Treatment Nonadherence and Neurocognitive Impairment in Bipolar Disorder

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Objective: Little is known regarding the relationship between treatment adherence and residual cognitive dysfunction in euthymic bipolar disorder patients. This study aimed to investigate whether poor treatment adherence is associated with cognitive impairment in euthymic bipolar patients and whether other factors may be associated with both adherence and cognitive functioning.

Method: Euthymic DSM-IV bipolar I or II disorder patients (N = 103: 61 with high levels of treatment adherence and 42 with poor treatment adherence) were assessed using a neuropsychological battery targeting attention, psychomotor speed, verbal memory, and executive functions and compared with 35 healthy controls of similar age, sex distribution, and education. Data were collected from September 2005 to June 2007.

Results: Bipolar patients with poor treatment adherence had more hospitalizations than those with high adherence. After controlling for age, gender, estimated IQ score, and Young Mania Rating Scale and 17-item Hamilton Rating Scale for Depression scores, non–treatment-adherent patients performed less well than normal controls in verbal learning and some executive functions. Among treatment-adherent and poorly adherent bipolar disorder patients, performance was similar in attention tasks and short-term and long-term verbal recall, but non–treatment-adherent patients were more impaired in ability to inhibit interferences and in spatial working memory. Poorer treatment adherence also was associated with the bipolar I subtype and with greater illness severity, as indicated by number of manic episodes and hospitalizations and history of psychosis. Pharmacologic factors, such as treatment with lithium, may also influence the relationship between neurocognition and adherence.

Conclusions: There is a close relationship between poor treatment adherence and cognitive impairment, but the causal inferences of these findings are uncertain. Poor treatment adherence may worsen the course of bipolar disorder and so indirectly worsen cognitive performance, or cognitive impairment may contribute to poor treatment adherence and reflect more severe illness.

J Clin Psychiatry 2009;70(7):1017–1023

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This study was partially supported by grants from the Ministerio de Educación y Ciencia (Dr. Vieta), the Instituto de Salud Carlos III (FIS PI050206), Centro de Investigación en Red de Salud Mental, the European Union 7th Framework Programme (European Network of Bipolar Research Centres), and the European College of Neuropsychopharmacology. Dr. Martinez-Aran is funded by the Spanish Ministry of Health, Instituto Carlos III, through a "Miguel Servet" postdoctoral contract (CP07/00144).

Financial disclosure appears at the end of this article.

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The prevalence of treatment nonadherence among patients with bipolar disorder ranges from 25% to 64%.[1–3] Using a combination of adherence assessment methodologies, the Barcelona group found that only 60% of euthymic bipolar patients in a previous study were fully adherent, whereas 27% were partially compliant and 13% were poorly adherent with prescribed treatments.[4,5] Partial adherence or nonadherence is associated with a worse clinical and social outcome in bipolar disorders.[1,6]

Cognitive impairment is partly responsible for the poor functional outcome in bipolar disorder.[7,8] Bipolar patients show persistent cognitive dysfunction, including verbal memory and frontal executive impairments that extend beyond the acute phases of the illness.[9] Patients with bipolar I disorder who have a history of psychotic symptoms, a longer duration of illness, or a higher number of previous episodes are more likely to show neurocognitive impairment.[7,9,10] Early diagnosis and treatment are important for

preventing cognitive dysfunction and its potential negative impact on the psychosocial functioning of bipolar patients as is adherence with the treatment regimen.[11]

No previous report focuses on the relationship between therapeutic adherence and neurocognitive performance in bipolar patients. Only 1 study, by Kemp and David,[12] has explored cognitive functioning and adherence levels over time. However, the study sample included acutely psychotic inpatients who participated in a randomized controlled trial of "compliance therapy." Patient performance on neuropsychological tests improved in both groups during the course of the study. The authors concluded that clinical variables and attitudes to treatment appeared to be more relevant to adherence in acute psychosis (predominantly schizophrenia) than did neuropsychological impairment.[12] However, several authors have pointed out an obvious potential association between cognition and adherence, noting that memory difficulties may impair adherence due to forgetfulness.[13,14] Given the paucity of studies examining this issue in bipolar disorder, we aimed to investigate whether poor treatment adherence was associated with cognitive impairment in euthymic bipolar patients and whether other factors may be associated with both adherence and cognitive functioning.

