Lithium Treatment Effects on the Neuropsychological Functioning of Patients With Bipolar I Disorder

Carlos López-Jaramillo, MD, Msc; Juan Lopera-Vásquez, PsyD; Jorge Ospina-Duque, MD; Jenny García, MD, Msc; Aurora Gallo, PsyD; Vladimir Cortez, MD; Carlos Palacio, MD, Msc; Carla Torrent, PsyD; Anabel Martínez-Arán, PhD; and Eduard Vieta, MD, PhD

Objective: To determine if medication plays a major role in cognitive impairment in bipolar disorder and if regular treatment with lithium influences the cognitive performance of a group of euthymic patients with bipolar I disorder.

Method: Cognitive performance was assessed using neuropsychological tests of attention, memory, and executive function on 60 subjects: 20 euthymic bipolar I patients with no medication intake, 20 euthymic bipolar I patients who were following regular treatment with lithium carbonate monotherapy, and a third group of 20 control healthy subjects. The subjects were evaluated from January 2005 to October 2006. Patients were diagnosed using *DSM-IV* criteria for bipolar disorder.

Results: Compared to the healthy group, bipolar I patients had significantly lower performance on episodic verbal and visual-verbal memory regardless of their medication status. No significant cognitive performance differences were found between the two groups of patients with bipolar disorder, suggesting that lithium therapy had no deleterious effects on cognition.

Conclusion: Patients with bipolar I disorder have verbal memory deficits that are not explained by medication or by lithium monotherapy, but by the condition itself.

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Corresponding author: *Carlos López-Jaramillo, MD, Msc, Department of Psychiatry, School of Medicine, Universidad de Antioquia, Cra 43A No 1-50 Of 954, Medellín, Colombia (clopez@medicina.udea.edu.co).*

Growing evidence indicates that bipolar disorder is associated with cognitive deficits,[1] and that those deficits persist beyond acute episodes and during long-term remission.[2–5] Neurocognitive impairment has been reported to affect verbal memory, executive function, processing speed, psychomotor speed, and attention, but studies are not consistent, and differences were found in the set of altered cognitive processes.[1,6] Such differences in the results may be due to methodology issues and the neurocognitive tests used to assess neuropsychological functioning. Furthermore, the number of noncontrolled variables may alter the results obtained, as they have an important influence on cognition. These variables include age, level of education, illness history, chronicity, number of previous episodes, subthreshold symptoms, and especially the effects of medication.[1,7] Studies involving unmedicated subjects are extremely rare.[8]

Lithium is one of the most widely used medications for the treatment of bipolar disorders[9] and its potential benefits and downsides with regard to its effects on cognition are still a matter of controversy.[10] Patients on lithium treatment may complain about psychomotor slowness[11–13] and problems with attention, concentration, and memory,[12] short-term memory,[14] creativity,[15] and verbal fluency.[12,16] In a comparative study between 5 anticonvulsants and lithium,[17] the effects of the latter on neurocognition were intermediate. In a recent study comparing remitted bipolar patients on monotherapy with lithium or valproate,[18] both groups were associated with mild to moderate verbal memory impairment. There is, however, a lack of consistency among the findings, and preclinical studies have suggested that lithium could have neuroprotective effects.[19,20] Hence, the potential cognitive side effects of lithium have to be balanced with potential benefits on the long-term; in fact, there is some evidence that bipolar patients on long-term lithium therapy do not worsen from the cognitive point of view.[21]

Given the extremely limited data on unmedicated bipolar patients and on the cognitive effects of lithium, this study enrolled strictly-defined euthymic bipolar patients, nonmedicated or receiving lithium treatment as monotherapy, and a control group of healthy individuals, and compared them across several neuropsychological measures.

METHOD

Participants

We evaluated 60 subjects by means of psychiatric history and neuropsychological profile. The subjects were evaluated from January 2005 to October 2006. Twenty of them were patients diagnosed with *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) bipolar I disorder and had been euthymic for at least 6 months despite being on no medication at the time of the assessment. The second group was also fulfilling *DSM-IV* criteria for bipolar disorder but under regular treatment over at least 2 months with lithium carbonate monotherapy at therapeutic blood levels (0.6–1.2 mEq/L) and was composed of 20 patients. In addition, a third group of 20 healthy control subjects without history of psychiatric pathology was also evaluated.

None of the subjects in any group had taken benzodiazepines, antipsychotics, or any other medication that affects the central nervous system (eg, β-blockers, steroids, anticholinergics) during the 4 weeks prior to the evaluation, with the exception of lithium for the second group. Likewise, subjects with a history of other psychiatric or neurologic disorders that could be related to neuropsychological impairment, epilepsy, mental retardation, or electroconvulsive therapy were excluded. Other inclusion criteria were age and schooling. The ages of the subjects ranged between 18 and 50 years, and all subjects had between 5 and 16 years of schooling in order to control for the influence of illiteracy and of the low and high level of education.

