Neurocognitive Dysfunctions in Euthymic Bipolar Patients With and Without Prior History of Alcohol Use

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Objective: Despite the additional complications associated with alcohol misuse in bipolar populations, it is generally the case that studies exploring neurocognitive aspects of bipolar disorder specifically exclude patients with alcohol abuse or dependence. Given the role of cognitive dysfunctions in overall illness outcome, this study addressed the neurocognitive functioning of patients with a history of alcohol abuse or dependence as compared to bipolar patients without such a history and healthy controls.

Method: The study sample included 100 subjects: 65 bipolar patients, 30 of whom with a history of alcohol abuse or dependence and 35 without a previous history of alcohol abuse or dependence, based on DSM-IV criteria, and a control group of 35 healthy subjects. Comprehensive neuropsychological tests were carried out during strictly defined clinical remission. Differences between groups were analyzed and a linear regression analysis was undertaken to establish predictors of psychosocial functioning as measured using the Global Assessment of Functioning. Data were collected from September 2006 to July 2007.

Results: Bipolar patients with a history of alcohol abuse or dependence obtained lower scores in the interference task of the Stroop test compared to the control group. Both patient groups showed a poorer performance in some verbal memory and executive function measures than healthy controls. Verbal learning impairment was significantly associated with poor psychosocial functioning.

Conclusions: Cognitive dysfunctions appeared to be more strongly associated with bipolar disorder than with the "history of alcohol abuse or dependence" factor. Bipolar patients with history of alcohol misuse may have greater difficulties of inhibitory control, probably due to higher impulsivity.

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Bipolar disorder is a severe, chronic, and recurrent disorder that ranks sixth in the global burden of disease.[1] Even patients who meet criteria for clinical remission struggle to attain functional remission, and only about 30% of individuals return to their premorbid level of functioning.[2–4] More and more data point toward the presence of cognitive dysfunction in bipolar patients, not only during acute episodes but also during euthymia.[5] However, the exact nature of which cognitive functions are altered during acute phases and which deficits persist during periods of remission is still a matter of controversy. Furthermore, research on cognitive and psychosocial functioning in bipolar disorders is hampered by the fact that bipolar disorder is one of the most comorbid disorders, with physical and psychiatric complications being the rule rather than the exception. While some comorbidities may not contribute significantly to neurocognitive dysfunction, it is clear that certain specific and highly prevalent problems may compound the clinical picture. The most obvious comorbidity in this regard is substance misuse, which the National Institute of Mental Health Epidemiologic

Catchment Area Study[6] reported to be present in 60.7% of bipolar patients. Another more recent epidemiologic study (the National Comorbidity Survey) reported that the risk of alcohol dependence was 10 times higher among bipolar patients than among the general population.[7–9] In comparison to those without substance use disorders, bipolar patients fulfilling criteria of abuse or dependence of substances are reported to have an earlier age at onset,[10–16] a greater number of hospital admissions,[11,15–18] higher suicide ideation and attempts,[11–13,19,20] poorer treatment adherence,[21–23] and worse psychosocial functioning.[15,16] Only 1 small scale study has focused on the impact of alcohol dependence on both the course of the illness and cognitive function,[24] reporting a poorer performance in some executive measures in patients with prior history of alcohol dependence. A further study by this research team compared patients with and without history of alcohol abuse and found that both groups performed worse in the verbal memory task than healthy control subjects and concluded that the poorer performance in bipolar subjects would not be primarily associated with the effect of alcohol.[25] Alcohol abuse and dependence also have been reported to be associated with executive dysfunction and verbal memory deficits.[26–28] However, the scarcity of data related to the potential impact of alcohol use on cognition in bipolar patients has led us to question whether patients with a history of alcohol abuse or dependence might present more cognitive dysfunctions than those without such a history. Previous reports on this issue are scant. For this reason, the aim of the present study was to establish any associations between neurocognitive functioning, alcohol use/misuse, and overall psychosocial functioning. In this regard, we used stricter euthymia criteria, DSM-IV criteria to determine past history of alcohol abuse/dependence, a comprehensive neuropsychological battery, and a larger sample size in comparison with previous studies. Our hypothesis was that, in spite of current abstinence, some cognitive domains, especially verbal memory and executive functions, may be more impaired in those bipolar patients with previous history of alcohol abuse/dependence. Therefore, bipolar patients with positive history of alcohol use disorders will suffer greater cognitive deficits than patients without such a history.