METHOD

With local ethics committee approval, study participants were enrolled from the Bipolar Disorders Program of the Hospital Clinic of Barcelona, Spain. All patients met DSM-IV criteria for bipolar I or II disorder and were euthymic. The clinical status of the patients was determined by the psychiatrist responsible for the individuals' follow-up using the Structured Clinical Interview for DSM-IV (SCID)[15] and the Spanish versions of the 17-item Hamilton Rating Scale for Depression (HAM-D)[16,17] and the Young Mania Rating Scale (YMRS).[18,19] Euthymia was defined as a YMRS score ≤6 and a HAM-D score ≤8 during 6 consecutive months. In order to confirm the euthymic state, the clinical scales were administered monthly.

Adherence was assessed by direct interview with the patients and a "compliance-focused" interview with first-degree significant relatives or a partner, plus plasma concentrations of mood stabilizers assessed during the previous 2 years. The latter is an objective parameter, which can be very useful when nonadherence is denied by the patient and ignored by the family. The interview administered to the patient included questions relevant to the patient's attitude toward medication, illness denial, number of medication omissions, or doses missed per month and is described in detail elsewhere.[4,5] The interview administered to family members estimated attitude toward medication and observed signs of poor adherence. High levels of adherence were shown when all 3 assessments indicated it, whereas poor adherence was indicated if at least 1 of the 3 criteria suggested problems. Of 120 potential participants, 70 patients were categorized as having high adherence, and 50 were categorized as showing poor adherence.

The exclusion criteria for the neuropsychological protocol were failure to meet criteria for euthymia, history of head injury or loss of consciousness, neurologic illness, substance dependence in the last year, mental retardation (IQ score <70), significant medical illness, and treatment with electroconvulsive therapy in the last year. Of 120 initial potential participants, 15 met 1 or more exclusion criteria. The most common reason for exclusion (N=11) was the presence of persistent subsyndromal symptoms during the prior 6 months.

Of 105 bipolar patients who met criteria for euthymia, 103 gave written informed consent to participate in the study after procedures had been fully explained. Medication was kept constant during the 4 weeks before neuropsychological testing in 94% of patients. In the final sample, 61 patients were included as highly adherent and 42 as poorly adherent.

Thirty-five healthy comparison subjects without psychiatric or neurologic history were also recruited via advertisement and from a known pool of healthy volunteers. Controls were screened for Axis I psychiatric disorders using the SCID.[15] Six of 44 potential controls had to be excluded (2 due to history of head injury and 4 due to anxiety disorders). Data were collected from September 2005 to June 2007.

Clinical and Psychosocial Assessment

These data were collected routinely as part of the clinical protocol at the Bipolar Disorders Program. Clinical status of bipolar patients was established using the SCID, YMRS, and HAM-D, while functional status was assessed using the Social and Occupational Functioning Assessment Scale.[20] Adherence treatment was assessed as described above.