All the subjects with bipolar disorder regularly visited the Mood Disorders Program of the Faculty of Medicine of the University of Antioquia at the University Hospital San Vicente de Paúl in Medellín. The research protocol used was approved by the Ethics Committees from both institutions, and all the subjects read, understood, and signed an informed consent form before any evaluation.

Clinical Assessments

Patients had to fulfill *DSM-IV* criteria for lifetime bipolar disorder in remission for at least 6 months. Throughout this period, they were assessed on a regular basis in the psychiatry service of the Hospital San Vicente de Paúl. Thus, euthymia could be corroborated by an expert psychiatrist, who also used the Spanish versions of the Young Mania Rating Scale (YMRS)[22,23] and the Hamilton Depression Rating Scale (HDRS)[24] in order to guarantee that there were no subclinical symptoms when the patients were being evaluated. The criteria for euthymia were a HDRS score ≤ 4 and a YMRS score ≤ 6.

Neuropsychological Assessment

Following the psychiatric interview, a battery of neuropsychological tests was applied to the 3 groups. The tests were selected as they were the most frequently used for such a population and also because they evaluate the cognitive functions that usually show some kind of alteration in bipolar patients, like memory, executive function, and attention.[6,25] Additionally, the simplified Wechsler Adult Intelligence Scale (WAIS),[26] consisting of vocabulary, similarities, arithmetic, comprehension, cubes, and picture completion subtests, was applied to them in order to test their intellectual ability.

The administration of these tests took approximately 2 hours. For each individual, the battery of tests was carried out on a date and at a time when he or she felt in ideal physical and mental condition for its application. Standard instructions were given to every subject. Fifteen-minute breaks were allowed in some cases, in order to avoid bias related to mental fatigue.

For the assessment of alertness and supported attention abilities, we used the Continuous Visual Performance Test.[27] For the assessment of executive control of attention, in contrast, we used the Trail Making Test Part B,[28] together with the Stroop Test,[29] which also provides information on inhibitory capacity. Likewise, we applied the Wisconsin Card Sorting Test[30] for the assessment of other components of the executive function such as the ability for categorizing, modifying the behavior, and learning from experience. Besides, the Test of Verbal Semantic and Phonological Fluency[31] provides information about both executive skills, such as searching strategy design and verbal fluency.

Episodic verbal memory was evaluated with the California Verbal Learning Test (CVLT),[32] to obtain information about the verbal learning capacity from a list of words, free and cued delayed recall, and immediate free and cued recall. The subtest of logical memory of the Wechsler Scale was also used in both free recall and recognition.[33] The associative memory test with semantic increase[34] was applied to obtain information about episodic memory when associating a verbal stimulus with its visual representation. To assess visual memory, we used the visual reproduction subtest from the original Wechsler Scale,[33] or the immediate recall of the Rey Figure[35] for more complex stimuli. Operative memory was obtained using the Wechsler Scale's backward digit subtest,[33] and the forward digits of the same scale were used to obtain immediate memory.

Psychomotor speed was measured using the digit-symbol test from the (WAIS),[26] as well as the Trail Making Test (parts A and B) and the Stroop Test.

Data Analysis

The data were scrubbed using statistic resources such as frequencies, averages, and graphic distribution. To describe the participant subjects, central tendency and dispersion measures were used for quantitative variables, and frequency and percentages were used for qualitative variables.

For the statistical analysis, the SPSS 14.0 (SPSS Inc., Chicago, Illinois) software was used. The sociodemographic and clinical features of the subjects of each group were described using measures of central tendency and measures of dispersion for continuous variables, and frequencies and percentages were used for categorical variables. Continuous variables were evaluated with a Shapiro-Wilk test to determine the normal distribution of the data.

Because the variables did not have normal distribution, we used nonparametric tests. The nonparametric Kruskal-Wallis test was implemented to compare the results of neuropsychological tests in the studied population and to determine the differences. We used the Mann-Whitney *U* test for comparison between the 3 groups; *P* values less than .05 were considered to be significant. The magnitude of difference among the groups was calculated using the effect size (ES) proposed by Cohen[36]; effect sizes > 0.75 were considered significantly high.