METHOD

Subjects

Subjects in this study all gave written informed consent to participate in the systematic prospective follow-up of patients at the Bipolar Disorder Program of the Hospital Clinic of Barcelona, which was approved by the institutional review board. Data were collected from September 2006 to July 2007. Inclusion criteria were as follows: age between 18 and 65 years, meeting DSM-IV criteria for bipolar disorder I or II but currently euthymic (defined as at least 6 consecutive months of remission, with a Young Mania Rating Scale [YMRS] score ≤ 6 and a Hamilton Rating Scale for Depression [HAM-D] score ≤ 8), plus detailed recording of information regarding substance use before and/or after the diagnosis of bipolar disorder was made. Our interest was to ascertain the long-term impact of comorbid alcohol use (specifically without the interaction of other substances), according to DSM-IV criteria, on the clinical course and neurocognitive outcome of bipolar disorder, independent of the abstinence. Patients who had a history of use of substances other than alcohol were also excluded in order to avoid the potential interactions. One hundred fifteen potential participants were identified and underwent urine screening (to exclude other substance use). The majority excluded at this stage tested positive for prescribed or illicit use of other drugs, especially benzodiazepines (N = 42). Other reasons for exclusion were significant medical illnesses (cardiorespiratory, neurologic or endocrine disorders), mental retardation (IQ < 70), history of head injury or loss of consciousness, and electroconvulsive therapy in the previous year. The final patient sample included 30 individuals with a lifetime history of alcohol abuse or dependence (OH+) and 35 patients without a previous history of alcohol abuse or dependence (OH–).

A control group was recruited of 35 healthy subjects aged between 18 and 65 years, with no personal history of psychiatric, organic, neurologic, or serious medical illnesses and no family history of affective or psychotic disorders in first-degree relatives. The comparison group was recruited from a pool of healthy volunteers from the Barcelona Hospital Clinic and from advertising. Controls were screened for Axis I psychiatric disorders using the Structured Clinical Interview for DSM-IV.[29]

Clinical and Psychosocial Assessment

As part of the data collection protocol of the Barcelona Bipolar Disorders Program, clinical variables (e.g., age at onset, number and type of previous episodes, number of hospital admissions, suicide attempts, seasonality, rapid-cycling, previous history of psychotic symptoms) and general demographic information (e.g., gender, age, civil status, employment status) are recorded. Additionally, as in our previous studies,[30,31] ability to function at work and in social settings during the month preceding the assessment interview was evaluated using the Global Assessment of Functioning (GAF[32]; DSM-IV); information related to symptoms in the GAF was not taken into account. Ratings of mood disorder symptoms were undertaken by trained examiners using the Spanish validated version of the HAM-D[33,34] and the YMRS.[35,36]

Neuropsychological Assessment

Neuropsychological tests were undertaken of cognitive functioning during euthymia (as defined above). As well as measuring IQ, the neuropsychological battery was chosen on the basis of an extensive review of the literature, and we

Table 1. Clinical, Demographic, and Pharmacologic Variables in Bipolar Patients (A) With and (B) Without History of Alcohol Use and in (C) Healthy Control Subjects