Neuropsychological Assessment

The neuropsychological evaluation was carried out by a trained neuropsychologist who was blind to the data from the clinical and psychosocial assessments. An extensive review of previous literature guided the choice of neuropsychological tests used in the present study. In order to enhance comparability, only tests frequently documented by the neuropsychological literature were employed.[21,22] These tests included estimated IQ: vocabulary subtest (Wechsler Adult Intelligence Scale [WAIS][23]); frontal executive functions: Wisconsin Card Sorting Test (WCST),[24] Stroop Color-Word Interference Test (SCWT),[25] and Controlled Oral Word Association Test (FAS and animal naming)[26]; attention/concentration and mental tracking: digit subtest (digits forward and backward from the WAIS)[23] and Trail Making Test (TMT, parts A and B)[27]; and verbal learning and memory: California Verbal Learning Test (CVLT).[28]

Table 1. Demographic, Clinical, and Pharmacologic Variables of Treatment-Adherent and Non–Treatment Adherent Bipolar Patients

Variable	Good-Compliance Group (n = 61)	Poor-Compliance Group (n = 42)	Control Group (n = 35)	Statistic (ANOVA) F or χ^2	df	p
Age, mean (SD) (range), y	39.6 (10.7) (20–62)	39.9 (10.7) (18–59)	39.1 (12.1) (22–60)	F = 0.04	2,135	.958
Education, mean (SD) (range), y	13.5 (3.4) (4–19)	12.2 (3.3) (6–17)	12.9 (3.3) (8–19)	F = 1.69	2,119	.187
Estimated premorbid IQ score, mean (SD) (range)	110.7 (9.0) (86–126)	106.8 (8.0) (94–130)	113.9 (9.2) (94–126)	F = 6.42	2,135	.002
Age at onset, mean (SD) (range), y	26.6 (9.3) (12–57)	24.7 (7.8) (13–43)	NA	F = 0.97	1,85	.327
Chronicity (duration of illness), mean (SD) (range), y	13.0 (8.2) (2–32)	15.1 (9.2) (2–36)	NA	F = 1.18	1,82	.280
No. of total episodes, mean (SD) (range)	12.6 (13.1) (2–60)	11.2 (7.6) (1–36)	NA	F = 0.33	1,87	.569
No. of manic episodes, mean (SD) (range)	1.7 (3.4) (0–21)	3.0 (3.0) (0–12)	NA	F = 3.20	1,85	.077
No. of hypomanic episodes, mean (SD) (range)	4.3 (6.5) (0–30)	2.8 (4.0) (0–19)	NA	F = 1.56	1,86	.215
No. of depressed episodes, mean (SD) (range)	6.1 (6.9) (1–30)	4.9 (4.0) (0–21)	NA	F = 0.89	1,87	.350
No. of mixed episodes, mean (SD) (range)	0.6 (1.8) (0–11)	0.7 (1.1) (0–5)	NA	F = 0.11	1,83	.737
No. of hospitalizations, mean (SD) (range)	1.5 (2.6) (0–12)	2.9 (2.5) (0–11)	NA	F = 5.75	1,84	.019
No. of suicide attempts, mean (SD) (range)	0.5 (1.2) (0–6)	0.8 (1.4) (0–6)	NA	F = 0.62	1,78	.433
HAM-D score, mean (SD) (range)	2.8 (2.5) (0–8)	3.8 (2.3) (0–8)	1.8 (1.3) (0–4)	F = 7.15	2,13	.001
YMRS score, mean (SD) (range)	1.2 (1.8) (0–6)	1.3 (1.5) (0–6)	0.8 (0.9) (0–3)	F = 0.98	2,13	.379
SOFAS score, mean (SD) (range)	67.8 (15.4) (40–90)	62.2 (11.7) (45–89)	NA	F = 3.44	1,87	.067
No. of medications, mean (SD) (range)	2.42 (1.2)	2.76 (1.2)	NA	F = 1.90	1,99	.17
Sex, n (%)			NA			
Male	30 (49.2)	17 (40.5)	13 (37.1)	$\chi^2 = 1.53$	2,138	.465
Female	31 (50.8)	25 (59.5)	22 (62.9)			
Bipolar type I, n (%)	34 (56.7)	35 (85.4)	NA	$\chi^2 = 9.27$	1,103	.002
Prior psychotic symptoms, n (%)	24 (49.0)	26 (76.5)	NA	$\chi^2 = 6.33$	1,91	.013
Family history of affective disorder, n (%)	29 (61.7)	15 (50.0)	NA	$\chi^2 = 1.02$	1,77	.351
Medications, n (%)			NA			
Lithium	39 (68.4)	33 (84.6)	NA	$\chi^2 = 3.24$	1,96	.094
Carbamazepine	8 (15.4)	7 (20.0)	NA	$\chi^2 = 0.95$	1,87	.622
Valproate	6 (11.5)	6 (16.2)	NA	$\chi^2 = 1.77$	1,89	.412
Antidepressants	18 (36.7)	8 (22.2)	NA	$\chi^2 = 2.06$	1,85	.164
Antipsychotics	19 (38.0)	18 (50.0)	NA	$\chi^2 = 1.23$	1,86	.268