RESULTS

Clinical and Demographic Variables

No significant differences were found regarding several baseline parameters such as age, level of education, estimated premorbid IQ, or results of the YMRS and

Table 1. Sociodemographic and Clinical Features of the Studied Subjects

Features	Bipolar I Disorder Under Lithium Treatment (n = 20)		Bipolar I Disorder Without Pharmacologic Treatment (n = 20)		Control (n = 20)		Kruskal-Wallis Test, χ^2	Mann Whitney *U* Test	*P*
	Median	IQR	Median	IQR	Median	IQR			
Age, y	38.5	31.5–46.7	40	36–41.7	39.5	33.7–46	0.25	…	.88
Level of education, y	11	6.2–12.7	10	6.2–13.7	11	6.2–13.5	0.08	…	.96
WAIS score	91.5	79.2–106.2	95	84.7–102.7	95.5	86.2–110.5	1.49	…	.47
HDRS score	3	2–4	2	1–3	2	0.25–3	4.7	…	.03
YMRS score	0	0–2	1	0–1.7	0	0–2	2.04	…	.36
Total no. of episodes	3	2–3	3	2–3.7	…	…	…	189	.98
No. of depressive episodes	0	0–0	1	0–2	…	…	…	116.5	.06
No. of manic episodes	1	1–3	1	0–2	…	…	…	160.5	.56
No. of mixed episodes	0	0–1	0	0–1	…	…	…	176.5	.91
No. of hypomanic episodes	0	0–0	0	0–0	…	…	…	135	.81
Age at onset, y	28	21–36	22	18.2–28.5	…	…	…	120	.05
History of bipolar I disorder, y	11	7–18	18	10.2–22.7	…	…	…	116.5	.04
No. of psychiatric hospitalizations	3	1–4	2	1–3.7	…	…	…	175.5	.68
Lifetime exposure to lithium, mo	72	39–117	6	2–70	…	…	86.5	…	.01

Abbreviations: HDRS = Hamilton Depression Rating Scale, IQR = interquartile range, WAIS = Wechsler Adult Intelligence Scale, YMRS = Young Mania Rating Scale.

HDRS scales. Table 1 shows the demographic variables and scores provided by the mania and depression scales in the 3 assessed groups. The data are expressed in terms of median and interquartile range because of the reduced sample size used. The arithmetic mean would not be truly representative of the data because there is too much variability.

No differences were found for clinical features of the two bipolar patient groups either, as shown in Table 1. Such features included total number of episodes in general, total number of depressive, manic, mixed and hypomanic episodes, and number of psychiatric hospitalizations. Besides, the low scores in both the YMRS and HDRS scales confirmed the absence of relevant residual affective symptoms. Other clinical variables such as age at onset, illness history, and lifetime exposure to lithium showed statistical differences among the groups. The 3 variables were adjusted using an analysis of covariance, and the results show that, from the statistical point of view, none of these 3 variables had any effect.

Neuropsychological Variables

No statistically significant differences were found between the patients who did not consume any medication and those regularly treated with lithium. However, statistically significant differences were found between the group of lithium-treated patients suffering from bipolar I disorder and the control group in the cued recall ($P = .06$; ES = 1.00) and cued delayed recall ($P = .017$; ES = 0.90) variables of the test for associative memory with semantic increase. Differences were also found in the recognition of logical memory ($P < .001$; ES = 1.35) of the Wechsler Memory Scale, as well as in the CVLT's free short recall ($P = .018$; ES = 0.99), cued short recall ($P = .085$; ES = 0.87), and cued delayed recall ($P = .005$; ES = 1.81) variables.

On the other hand, when comparing the control group with the group of bipolar I patients who did not take any medication, significant differences were found in the cued short recall ($P = .020$; ES = 0.85) and cued delayed recall ($P = .009$; ES = 0.89) variables of the test for associative memory with semantic increase. Differences were also found in the backward digits ($P = .024$; ES = 0.79) and recognition of logical memory ($P = .000$; ES = 1.29) variables of the Wechsler Scale, as well as in the CVLT's free short recall ($P = .003$; ES = 1.28), cued short recall ($P = .123$; ES = 0.78), and cued delayed recall ($P = .040$; ES = 0.80).Otherwise, the age at onset, the illness history, and neuropsychological variables in the 2 groups of patients with bipolar I disorder were not significantly correlated. A complete account of the neuropsychological variables is shown in Table 2.

DISCUSSION

The results of this study confirm that there are medication-unrelated cognitive deficits associated with bipolar disorder during remission. This is a relevant finding, because the vast majority of studies claiming to find such deficits have been conducted on patients taking medication or acutely ill. The study also suggests that regular treatment with lithium may not have deleterious effects on cognitive performance of patients with bipolar disorder.

