Santiago Navarro[1]
Fernando Rodríguez[1]
Francisco J. Acosta[2,3]
Miguel García-Bello[4]

Variables associated with nonadherence in clinically stable patients with bipolar disorder

[1] Service of Psychiatry, University Hospital of Gran Canaria Dr. Negrín. Gran Canaria, The Canary Islands, Spain
[2] Mental Health Research Program of the Canary Islands. Service of Mental Health. General Direction of Healthcare Programs. Gran Canaria, The Canary Islands, Spain.
[3] Research Network for Health Services for Chronic Diseases (Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC)). Health Institute Carlos III. Spain
[4] Unidad de Investigación,University Hospital of Gran Canaria Dr. Negrín. Gran Canaria, The Canary Islands, Spain

Introduction. Nonadherence is an important and highly prevalent issue in bipolar disorder, which may have serious consequences. Surprisingly, few studies have been carried out in patients with clinical stability to explore risk factors for nonadherence.

Method. Adherence was assessed in 76 bipolar disorder patients with clinical stability using objective and subjective methods, both with a cross-sectional approach and a 3-year retrospective period. Possible associations between nonadherence and sociodemographic, clinical, treatment-related, psychopathological, psychological-subjective and result variables were also assessed.

Results. 36.8% of patients were nonadherent. These patients showed greater concerns about medicines, worse functionality, a greater number of episodes and depressive episodes, higher prevalence of psychiatric comorbidities, present and/or past substance use or abuse and a history of depressive episodes with psychotic symptoms. A multivariate analysis revealed that concern about medicines, present and/or past substance use or abuse and psychiatric comorbidities were independently associated with nonadherence.

Conclusions. Nonadherence is a frequent phenomenon in bipolar disorder, even in patients with clinical stability. Clinicians should assess patients' beliefs and attitudes towards medicines and help them reevaluate those issues with a more realistic perspective. Clinicians should also take actions to prevent substance use or abuse. Identification of nonadherence risk profile in bipolar disorder patients in clinical stability, adds complementary information to the identified risk profile in acute phases of the disease.

Keywords: Medication adherence, Bipolar disorder, Clinical stability, Risk factors, Beliefs

Actas Esp Psiquiatr 2016;44(5):157-65

Variables asociadas a la no adherencia en pacientes con trastorno bipolar en estabilidad clínica

Introducción. La no adherencia es un problema altamente prevalente en el trastorno bipolar y puede conllevar importantes consecuencias. Sorprendentemente apenas existen estudios sobre factores de riesgo en pacientes en estado de estabilidad clínica.

Metodología. La adherencia se evaluó en 76 pacientes con trastorno bipolar en estabilidad clínica, mediante métodos objetivos y subjetivos, abarcando el momento transversal y un periodo retrospectivo de 3 años. Se evaluó su posible asociación con variables sociodemográficas, clínicas, relacionadas con el tratamiento, psicopatológicas, psicológicas y de aspectos subjetivos, y de resultado.

Resultados. Un 36,8% de los pacientes fueron no adherentes. Estos mostraron mayor preocupación sobre la medicación, peor funcionalidad, mayor número de episodios, episodios depresivos, y mayores prevalencias de comorbilidad con otros trastornos psiquiátricos, consumo de tóxicos actual y/o pasado y de antecedentes de episodios con síntomas psicóticos. Tras el análisis multivariante, la preocupación por la medicación, el consumo actual y/o pasado de tóxicos y la comorbilidad con otros trastornos psiquiátricos se asociaron de manera independiente con la no adherencia.

Conclusiones. La no adherencia en el trastorno bipolar es un fenómeno frecuente, incluso en pacientes en estabilidad. El clínico debería explorar las creencias y actitudes

Correspondence:
Francisco Javier Acosta Artiles
Servicio de Salud Mental
Dirección General de Programas Asistenciales
Servicio Canario de la Salud.
Consejería de Sanidad. 3ª planta.
C/ Pérez del Toro (Plaza Dr. Juan Bosch Millares, 1)
35004 Las Palmas de Gran Canaria (Spain)
Tel: 928 302764
Fax: 928 302797
E-mail: fjacostaartiles@hotmail.com

del paciente hacia la medicación, y ayudarle a reevaluarlas desde un punto de vista más realista. Por su parte, deben realizarse intervenciones para evitar el consumo de tóxicos. La identificación de factores de riesgo asociados a la no adherencia en estabilidad añade información al perfil de riesgo disponible para el trastorno bipolar.