Abbreviations: ANOVA = analysis of variance, HAM-D = Hamilton Rating Scale for Depression, NA = not applicable, SOFAS = Social and Occupational Functioning Assessment Scale, YMRS = Young Mania Rating Scale.

Statistical Analyses

Data analyses were performed using SPSS 14.0 (SPSS Inc., Chicago, Ill.). Comparison of clinical and sociodemographic characteristics across groups (bipolar patients with high adherence, bipolar patients with poor adherence, and healthy controls) was carried out using analysis of variance (ANOVA) and χ^2 tests. Performance on the neuropsychological tests was compared across the 3 groups by means of ANOVA. Since multiple dependent variables were used, a prior protective multivariate analysis of covariance (MANCOVA) analysis was performed with group as the main factor and gender, age, estimated IQ, and HAM-D and YMRS scores as covariates. Since neuropsychological tests are naturally correlated, this procedure was considered superior to a Bonferroni inequality correction, as the latter would increase type II errors. Group differences were tested in 1-way ANOVA, followed by the Tukey post hoc comparison procedure when significant main effects were present. Effect sizes (Cohen d) were also calculated. Raw scores as well as effect sizes were considered the primary outcomes of the present study.

The potential impact of clinical variables such as diagnostic subtype (bipolar I or II), prior number of manic episodes, hospitalizations, history of psychosis, and treatment with lithium was controlled for in the analysis of differences in the cognitive performance between the 2 patient groups. First, an ANOVA was performed, and after that, we controlled for the effect of all these potential confounders on cognition using multivariate ANOVA.

RESULTS

The clinical and demographic characteristics of the 3 groups are shown in Table 1. No differences between groups were found with respect to age, gender, and years of education, whereas statistical but not clinically significant differences were detected in estimated IQ scores. Differences between groups were found in HAM-D but not in YMRS scores. The patient groups differed on number of hospitalizations, which were more frequent in the poor adherence group as compared with the high adherence group. A trend toward having more manic episodes was also observed in the poor adherence group (Table 1). Significant differences were found between adherence groups with respect to bipolar I subtype and prior history of psychotic symptoms, which were both more prevalent in the poor adherence group. Another interesting finding was that bipolar patients with poor treatment adherence showed a trend toward poorer psychosocial functioning as measured on the Social and Occupational Functioning and Assessment Scale.[15] There were no significant differences in the number of prescribed medications between the patient groups.

Neuropsychological performance is shown in Table 2. The MANCOVA revealed significant between-group differences

Table 2. Neuropsychological Performance of Treatment-Adherent and Non–Treatment Adherent Bipolar Patients[a]