A recent meta-analysis[6] gathered the results of 26 studies on euthymic bipolar subjects and found strong evidence for verbal memory and executive function alterations in bipolar subjects. Nevertheless, the authors stated that it cannot be concluded that the cognitive deficits are a characteristic feature of the illness, as the medication and residual mood symptoms are confusing factors. However, recently, Mur et al[37] found, in a sample of bipolar outpatients treated with lithium as the main mood stabilizer, that impaired executive function and loss of inhibition might be an important feature in bipolar disorder regardless of the effects of medication. Our study provides further insight on the hypothesis that the capacity to use appropriate storing strategies leads to memory alteration, which could be considered as one of the features of bipolar I disorder. The 3 groups' high similarity in variables such as age, level of education, and intellectual coefficient shows that these had no influence on the reported

Table 2. Neuropsychological Features of the Studied Subjects

Features	Bipolar I Disorder Under Lithium Treatment (n = 20)		Bipolar I Disorder Without Pharmacologic Treatment (n = 20)		Control (n = 20)		Kruskal-Wallis Test, χ^2_2	P^a
	Median	IQR	Median	IQR	Median	IQR		
Trail Making Test A time	67.5	51.2–89.2	54.5	42.7–80.2	62.5	49–79.2	2.17	.34
Trail Making Test B time	124.5	83.2–181	104.5	76.2–235	101	70.2–155	1.50	.47
Stroop test-interference	72.5	57.5–81.2	66.5	58.7–84	61.5	53.5–70.7	2.46	.29
Semantic verbal fluency	15.7	13.5–20.5	16.5	12.6–19.4	17.7	15–23	3.01	.22
Phonological verbal fluency	8.8	7–12	10.1	8.3–13.4	12.1	9.8–15.6	6.64	.04
Continuous Visual Performance Test	29	25.5–41.2	35	27–39	28	22–32	4.23	.12
Rey Figure–immediate recall	14.5	8.5–20.7	11	6.6–14.4	16.5	10.1–20.5	3.28	.19
Associative memory with semantic increase								
Free recall	19	15.2–20.7	18.5	16.2–21.7	23	17–25.5	5.54	.06
Cued short recall	12	10.2–14	13	11–13	14	12–15	8.89	.01
Cued delayed recall	12.5	10–14	12	11–14	14	13–15	8.35	.01
WCST (abbreviated version)								
Categories	3	2–3	2	1.25–3	3	2–3.7	2.95	.23
Perseverative responses	18	13.5–24	17.5	12.5–23.7	17	10.5–18.7	2.45	.29
Correct	20.5	14.2–26.7	22	11–25	23	20.2–29	2.52	.28
Wechsler Memory Scale								
Logical memory–free recall	8.5	5–11.4	6	5–9.8	10	6.1–12	4.67	.09
Visual reproduction	7.5	5.2–9.7	8.5	3–10	8.5	7–11	1.85	.39
Logical memory-recognition	16	13.2–18	16	14–18	19	17.2–20	17.09	< .0001
Digits forward	5	4.2–5.7	5	5–6	5	4–5.7	1.84	.39
Digits backward	3	3–4	3	2–3.7	4	3–4	6.37	.04
WAIS								
Code of numbers	31	22.7–38.7	33.5	21.2–46.7	40.5	30–43.7	4.51	.10
CVLT								
List A trials 1–5	42.5	39.7–52.7	47	35.5–52.7	52	43–54	2.14	.34
Free short recall	9	7–11	9	7–11	12	10–13	9.29	.01
Free delayed recall	10	7–12.2	11	7.2–12	12	10–13	2.21	.33
Cued short recall	11	9–12	11	8–12	11	11–14	3.49	.17
Cued delayed recall	10	9–12	12	8.5–12	13	12–14	8.01	.02
Discriminability	90.9	86.3–97.7	95.5	89–96	95.5	93.2–97.7	3.23	.19

[a]Significance level: .05.
Abbreviations: CVLT = California Verbal Learning Test, IQR = interquartile range, WAIS = Wechsler Adult Intelligence Scale, WCST = Wisconsin Card Sorting Test.

differences. Likewise, both bipolar groups showed very similar scores in the mania and depression scales, as well as in other clinical variables, thus granting a higher value to the difference found with regard to the normal controls and to the hypothesis that this is a feature of the illness.

In our study, the test for associative memory with semantic increase, in which there is visual support, showed significant differences across groups. However, this does not necessarily indicate that there are alterations in visual memory. The encountered difficulties may be rather due to shortcomings in verbal memory and in semantic affiliation ability. Moreover, there were no significant differences in terms of visual immediate memory between the groups in either of the 2 tests used, which indicates that it is not affected by the treatment as already found in other studies.[38–40] Our hypothesis is that the lower performance shown in the tests for verbal and visual-verbal episodic memory is related to a possible difficulty of bipolar I patients to use semantic associations that favor their information storing and recall processes; this would be evidenced by the difference found between the two patient groups and the controls in both the test for associative memory with semantic increase and the CVLT.