	A. OH+ Bipolar Patients (N = 30)		B. OH– Bipolar Patients (N = 35)		C. Control Group (N = 35)		ANOVA		
Variable	Mean	SD	Mean	SD	Mean	SD	F	df	p
Age, y	35.8	9.7	41.1	8.9	39.1	12.1	2.17	2,99	.12
Educational level, y	12.6	3.0	13.3	2.9	12.9	3.3	0.43	2,99	.65
Estimated IQ	108.3	9.4	107.7	6.3	113.9	9.2	5.84	2,99	.004
GAF score	63.0	12.8	66.0	15.1	…	…	0.72	1,64	.40
Age at onset, y	24.0	8.5	25.1	7.3	…	…	0.26	1,58	.61
Duration of illness, y	11.4	7.5	16.2	8.7	…	…	4.86	1,56	.032
Total episodes	12.5	10.2	11.1	10.8	…	…	0.25	1,58	.62
Manic episodes	3.9	4.8	2.5	2.5	…	…	1.99	1,59	.16
Hypomanic episodes	2.6	2.9	2.3	5.6	…	…	0.06	1,57	.80
Depressive episodes	5.0	5.6	5.6	5.4	…	…	0.13	1,58	.72
Mixed episodes	0.7	1.2	0.6	1.2	…	…	0.10	1,58	.75
Hospitalizations	2.6	3.2	2.6	2.2	…	…	0.01	1,59	.92
Suicide attempts	0.6	1.4	0.5	0.8	…	…	0.19	1,57	.66
HAM-D score	3.4	2.2	3.5	2.3	1.8	1.3	7.59	2,97	.001
No. of medications	2.4	1.1	2.5	1.3	…	…	0.22	1,61	.63
	N	%	N	%	N	%	χ^2	df	p
Sex							3.41	2,100	.18
Men	16	53.3	11	31.4	13	37.1			
Women	14	46.7	24	68.6	22	62.9			
Unemployed	15	50	21	61.8	…	…	0.89	1,64	.45
Prior psychotic symptoms	20	69.0	25	78.1	…	…	0.66	1,61	.56
Bipolar I	25	83.3	26	76.5	…	…	0.46	1,64	.54
Family history of affective disorders	15	60.0	14	45.2	…	…	1.22	1,56	.29
Medications									
Lithium	24	82.8	27	77.1	…	…	0.31	1,64	.76
Carbamazepine	6	20.7	8	22.9	…	…	0.04	1,64	.83
Valproate	3	10.3	2	5.7	…	…	0.47	1,64	.65
Antidepressants	5	17.2	10	28.6	…	…	1.14	1,64	.38
Antipsychotics	15	51.7	19	54.3	…	…	0.04	1,64	.84

Abbreviations: ANOVA = analysis of variance, GAF = Global Assessment of Functioning, HAM-D = Hamilton Rating Scale for Depression, OH+ = lifetime history of alcohol abuse or dependence, OH– = no previous history of alcohol abuse or dependence.
Symbol: … = not applicable.

then selected appropriate, well-documented tests[37,38] that are frequently used with bipolar patients.[39,40]

The battery of tests has been extensively used and is described elsewhere.[30,31,41–43] The neuropsychological tests used are listed in Table 2.

Statistical Analysis

The groups were initially compared on sociodemographic and clinical variables. Chi-square (with Fisher correction) analysis was used for qualitative variables, and analysis of variance (ANOVA) for quantitative variables. Performance of the 2 groups on different neuropsychological tests was compared using multivariate analysis of variance (MANOVA). We used the same approach to analysis as reported in previous studies.[30,31,41] Namely, given that many dependent variables were used, an initial MANOVA is carried out using age and estimated IQ as covariates and group as the main factor. Since neuropsychological tests correlate between each other naturally, this procedure was considered to be better than the Bonferroni correction, which can increase type II errors. Differences between groups were then studied (euthymic bipolar patients with a history of alcohol use, euthymic bipolar patients without a previous history of alcohol use, and healthy control subjects) using a 1-way ANOVA followed by Tukey post hoc comparisons. Pearson bivariate correlations between clinical (e.g., number of episodes) and neurocognitive variables (e.g., differed memory in the verbal learning test of California) were also calculated. Finally, a linear regression analysis was undertaken to establish predictors of psychosocial functioning as measured using the GAF. The clinical and neuropsychological variables that correlated with the results obtained in the GAF were introduced into the regression model. In the first block, appropriate ratings were introduced to control for symptoms, with neurocognitive measures introduced in the second block.