Measure	A. Good-Compliance Group (n = 61)	B. Poor-Compliance Group (n = 42)	C. Control Group (n = 35)	Statistic (MANCOVA) F	p	Tukey Post Hoc Test	Cohen d[b] A/B	A/C	B/C
Frontal executive function									
WCST									
No. of categories	4.98 (1.75)	4.87 (1.71)	5.46 (1.31)	0.54	.583		0.06	–0.31	–0.39
Perseverative errors	15.63 (15.04)	18.86 (18.15)	8.69 (6.79)	2.36	.099	B < C	–0.19	0.59	0.74
SCWT									
Interference	1.59 (6.74)	0.62 (6.49)	4.71 (7.02)	3.44	.035	B < C	0.14	–0.45	–0.60
Attention/concentration and mental tracking									
Subtest digits (WAIS)									
Digits forward	5.64 (1.36)	5.36 (1.18)	6.49 (1.34)	4.52	.013	A = B < C	0.22	–0.62	–0.89
Digits backward	4.27 (0.93)	3.98 (1.0)	5.0 (1.16)	4.53	.013	A = B < C	0.30	–0.69	–0.94
Trail Making Test									
Part A	41.89 (14.62)	47.83 (22.55)	30.17 (11.58)	6.61	.002	A = B < C	–0.31	0.88	0.99
Part B	89.93 (44.73)	128.45 (77.81)	74.63 (37.12)	6.45	.002	B < A = C	–0.60	0.37	0.88
Verbal fluency									
FAS	35.03 (10.63)	33.05 (10.99)	39.63 (11.87)	1.26	.300		0.18	–0.41	–0.58
Animal naming	18.33 (4.23)	17.36 (3.93)	22.06 (6.09)	2.72	.070	A = B < C	0.28	–0.71	–0.92
Verbal learning and memory									
CVLT									
List A (total)	48.07 (10.69)	42.52 (9.54)	53.54 (9.58)	4.19	.017	B < A < C	0.55	–0.54	–1.15
Free short recall	9.98 (3.39)	8.38 (3.11)	11.31 (3.26)	1.92	.151		0.49	–0.40	–0.92
Cued short recall	11.08 (2.68)	9.79 (2.75)	12.66 (2.31)	3.59	.031	B < A < C	0.48	–0.63	–1.13
Free delayed recall	10.38 (3.40)	8.98 (3.08)	12.49 (3.02)	4.43	.014	A = B < C	0.43	–0.66	–1.15
Cued delayed recall	10.89 (3.05)	9.79 (2.87)	13.03 (2.57)	5.17	.007	A = B < C	0.37	–0.76	–1.19
Recognition	13.89 (2.17)	13.48 (2.35)	15.00 (1.28)	2.57	.081	A = B < C	0.18	–0.62	–0.80

[a]Values are presented as mean (SD).
[b]< 0.5 = small, 0.5–0.8 = moderate, and > 0.8 = large effect size.
Abbreviations: CVLT = California Verbal Learning Test, FAS = verbal fluency test, MANCOVA = multivariate analysis of covariance, SCWT = Stroop Color-Word Interference Test, WAIS = Wechsler Adult Intelligence Scale, WCST = Wisconsin Card Sorting Test.

(Pillai trace, F=1.82; df=30,214; p=.008) after controlling for the effect of 5 potential confounders (gender, age, estimated IQ, and YMRS and HAM-D scores). The 2 patient groups were both more impaired than the healthy controls on several neurocognitive measures, such as verbal delayed recall and free and cued conditions on the CVLT, as well as in attention and psychomotor speed tasks (digits forward and backward and TMT-A) and semantic fluency (animal naming). Bipolar patients in the poor adherence group showed a significantly poorer performance on the CVLT since they were more impaired in the verbal learning and cued short recall tasks than were the other groups, with the high adherence group at an intermediate level. In addition, the patients with treatment adherence problems showed poorer performance on the SCWT interference task compared to controls and showed poorer performance on spatial working memory (TMT-B) compared to both the high adherence patients and controls; both of these measures relate to frontal executive functioning.

Medium effect sizes were observed in the differences between the high adherence and control groups on most neuropsychological measures, except for the SCWT, which showed a large effect size. Larger effect sizes were detected on most measures comparing the poor adherence with the control group. When the neuropsychological performance of the 2 patient groups was compared, medium effect sizes were found on the CVLT learning task as well as on the TMT-B.