Palabras clave: Adherencia a la medicación, Trastorno bipolar, Estabilidad clínica, Factores de riesgo, Creencias

INTRODUCTION

Nonadherence to a pharmacological treatment is a major concern in medical[1] and psychiatric[2] clinical practice. The prevalence of nonadherence to a pharmacological treatment in bipolar disorder is between 12-64%[3] with an average of 41%[4]. The clinical consequences of nonadherence are well established and include higher rates of relapse and hospitalization[5], higher risk of suicidal behavior and suicide[6], higher functional deterioration[7], higher morbidity, chronicity[8,9], use of healthcare resources[8] and financial costs[10].

The main identified risk factors have been substance abuse[2,11], deficient insight[12], erroneous beliefs on medication[13], forgetting to take medication[14], adverse effects – especially weight gain – and concern about suffering adverse effects[2].

The identification of variables associated with nonadherence is essential to develop suitable strategies to reduce it. Surprisingly, nonadherence in bipolar disorder has been scarcely studied[3] and more studies aimed at the evaluation of nonadherence in this type of disorder are still needed[15]. Moreover, unfortunately most of the existing studies are biased, e.g. because they were conducted with patients in acute episodes. Evaluating variables associated with nonadherence in patients in stability would prevent interferences by the clinical signs of episodes. However, such studies are very scarce[9]. Evaluation in stability is especially relevant because subjective aspects can be assessed, such as the attitude towards and the beliefs on medication, or areas directly influenced by clinical symptoms such as functionality.

In this context, we conducted this study with the following objectives:

1. To evaluate the prevalence of nonadherence to treatment in outpatient bipolar disorder patients in stability.
2. To identify possible variables associated with nonadherence in outpatient bipolar disorder patients in stability.

METHOD

Patients

This observational analytical study with transversal and longitudinal retrospective evaluation was conducted on a sample of 76 consecutive bipolar disorder patients in clinical stability, who were managed at the Mental Health Units (MHUs) El Puerto and La Feria, in Gran Canaria, between November 1st 2010 and March 31st 2011. These MHUs cover a metropolitan area and have 111,392 and 90,139 health insurance cards allocated to them, respectively. In the Canary Islands, outpatient specialized care is provided in MHUs. In case emergency hospital care or hospitalization is needed, patients are referred to the Emergency Services of the reference hospital for examination and admission if needed. Inclusion criteria were: minimum age 18 years, diagnosed with bipolar disorder, clinical stability according to established criteria (scores 1 or 2 in subscales for mania, depression and general, from the Modification of the Clinical Global Impressions Scale for use in bipolar illness) and consent to participate in the study. Diagnoses were based on the criteria of the ICD-10, established through the medical record and the clinical interview. All patients were evaluated by psychiatrists (FR and SN). The presence of mental retardation was the exclusion criterion.

The study was approved by the Ethics Committee of the University Hospital of Gran Canaria Dr. Negrín and was in accordance with the recommendations of the World Medical Association, Declaration of Helsinki. All patients were informed about the characteristics of the study and they gave written consent.

Procedure

The transversal evaluation included sociodemographic variables (age, sex, marital status, education, cohabitation, working situation, socioeconomic level), general clinical variables (age at onset, time of evolution since the onset of symptoms, history of psychiatric admission to hospital, time since last admission, total number of episodes, number of manic, depressive, mixed and hypomanic episodes, previous attempts of suicide, present and past drug abuse, psychiatric comorbidities), treatment-related variables (type of treatment, type of mood stabilizer, number of psychotropic tablets per day, concomitant medication for somatic diseases), psychopathological variables (awareness of disease, presence of psychotic symptoms in previous affective episodes), psychological variables and variables related to subjective aspects (attitude towards medication, beliefs on medication) and result variables (functionality).

Adherence was evaluated both with a transversal and a longitudinal retrospective approach. Substance abuse was

evaluated as a clustered variable (present and past harmful drug use or drug dependence) and specifically itemizing every possible variant.

General clinical variables, treatment-related variables and the presence of psychotic symptoms in previous affective episodes were preferentially collected from the MHUs' medical records (which included previous hospitalizations discharge reports), or from patient interviews when it was considered necessary. Sociodemographic variables were collected both through the clinical interviews and the medical records, according to the nature of each variable. The tools used to evaluate the other variables are described below.