RESULTS

Clinical and Sociodemographic Variables

As shown in Table 1, ANOVA revealed no significant between-group differences in sociodemographic variables. However, in comparison to control subjects, the estimated premorbid IQ was statistically significantly lower in both groups of patients. Clinically there were few differences between the patient groups except for mean duration of

Table 2. Neurocognitive Performance in Bipolar Patients (A) With and (B) Without History of Alcohol Use and in (C) Healthy Control Subjects

	A. OH+ Bipolar Patients (N = 30)		B. OH– Bipolar Patients (N = 35)		C. Control Group (N = 35)		MANOVA		Tukey	Cohen d		
Performance Test	Mean	SD	Mean	SD	Mean	SD	F (df = 2,97)	p	Post Hoc Tests	A/B	A/C	B/C
Frontal Executive Functions												
WCST												
Categories	4.9	1.8	5.0	1.5	5.5	1.3	0.83	.44	…	–0.06	–0.38	–0.36
Perseverative errors	14.9	13.9	15.1	10.9	8.7	6.8	2.78	.07	…	–0.02	0.57	0.7
Stroop test												
Interference	0.5	7.4	1.4	5.8	4.7	7.0	4.35	.02	A < C	–0.14	–0.58	–0.51
Attention/working memory												
Digits subtest (WAIS)												
Digits forward	5.5	1.5	5.4	1.3	6.5	1.3	3.97	.02	A,B < C	0.07	–0.71	–0.85
Digits backward	4.2	1.0	3.8	0.8	5.0	1.2	6.60	.002	A,B < C	0.44	–0.72	–1.18
TMT												
Trail A	40.7	19.6	46.4	22.1	30.2	11.6	3.94	.02	B < C	–0.27	0.65	0.92
Trail B	90.3	35.1	124.4	89.9	74.6	37.1	2.49	.09	…	–0.5	0.43	0.72
Verbal fluency												
Controlled Oral Word Association Test												
FAS[a]	34.8	10.3	33.1	10.9	39.6	11.9	1.09	.34	…	0.16	–0.43	–0.57
Animal naming	18.1	3.4	17.4	4.0	22.1	6.1	5.84	.004	A,B < C	0.19	–0.81	–0.91
Verbal memory												
CVLT												
Learning task (trials 1–5)	47.2	11.4	45.0	10.2	53.5	9.6	3.59	.03	A,B < C	0.2	–0.6	–0.86
Free short-delay recall	9.6	3.1	9.2	3.5	11.3	3.3	2.11	.13	…	0.12	–0.53	–0.62
Cued short-delay recall	10.9	2.7	10.3	2.6	12.6	2.3	4.68	.12	A,B < C	0.23	–0.68	–0.94
Free long-delay recall	10.0	3.4	9.7	3.4	12.5	3.0	5.21	.007	A,B < C	0.09	–0.78	–0.87
Cued long-delay recall	10.9	3.0	10.3	2.9	13.0	2.6	6.42	.002	A,B < C	0.2	–0.75	–0.98
Recognition hits	14.0	2.4	14.0	1.9	15.0	1.3	2.68	.07	…	0	–0.52	–0.61

[a]FAS is a subtest of the Controlled Oral Word Association Test; F, A, and S are the letters used to ask for names of things starting with those letters.
Abbreviations: CVLT = California Verbal Learning Test, MANOVA = multivariate analysis of variance, OH+ = lifetime history of alcohol abuse or dependence, OH– = no previous history of alcohol abuse or dependence, TMT = Trail Making Test, WAIS = Wechsler Adult Intelligence Scale, WCST = Wisconsin Card Sorting Test.

disorder, which was longer in OH– as compared to OH+ patients. Furthermore, OH+ patients had lower levels of treatment adherence in comparison to OH– patients, although there were no differences in number of prescribed medications.