We examined differences between the high- and poor-adherence groups on neurocognitive performance after controlling for the effect of the potential confounders identified in Table 1. Findings from ANOVA revealed significant differences between the 2 patient groups on TMT-B (F = 10.12; df = 1,101; p = .002), CVLT verbal learning (F = 7.24; df = 1,101; p = .008), free short recall (F = 5.94; df = 1,101; p = .017), cued short recall (F = 5.69; df = 1,101; p = .019), and free delayed recall (F = 4.54; df = 1,101; p = .035). Nevertheless, several variables may influence the relationship between adherence and neurocognitive performance. For this

reason, diagnostic subtype, history of psychosis (yes/no), prior number of manic episodes and hospitalizations, and treatment with lithium (yes/no) were statistically controlled for with multivariate ANOVA. After that, only differences on the TMT-B performance remained ($F = 4.81$; $df = 6,72$; $p = .032$).

CONCLUSIONS

Little is known about the relationship between neurocognition and treatment adherence in bipolar disorder. Our findings suggest that euthymic bipolar patients with poor adherence are cognitively more impaired than healthy subjects, but in some areas of functioning, highly adherent patients also demonstrate cognitive difficulties, the latter showing small to medium effect sizes. Thus, both patient groups showed similar impairments in attention, psychomotor speed, and semantic verbal fluency compared to healthy controls. But, the poor adherence group showed a worse performance on frontal executive tasks, such as the TMT-B and the SCWT interference task, and a trend toward more perseverative errors and worse performance on the CVLT learning and immediate recall measures. These differences between all 3 groups were evident even after controlling for the effect of potential confounders, such as age, gender, estimated IQ score, and HAM-D and YMRS scores. Thus, patients with poor adherence are more likely to show cognitive impairment of larger effect size, so adherence is important in avoiding a negative impact of not taking medication on the cognitive functions. On one hand, impairment of memory or executive function may then lead the patient to not take the medication. On the other hand, as part of a vicious circle, nonadherence may lead to more relapses and hospitalizations and may have indirect negative consequences on cognitive function.

We had wondered whether differences in neurocognitive performance between the patient groups were related to clinical characteristics, as there were some between-group differences identified at baseline assessment. When the effect of these covariates (bipolar subtype, prior number of manic episodes and hospitalizations, history of psychosis, and treatment with lithium) were controlled for, we found a poorer performance only on the TMT-B, a spatial working memory measure related to frontal executive functioning. This finding seems to be consistent with previous reports suggesting that executive function impairment may constitute a core deficit or an endophenotype of bipolar disorder.[29,30]

An overlap between verbal memory and executive functioning has been observed, with up to 50% of the variance shared. This may mean that the encoding of memories involves frontal executive functions as part of semantic strategies to encode information.[9,10] In this regard, patients showing frontal executive deficits seem to be more likely to show a severe course of bipolar disorder as well as poor treatment adherence. Therefore, treatment nonadherence can be a causal factor for poor illness course and outcome, leading indirectly to cognitive impairment. Nevertheless, these findings can be interpreted in the opposite direction too; so, cognitive dysfunctions may be associated with poor insight and adherence, leading to more severe illness and outcome as well. The current study, however, does not allow one to determine in an unequivocal way the directionality of the observed associations.

Cross-sectional studies offer, in this regard, limited information, and longitudinal studies are needed to elucidate the relationship between adherence and cognition. We may consider that recurrence of illness, particularly mania, is associated with progressive brain insults and leads to the loss of cerebral volume, which is shown in recent studies[31] documenting preserved volume at the first episode and loss with recurrence or chronicity. Other authors also support this hypothesis.[32–34] As such, cognitive changes may progress with stage of illness, and poorer adherence may be a marker of chronicity via secondary cognitive changes.