As for executive function, several studies have reported poor performance in bipolar euthymic patients,[5,41,42] which does not concur with the results of this study, since no significant differences in the 3 assessed groups were found. Particularly in the Wisconsin Card Sorting Test, the values show no significance, which is the opposite of what we expected. This result might be influenced by the fact that we used the test's short version that contains 48 stimuli instead of 128, which is less effective for determining executive alteration in patients who do not exhibit obvious structural damage in their frontal lobe, which is the case in bipolar patients. Additionally, other studies in which executive alteration has been found have used the Tower of London Test[2,5] instead of the Wisconsin Card Sorting Test. However, the most outstanding aspect at the executive level is that the scores of both bipolar subject groups are very similar for this test and for the phonological verbal fluency test, additionally, the capacity to use semantic association strategies was altered in both groups, which shows the little effect that lithium treatment has on the assessed subjects' executive function. A further potential explanation of these results may be that the patients in our study may not be representative of the most severe cases of bipolar disorder, as it is very hard to recruit patients on lithium monotherapy or untreated who do not have high recurrence of acute episodes. The reason why patients with high recurrence cannot be recruited is that they are more resistant to monotherapy,

as they are likely to be taking various medications and often have a psychosis history. In turn, patients with a psychosis history have been reported to be the ones with the most severe cognitive problems.[43,44]

Processing and psychomotor performance speed are probably the central concerns regarding lithium effects because of the complaints about cognitive slowing reported by lithium-treated patients[11,45] and studies suggesting that lithium may indeed be the cause.[12,46] Other studies also suggest that lithium may impair verbal memory.[38,47,48] However, our study indicates that there were no significant differences between the group of bipolar patients taking lithium and the nonmedicated group on psychomotor speed. The lack of objective evidence supporting the subjective claims about cognitive slowness in lithium-treated bipolar patients has been already called into question.[40] Likewise, healthy volunteers have been assessed in a 2-month study (1 month placebo trial, 1 month lithium ingestion),[49] and they exhibited no cognitive alteration in processing speed either, although a learning effect could have taken place as there were no alternative forms of evaluation. In the same line, Amado et al[50] did not find any effect of lithium on alertness or on working memory in a 10-day lithium-placebo, randomized, double-blind study carried out with 12 healthy volunteers. A possible explanation for the discrepancy between studies in which the cognitive effect derived from lithium has been explored is that its intake might produce some kind of cognitive alteration during the initial phase of the treatment. However its regular and extended intake over time might produce positive changes in cognition resulting from neuroprotective and neurotrophic effects.[10,51] Recent findings support the preclinical literature on lithium neurotrophic effects[19,52] and suggest that long-term lithium treatment is associated with preservation of memory function, increased hippocampal size in vivo, and increased gray matter.[53–55]

The limitations of this study have to do with sample size and generalizability. The sample size is not very large, but it is obviously difficult nowadays to recruit unmedicated bipolar patients or patients on lithium monotherapy, and to ensure that they are truly euthymic at the time of the assessment, because polypharmacy is a clinical reality in bipolar disorder. The characteristics of mental health access in Colombia make this possible, but it took several years to gather the samples. Generalizations may be limited to some extent because unmedicated and lithium-treated bipolar patients may not be representative of the majority of bipolar patients; however, these two groups yielded higher internal validity to the study findings by excluding confounding factors such as polypharmacy.

There are potentially relevant clinical implications deriving from the findings of this study; not only cognitive impairment seems to be independent of medication, but also lithium looks quite safe with this regard. It has been reported that some patients might stop pharmacologic treatment as a consequence of their concern for the negative effects that lithium intake could bear on cognition, substantially increasing their risk of relapse as a consequence. This study suggests that neither lithium intake impairs cognition, nor is there evidence that it helps recovering from neurocognitive dysfunction. Further studies with a larger sample size are therefore necessary to identify the actual benefit of lithium treatment.

Drug name: lithium (Eskalith, Lithobid, and others).

Author affiliations: Research Group on Psychiatric Disorders, Department of Psychiatry, School of Medicine, Universidad de Antioquia, Medellín, Colombia (Drs López-Jaramillo, Lopera-Vásquez, Ospina-Duque, García, Gallo, Cortez, and Palacio); and Bipolar Disorders Program, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain (Drs Torrent, Martínez-Arán, and Vieta).

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