Neuropsychological Variables

The results of the neuropsychological performance comparing the 3 groups (bipolar OH+ patients, bipolar OH– patients, and healthy control subjects) are shown in Table 2. MANOVA revealed significant between-group differences (Wilks Λ, F = 1.74, df = 30,158; p = .016); 8 of 15 comparisons remained statistically significant (p < .05) after controlling for age and estimated IQ level. Both patient groups obtained significantly worse results in the verbal memory tests: learning task trials 1–5 and long-delay recall in both free and cued conditions. Moreover, a trend toward a poorer performance in the recognition trial (hits) was found in the patient groups compared to controls, but no differences between groups were found regarding the number of false positives in this task (F = 0.079, p = .78). Similarly, the 2 patient groups, independent of history of alcohol use, obtained worse results in tasks related both to executive functions and to working memory, such as the digits backward, and a trend toward a poorer performance in the trail B and in the number of perseverative errors in the Wisconsin Card Sorting Test (WCST). An interesting finding was that the OH+ patient group obtained lower scores in the interference task of the Stroop test in comparison with the control group, with a moderate effect size (Cohen d = 0.58). In the semantic verbal fluency task both patient groups demonstrated statistically significantly lower performances in comparison with control subjects. The OH– patient group demonstrated a poorer performance on Trail A of the Trail Making Test (TMT-A) compared to the control group, and both groups of patients showed poorer performances on other tasks related to attention, such as the digits forward. When a further

MANOVA, controlling for the effect of chronicity, was performed, nonsignificant neurocognitive differences between the patient groups were identified. However, moderate-to-large effect sizes were obtained when comparing both patient groups to healthy controls.

In this regard, Pearson correlations revealed that the duration of disorder was the clinical variable that best correlated with the neurocognitive variables, such as the number of perseverative errors in the WCST ($r = 0.41$, $p = .002$), Trail A ($r = 0.37$, $p = .005$), Trail B ($r = 0.37$, $p = .005$), backward digits ($r = -0.32$, $p = .01$), and in the California Verbal Learning Test (CVLT): total list A 1–5 ($r = -0.29$, $p = .03$), free short-delay recall ($r = -0.33$, $p = .02$), cued short-delay recall ($r = -0.28$, $p = .04$), free long-delay recall ($r = -0.32$, $p = .01$), and cued long-delay recall ($r = -0.26$, $p = .05$). Surprisingly, no additional correlations were found between scores on the symptom rating scales (HAM-D and YMRS) and neurocognitive measures, or between the number of previous episodes and the neurocognitive measures. However, psychosocial functioning as measured using the GAF correlated with Trail B ($r = -0.30$, $p = .02$), FAS ($r = 0.33$, $p = .007$), and CVLT: learning task (trials 1–5) ($r = -0.46$, $p < .001$), free short-delay recall ($r = 0.38$, $p = .002$), cued short-delay recall ($r = 0.36$, $p = .003$), free long-delay recall ($r = 0.42$, $p < .001$), and cued long-delay recall ($r = 0.44$, $p < .001$).

Forward stepwise linear regression analysis including clinical variables showed a trend for the general functioning of the patients to be associated with the presence of subsyndromal depressive symptoms ($t = -1.82$, $df = 63$, $p = .07$) as measured on the HAM-D. When neuropsychological variables were introduced into the analysis in the second block, only CVLT learning task (trials 1–5) was significantly associated with psychosocial functioning, accounting for 18% of the variance ($F = 10.43$, $df = 2,63$; $p < .001$).

DISCUSSION

Our findings indicate that bipolar patients, regardless of being euthymic and independent of their previous history of alcohol consumption, performed less efficiently on neurocognitive tasks related to verbal memory and executive functions in comparison with healthy control subjects. The cognitive dysfunctions, however, were not severe, although moderate-to-large effect sizes were found in most cognitive measures when the patient groups were compared to healthy controls

It would have been reasonable to expect that bipolar patients who had a history of alcohol use disorder would have a worse clinical course. However, with the exception of longer illness duration in patients without a previous history of alcohol consumption, and treatment adherence, no statistically significant differences were observed between the 2 patient groups regarding clinical characteristics. The fact that patients with a previous history of alcohol use had worse treatment adherence has been reported before and was confirmed in this sample.[21–23]

