=2, p=0.02 for the WAIS-R Arithmetic scores). Univariate comparisons indicated that the only significant difference was between the lithium and the antipsychotic groups with a higher performance by lithium. The differences were non-significant between the lithium and valproate or the antipsychotic and valproate groups (Table 3).

Associations Between Sociodemographic, Clinical Variables, and Cognitive Dysfunction in Lithium, Valproate, and Atypical Antipsychotic Groups

The MANCOVA model was used to detect possible further associations between sociodemographic, clinical variables, and cognitive dysfunction.

Table 2. Neuropsychological performance of bipolar patients on monotherapy treatment groups Li, VPA, AP, and control subjects

| | Li | VPA | AA | Control | MANOVA | | MANOVA | |
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	p	F	p
Executive function, concept formation								
WCST-categories	4.9 (1.8)	5.4 (1.5)	4.7 (1.9)	5.6 (0.8)	2.45	0.07	0.46	0.71
Executive function, mental flexibility								
WCST-preservative errors	17.9 (15.6)	17.1 (17.4)	24.1 (19.1)	13.0 (9.7)	2.37	0.08	0.48	0.69
Working memory								
WAIS-R-arithmetic	12.6 (3.6)	11.1 (4.2)	8.8 (3.4)	11.0 (3.3)	3.36	0.02*	3.59	0.02 *
psychomotor speed								
WAIS-R-digit symbol substitution	44.6 (14.3)	44.2 (14.1)	41.4 (17.2)	55.6 (10.7)	6.74	<0.01*	1.95	0.13
Visio-spatial abilities								
WAIS-R-block design	26.6 (9.9)	30.4 (7.0)	23.4 (9.3)	30.0 (9.8)	2.52	0.06	1.35	0.26
Verbal memory								
WMS	10.7 (3.8)	10.9 (3.1)	9.8.0 (4.1)	29.4 (4.9)	158.05	<0.01*	123.64	<0.01*

AP: novel antipsychotics; SD: standard deviation; VPA: valproic acid; WAIS-R: Wechsler Adult Intelligence Scale-Revised; WCST: Wisconsin Cart Sorting Test; WMS: Wechsler Memory Scale
MANOVA model shows crude analysis
MANCOVA model shows adjusting for age
*: p<0.05
Post-hoc tests: Li=control=VPA>AP for working memory, Control>Li=VPA=AP for verbal memory

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Table 3. Neuropsychological performance of bipolar patients on monotherapy treatment groups Li, VPA, and AP

	Li Mean (SD)	VPA Mean (SD)	AP Mean (SD)	MANOVA F	MANOVA p	MANOVA F	MANOVA p
Executive function, Concept formation							
WCST-Categories completed	4.9 (1.8)	5.4(1.5)	4.7 (1.9)	0.44	0.65	0.28	0.76
Executive function, Mental flexibility							
WCST-Preservative errors	17.9 (15.6)	17.1 (17.4)	24.1 (19.1)	0.87	0.42	0.51	0.61
Working memory							
WAIS-R-Arithmetic	12.6(3.6)	11.1 (4.2)	8.8 (3.4)	4.46	0.02*	4.02	0.02*
Psychomotor speed							
WAIS-R-Digit Symbol Substitution	44.6(14.3)	44.2(14.1)	41.4 (17.2)	0.22	0.80	0.36	0.70
Visio-spatial abilities							
WAIS-R-Block design	26.6(9.9)	30.4 (7.0)	23.4 (9.3)	2.90	0.06	1.74	0.19
Verbal memory							
WMS Logical Memory	10.7(3.8)	10.9 (3.1)	9.8 (4.1)	0.44	0.65	0.08	0.93

AP: novel antipsychotics; SD: standard deviation; VPA: valproic acid; WAIS-R: Wechsler Adult Intelligence Scale-Revised; WCST: Wisconsin Cart Sorting Test; WMS: Wechsler Memory Scale
*: $p < 0.05$, difference between lithium and atypical antipsychotic groups
Adjusted for age, duration of illness, age at onset, YMRS scores, and BPRS scores

To achieve a strict control over confounders, a p value of as high as 0.1 was set as the criterion to include a potential covariate in the MANCOVA model. The variables included were age, duration of illness, age at onset, and the YMRS and BPRS scores (Table 3). In the cautious MANCOVA model that included all the covariates, the difference between the lithium and the antipsychotic groups in terms of working memory remained significant (p=0.02).

DISCUSSION

In this study, cognitive functions, namely executive functions, verbal memory, and working memory, of euthymic bipolar patients who were either on lithium, valproate, or atypical antipsychotics monotherapy were compared to each treatment group and control subjects. Cognitive performances, except working memory of patients in three treatment groups, were similar, whereas verbal memory was different between the patients and control subjects. Verbal declarative memory impairment is one of the most consistently reported cognitive dysfunctions in euthymic bipolar patients (5, 23, 24, 25). The impairing effects of subclinical symptoms and/or medication on short-term memory might explain these findings. Cognitive dysfunction also might be related to the underlying pathophysiology of bipolar disorder itself. The possible mechanism of memory deficits in bipolar patients could be attributable to the abnormal activity in frontal, occipital, and limbic regions (26, 27). Another study suggests that a disturbed right-hemispheric interaction between the amygdala and cortical brain regions may be responsible for amygdala hyperactivation and the related memory deficits in bipolar patients (28).