Previous studies have highlighted the relationship between clinical and pharmacologic factors and treatment compliance. Some of these studies suggest that cognitive dysfunction is a potential risk factor for treatment nonadherence.[1,11] Other studies have highlighted the importance of lack of insight, lack of illness awareness, and cognitive deficits in increasing the risk of nonadherence.[35] However, only 2 studies analyzed whether neuropsychological deficits were associated with poor adherence, and no association was reported[12,14]; the excess of patients with schizophrenia in the sample may reduce the relevance to the present study. More recently, we found that symptoms were better predictors of poor adherence than cognitive impairment.[14]

In the present study, some clinical factors seemed to be related to adherence and to therefore influence neurocognitive performance, such as diagnostic subtype, number of manic episodes and hospitalizations, and prior history of psychosis. When these potential confounders were controlled for, only the difference in TMT-B scores remained. These results suggest that clinical variables like diagnostic subtype, severity of illness, and psychotic symptoms might be stronger predictors for cognitive functioning than treatment adherence. Even though nonadherence probably accounts for a more severe course of the illness, it cannot be assumed that nonadherence itself might be a reason for cognitive impairment. As mentioned, this question could only be addressed by a longitudinal study.

Treatment factors may also be associated with poor adherence and cognitive impairment. As a study limitation, the side effect burden and related parameters concerning drug adverse effects, such as sedation, dry mouth, or anticholinergic complaints, were not controlled for given the high variability of these factors between the study groups. On the other hand, difficulties in assessing treatment

adherence arise, and unexpected blood draws would most likely be better than scheduled ones.[36] In the present study, some of the blood draws were scheduled (nearly 70%), whereas the remainder were unexpected. Future studies should include this information and address the impact on cognition and adherence. These additional studies are needed to better identify what components of the collaborative relationship are most amenable to change to optimize the important outcome of treatment adherence.[37]

In conclusion, treatment adherence should be routinely assessed and included as a relevant factor in neuropsychological studies since it may modulate some of the findings on the neurocognitive tests and vice versa. Interventions specifically aimed at improving adherence and outcome, such as psychoeducation,[38,39] might be enhanced by the inclusion of some sort of cognitive remediation.[36] Prospective as well as longitudinal studies may also elucidate whether neurocognitive deficits impair future adherence or whether nonadherence accounts for a significant proportion of the impaired cognitive functioning that is increasingly observed in individuals with bipolar disorders. It is likely that cognition and adherence are associated through functioning since adherence represents a kind of self-care. This theoretical link requires further research so that the identification of an association between cognitive deficits and poor treatment adherence can constitute an important first step for future investigations.

Financial disclosure: **Dr. Colom** has served on the speakers or advisory boards of AstraZeneca, Eli Lilly, and Sanofi-Aventis. **Dr. Goodwin** has received grant/research support from Sanofi-Aventis and Servier, has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eisai, Lundbeck, Sanofi-Aventis, and Servier; has served on the advisory boards of AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Lundbeck, P1Vital, Sanofi-Aventis, Servier, and Wyeth; and has served as an expert witness for Eli Lilly and Servier. **Dr. Gonzalez-Pinto** has received grant/research support from Eli Lilly and has served on the speakers or advisory boards of Eli Lilly, Pfizer, Janssen, AstraZeneca, Lundbeck, Bristol-Myers Squibb, GlaxoSmithKline, and Novartis. **Dr. Vieta** has served as a consultant to or on the speakers or advisory boards of AstraZeneca, Bial, Bristol-Myers Squibb, Eli Lilly, Forest Research Institute, GlaxoSmithKline, Janssen-Cilag, Jazz, Lundbeck, Merck-Sharp and Dohme, Novartis, Organon, Otsuka, Pfizer, Sanofi-Aventis, Servier, and UBC. **Drs. Martinez-Aran**, **Scott**, **Torrent**, **Tabares-Seisdedos**, **Daban**, **Leboyer**, **Henry**, **Cruz**, and **Sanchez-Moreno** report no other financial affiliations relevant to the subject of this article.

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