The lack of association between clinical variables and history of alcohol use could be partially explained by the fact that the sustained remission of substance abuse or dependence in bipolar patients may often improve the course of the illness. Therefore, had these patients been evaluated when they were actively consuming alcohol and other substances, both clinical indicators and neurocognitive performance might well have been more affected. The lack of association between mood and cognitive measures may be due to the restricted range of mood symptoms imposed by the euthymia criteria, which reduces statistical power. In a recently published study,[44] the clinical course and especially the general functioning of bipolar patients who achieved longer remission periods from substance use improved substantially, although not to the same level as patients who had no history of previous substance use. The results of the present study, similar to those of the study by Weiss and colleagues,[44] suggest that the negative effects of alcohol may be reversible, which would explain why the 2 groups of patients did not differ significantly in their clinical, neurocognitive, and functioning variables. These findings have relevant therapeutic implications, because several psychosocial interventions emphasize the importance of avoiding alcohol and other substance use in order to improve the illness course as well as the overall functioning. Interventions more specifically focused on neurocognitive remediation have not been tested in bipolar patients yet, but could also help to improve the outcome of patients with and without comorbid alcohol abuse.[45]

Both groups of patients showed significantly poorer performance than healthy control subjects on neurocognitive variables related to verbal memory and executive functions, which suggests that these dysfunctions could be more strongly associated with the bipolar disorder itself than with the "history of alcohol abuse or dependence" factor. This had already been indicated in previous studies: cognitive dysfunctions seem to constitute endophenotypes, representing a trait marker of the illness,[46] and they correlate with factors involved in the clinical course such as number of episodes and duration of the illness. That is, some clinical factors may worsen the neurocognitive outcome. In the present study, longer duration of the illness was associated with a worse neurocognitive performance in the previously mentioned tasks related to executive functions and verbal memory, which are the most consistently affected areas identified in the literature.[30,31,41,47,48]

Patients with a previous history of alcohol abuse or dependence showed a worse performance in the interference task of the Stroop test in comparison with healthy control subjects. This could be related to a greater difficulty in resisting interferences and a lower level of inhibitory control. Probably, alcohol consumption may have long-term implications on cognition especially regarding inhibitory

control of inadequate responses or behaviors. These results would support the hypothesis that subjects with a history of alcohol abuse or dependence may suffer from higher impulsivity and greater difficulties in inhibiting certain inadequate behavior as reported in previous studies.[49–51] These patients may have had more difficulties to stop or inhibit their customary behaviors (e.g., drinking alcohol) to adopt a new behavior. This finding has clinical and therapeutic implications, since they sometimes find alternative but also addictive behaviors, such as compulsive gambling or Internet addiction, for instance. The one previous (smaller scale) study that specifically aimed at evaluating cognitive dysfunctions in euthymic bipolar patients with and without a history of alcohol use[24] also indicated that the 2 groups of patients did not differ significantly on a number of clinical variables, but performed worse in verbal memory tasks than healthy control subjects. The only cognitive variable in which the patients with a history of alcohol use obtained worse results than patients without such a history was the number of completed categories of the WCST, which led the authors to suggest that prior alcohol dependence could have negative influence on executive functions. These authors also found a correlation between the duration of the illness and a worse performance in verbal memory and executive function tests. However, in a later study,[25] the same authors found dysfunctions in verbal memory in euthymic patients, independent of whether they had a previous history of alcohol abuse or not. In view of our findings, we suggest that most deficits could not be directly linked to the effects of alcohol. Probably, verbal memory and executive function impairments observed in alcoholic patients may improve with abstinence. In this regard, a reversibility of neuropsychological deficits has been reported in previous publications.[28,52–55]

We cannot rule out the impact of medication on cognitive functioning in our study, although the cognitive dysfunctions would not likely be the result of pharmacologic treatment only.[56,57] No significant differences were detected in relation to the type of medications used among the different groups of patients. This constitutes an essential difference between patients and healthy control subjects that is difficult to overcome, even with nonmedicated patients (because the problem is then low illness severity bias). As mentioned before, substance abuse or dependence is generally an exclusion criterion in most studies, so that it may be advisable to consider including patients with prior substance use disorders in clinical trials for new medications in bipolar disorder.[58]

A history of alcohol abuse could be associated with poorer therapeutic adherence; in fact, it is known that some patients use alcohol in an attempt to self-medicate. Moreover, regular drinkers, fearful of the interaction between alcohol and medication, are more likely to follow treatment incorrectly. On the other hand, the association found between duration of the illness and neurocognitive impairment in bipolar patients is consistent with the results of other previous studies in this field.