The findings suggest that the working memory might be differentially impaired in patients on lithium and those on antipsychotic's. In contrast, verbal memory appears to be adversely influenced either by the disease process or by all three types of medications to a comparable degree or both. In our previous study comparing the two mood stabilizers, we found similar levels of verbal memory impairments in the lithium and valproate groups and suggested that verbal memory deficits might be a trait of bipolar disorder (13). An alternative explanation could be a high sensitivity

of the logical memory task to any insult potentially associated with many nonspecific conditions including bipolar disorder as well as various types of treatment.

These results suggest that subclinical symptoms and the type of pharmacotherapy could have an effect on the cognitive functions where the working memory could be affected by pharmacotherapy, whereas verbal memory could be affected by symptoms. Although all patients in this study were euthymic according to the HDRS and YMRS scores, subclinical symptoms might have been detected with BPRS. These findings suggest that it is important to be aware of and to assess subclinical symptoms with different scales.

To our knowledge, the literature comparing cognitive functions of euthymic bipolar patients on monotherapy with lithium and valproate is limited to three studies (11, 12, 13), and assessing effect of atypical antipsychotics on cognitive functions in these patients is limited to one study (10). However, there is no literature comparing cognitive functions of euthymic bipolar patients on monotherapy with mood stabilizers and atypical antipsychotics and control subjects.

Gualtieri and Johnson (12) reported that valproic acid had the most neurotoxicity compared to other anticonvulsant, whereas the lithium effects on neurocognition were intermediate. Authors did not report the clinical variables, such as HDRS and YMRS scores. Therefore, it is difficult to compare of the results of the present study with that of Gualtieri and Johnson (12), where the symptoms could have an effect on cognitive functions. Goswami et al. (11) compared patients on lithium and valproate and those not on pharmacotherapy and control subjects; the three treatment groups performed worse on executive functions tests compared to controls. Senturk et al. (13) reported that impaired verbal memory was detected in euthymic bipolar patients compared to healthy controls.

Meta-analyses suggest that bipolar patients exhibit neuropsychological impairments that persist even during the euthymic state (1,3,4). Cogni- 248

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tive dysfunctions in bipolar illness are considered unlikely to be a primary effect of medication (29,30). However, findings of the present study are contrary of the previous findings suggesting that it might be due to effect of both bipolar illness and medication. The neuroprotective effects of chronic lithium treatment and other mood stabilizers could be another explanation for the selective cognitive impairment in our study sample (31,32).

Regarding the effects of atypical antipsychotics on neurocognition, Torent et al. (10) reported that euthymic patients on atypical antipsychotics performed worse than healthy subjects, particularly on verbal learning and memory, working memory, attention, and executive functions. Furthermore, medicated groups performed poorly on certain cognitive tests, such as semantic fluency. Authors have suggested that the iatrogenic pharmacological effect cannot be excluded. Findings from present study are in line with those results suggesting that cognitive side effects should be considered when treating patients with bipolar disorder (10). A recent review advises that pharmacotherapy for bipolar disorder should be chosen to minimize cognitive side effects, which is similar to the present study (9).

Olanzapine and risperidone are potent Dopamin D2 receptor antagonists. It might be an explanation of the poor performance on the working memory test of patients on monotherapy with atypical antipsychotic in this study.

The neurocognitive impairment could be a contributing factor to poor psychosocial functioning in bipolar disorder (6). However, the etiology of such impairment and its relation to progression of illness are not well understood. These deficits should be considered in rehabilitation programs in bipolar disorder.

The present study has some limitations, such as information bias regarding antipsychotic use in the past, sample size, and cross-sectional study design. Moreover, data on the history of antipsychotics use available through reviewing patient records is not representative of lifetime antipsychotics use.. Due to modest sample sizes of our treatment groups, partially due to the strict inclusion and exclusion criteria, the possibility of a type II error needs to be considered.

The study implications are limited by the cross-sectional nature of the design. A longitudinal design would allow evaluating whether some deficits have been present before illness onset or the effect of medication. As Donaldson et al. (29) suggested, the best way to elucidate medication-related effects would be to conduct studies on healthy subjects.

Although the best probable way to establish whether cognitive impairment is related to illness and not to medication is the inclusion of drug-free or drug-naive bipolar patients, conducting such a study would be challenging. In addition, here are other variables that need to be investigated, such as psychotic symptoms, rapid cycling, comorbidity, and family history of psychotic or affective disorders (6).

The findings of this study add to the existing literature with regard to specific, working memory, impairment in bipolar patients on monotherapy with atypical antipsychotic, whereas verbal memory impairment might be a state marker of bipolar disorder, which is in line with the recent meta-analysis results. This may also result from a similarity of lithium and valproate in terms of their adverse effects on verbal memory. Deficits in working memory might have important effects on daily functioning; therefore, caution is needed in patients on antipsychotics against cognitive dysfunction and its potential impact on daily functioning.

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