Awareness of the disease was evaluated through the first three items of the Scale to Asses Unawareness of Mental Disorder[16], in its version validated for Spain[17]. Scores range between 3 and 15. There are no cut-points; the higher the score, the lower the awareness of the disease. Attitude towards medication was evaluated through the Drug Attitude Inventory (DAI)[18]. Although originally developed to be administered to patients with schizophrenia, it has been used with different psychiatric disorders[19]. We used the brief 10-item version, which is referred to the perceived effect of medication. The scale has been translated and validated in Spain[20]. The total score may range between 10 and 20. There are no cut-points. The higher the score, the more positive the perceived effect of medication. Beliefs on medication were evaluated with the Beliefs about Medicines Questionnaire (BMQ)[21], which is composed of two subscales: one evaluating the beliefs on medication in general (BMQ-General), including factors "abuse" and "harm", and another one evaluating patients' opinions on their specific treatments (BMQ-Specific), including factors "need" and "concern". We used the Spanish validated version[22]. Functioning was evaluated through the Functioning Assessment Short Test (FAST). This scale was developed in Spain and originally used in bipolar disorder patients, showing good psychometric properties[23]. It assesses 6 areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time.

To determine possible clinical stability, patients were evaluated with the Modified Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP-M)[24], in its translated version validated for Spain[25]. It includes three subscales: one yielding a global score referred to the last six months and two ones referred to manic symptoms or depressive symptoms in the last month. Scores range from 1 (normal) to 6 (very severe). Clinical stability was defined for scores 1 (normal) or 2 (minimum) in the manic, depression and general subscales, similarly to other authors' research[26].

We established two groups according to adherence: adherents and nonadherents. Adherence was defined as concurrent *current adherence* and *prolonged previous adherence*. *Current adherence* was defined as a score 4 in the Morisky Green Test[27], Spanish-validated version[28]. The test consists of 4 questions relative to the global treatment intake, administered in the context of a clinical interview. It has been widely used in somatic diseases and several mental disorders, including bipolar disorder[19]. *Prolonged previous adherence* was considered when serum levels of mood stabilizer (unique or combined) adequate to the treatment were found in at least 80% of determinations during the 3 years prior to evaluation, or during the corresponding period in case the time of evolution was shorter than 3 years. Only mood stabilizers serum levels were evaluated and not those of substances belonging to other pharmacological groups, used for mood-stabilizing functions (e.g. antipsychotic agents). This evaluation was made retrospectively, with the results of laboratory determinations recorded on the Medical Record.

Statistical analysis

Quantitative variables with distributions close to normal were described by the arithmetic mean ± standard deviation. Quantitative variables with distribution far from normal were described by the median and interquartile range between brackets. The normality hypothesis was contrasted by using the Shapiro-Wilk test. Qualitative variables were described by absolute frequency of occurrence of each category and the corresponding percentage between brackets.

Qualitative variables were compared between adherent and nonadherent patients by using the Chi-square test or the Fisher's exact test when conditions for the former one were not met. Quantitative variables were compared by using the Student's t-test or the Mann–Whitney U test, depending on whether the normality criteria were fulfilled or not, respectively.

Nonadherence risk was analyzed by using a logistic regression model that included all those variables that showed at least marginally significant differences in a bivariate analysis, as well as age and time of evolution, which were necessarily included in the model. The level of statistical significance was established in $p<0.05$, and the tendency to significance in $p=0.05$-0.1. Data were analyzed with the statistical package SPSS, version 15 for Windows.

RESULTS

A sample of 76 patients was recruited, with a higher proportion of women (63.2%), mean age of 49 years and median time of evolution of 16 years; 37.3% of patients had present or past harmful use or dependence of alcohol, cannabis or cocaine. Only 12% of patients were treated only with mood stabilizers. The most frequent therapeutic combination was mood stabilizer and antipsychotic drugs (61.3%). Table 1 shows the characteristics of the total sample

in all evaluated variables. The most frequent types of mood stabilizer treatment were valproic acid (38.2%), lithium (28.9%) and the combination of lithium and valproic acid (10.5%).

According to the established criteria, 28 patients were nonadherent (36.8%) and 48 were adherent (63.2%). No association was found between nonadherence and sociodemographic variables. Regarding general clinical variables, nonadherent patients showed greater number of episodes (p=0.005), depressive episodes (p=0.029) and higher prevalence of psychiatric comorbidities (p=0.012), as well as higher present and/or past harmful use or dependence of drugs (p=0.001) and specifically, a history of harmful use of alcohol (p=0.005) and cannabis (p=0.026) and present harmful use of cannabis (p=0.023) (table 2).