The variable that best predicted the degree of psychosocial functioning in both work and social environments in the GAF was the learning task of CVLT. This indicates that, as pointed out in our previous studies,[30,31,41] alterations in the acquisition of new information can significantly affect successful adaptation to both occupational and social settings. The high rates of bipolar disorder and comorbid alcoholism require further research.[51,59]

Among limitations, the lack of control for time of abstinence may limit conclusions. The control of alcohol use through urine test apart from the structured interview may be not enough in order to rule out consumption. The duration and severity of alcohol drinking history would have been helpful, but getting detailed information in bipolar patients becomes extremely difficult. Although data were obtained using combined information from a structured interview, clinical history, urine tests, and psychiatrist's reports, these variables are difficult to measure in bipolar patients since alcohol consumption may precede relapses, may be increased during the acute affective episodes, or be intermittent according to mood fluctuations, alternating periods of remission without consumption or sporadic consumption, depending on the alcohol use disorder. In this regard, the alcohol pathology profile of this group may vary across participants and should be more widely studied using more homogeneous groups in future studies. Our program is primarily aimed at clinical research on the mood disorder and there may be some imbalance between the quantity and quality of the information that we collect on the mood disorder as compared to the addiction. Nevertheless, the aim of our study was not to report the epidemiology of alcohol addiction in bipolar disorder but rather to explore the neuropsychological consequences of past alcohol abuse. For this reason, the patients were requested to be abstinent for at least 1 year, limiting to some extent the representativity of the sample but also avoiding the methodological limitation of the confounding effects of alcohol consumption on neuropsychological testing. The retrospective collection of alcohol consumption patterns in such a population would have also carried problems of recall bias and limited reliability. On the other hand, the inclusion of bipolar II patients in the analysis could potentially add variability in cognitive functioning, and this could limit conclusions. However, bipolar II patients also show cognitive impairment, and comorbid substance abuse is particularly high in this group. Comorbidity is both a fact and an artifact of current nosology. Comorbidity is high in bipolar II disorder, especially if patients are symptomatic at the time of assessment. Anxiety disorders, substance abuse, and personality disorders, particularly those included in DSM-IV cluster B, are often associated with bipolar II disorder.[60] Finally, the use of instruments, such as the GAF to assess general functioning, also would be a matter of debate, since new tools, briefer and

more specific, examining different areas of functioning, may be useful in further research.[61,62]

CONCLUSIONS

Bipolar patients, in spite of being euthymic, and independent of whether they had a previous history of alcohol abuse, performed worse on neurocognitive tests than healthy control subjects. Effect sizes pointed out that the differences were minimal between the patient groups, whereas differences were moderate to large in comparison with healthy controls. These findings suggest that cognitive impairment is inherent to the illness itself. The most significantly affected tasks were verbal memory and executive functions, and even though these deficits were subtle they appeared to impact on the patients' psychosocial functioning. However, further investigation into the relationship between clinical, functional, and neurocognitive aspects is important in order to establish which subgroups of bipolar patients suffer most from neurocognitive dysfunctions. The patients included in the study did not fulfill criteria for abuse or dependence of alcohol at the time of evaluation; therefore, it is possible that the potentially negative effects of alcohol are reversible following extended periods of abstinence. However, the previously reported association between the duration of the illness and the cognitive dysfunction, which we have again confirmed, suggests that early diagnosis and treatment are of great importance in order to reduce the neurocognitive deficits and potential for decline in performance associated with bipolar disorder. Follow-up studies in first-episode patients would be needed in order to widely study the impact of comorbid alcohol use disorders in the long-term course of the bipolar illness and, especially on the cognitive functioning, give attention more carefully to the length and severity of alcohol use.

Drug names: carbamazepine (Carbatrol, Equetro, and others), lithium (Eskalith, Lithobid, and others).

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