Regarding psychopathological, psychological and result variables (table 3), nonadherent patients showed higher prevalence of a background of episodes with psychotic symptoms (p=0.049), higher "concern" in the scale of beliefs on medication (p<0.001), worse global functionality (p=0.037) and specifically, in the areas of occupational functioning (p<0.001) and leisure time (p=0.003).

In the resulting model of multivariate analysis (table 4), the predictor variables that kept independently associated were factors "concern" from the BMQ scale (odd ratio [OR] 3.7; p=0.008) and the present and/or past use of cannabis, cocaine or alcohol (OR 4.0; p=0.032). When the model was adjusted for variables sex and time of evolution, the same variables presented statistically significant odd ratios, while the presence of other psychiatric diagnoses had a marginally significant OR (OR=2.6; p=0.068).

DISCUSSION

In our sample, we found a prevalence of nonadherence of 36.8%, close to the mean prevalence in the literature, 41%[4], which is particularly striking since it corresponds to patients in stability. Nonadherent patients showed higher prevalence of present and/or past substance abuse. Furthermore, the present or past drug abuse was one of the two variables that remained in the model of multivariate analysis. Our findings are in agreement with earlier studies, since alcohol and drug abuse (especially cannabis) has been consistently associated with nonadherence in bipolar disorder[3,11,29,30]. Moreover, differently from a previous study[30] we found an association between the history of substance abuse (cannabis and alcohol) and nonadherence[30]. Specific psychosocial interventions[31] and motivational interviews[32] have been proposed in patients with this profile, with the aim of improving adherence.

Nonadherent patients showed a greater number of episodes, depressive episodes, background of episodes with psy-

Table 1 Characteristics of the total sample (n=76)

Sociodemographic variables	
Age	49.2 ± 11.3
Gender	
Man	28 (36.8)
Woman	48 (63.2)
Marital status	
Married or stable partner	29 (38.2)
Single, separated, divorced or widow/er	47 (61.8)
Education	
Primary	32 (42.1)
Secondary	31 (40.8)
Higher	13 (17.1)
Cohabitation	
With relatives or other	60 (78.9)
Alone	16 (21.1)
Occupational status	
Employed	17 (22.4)
Unemployed	10 (13.2)
Disability due to mental disorder	49 (64.5)
Socioeconomic status	
Low	36 (47.4)
Intermediate	38 (50)
High	2 (2.6)
General clinical variables	
Age at onset of the disease	30 (24-40)
Time of evolution since onset of symptoms (years)	16 (9-23)
History of psychiatric admission, Yes	60 (78.9)
Time since last admission (months) (n=60)	48 (21-96)
Number of episodes (per 10 years of evolution)	5.8 (3.9-10)
Manic episodes (per 10 years of evolution)	2 (1-3.7)
Depressive episodes (per 10 years of evolution)	2.9 (1.4-5.7)
Mixed episodes (per 10 years of evolution)	0 (0-0)
Hypomanic episodes (per 10 years of evolution)	0 (0-1)
History of suicide attempt	34 (44.7)

Table 1 Continuation

General clinical variables	
Present or past harmful use or dependency of alcohol, cannabis or cocaine	28 (37.3)
Comorbidity with other psychiatric disorders	20 (26.3)
Treatment-related variables	
Type of treatment	
Only mood stabilizer	9 (12.0)
Mood stabilizer and antipsychotic	46 (61.3)
Mood stabilizer and antidepressant	1 (1.3)
Mood stabilizer, antidepressant and antipsychotic	9 (12.0)
Number of psychotropic tablets per day	5.6 ± 2.2
Concomitant treatment for somatic chronic pathology	36 (47.4)
Psychopathological variables	
Awareness of the disease	3 (3-6.75)
Affective episodes with psychotic symptoms (per 10 years of evolution)	1.1 (0-3.0)
Psychological variables and subjective aspects	
Attitude towards medication (DAI)	18 (17-19)
Beliefs on medication (BMQ)	18 (16-23)
Result variables	
Functioning (FAST)	29 (14.2-40.5)

Qualitative variables are summarized as frequency (percentage), while quantitative variables with a distribution significantly far from normal are presented as median (percentile 25 - percentile 75) and those with a distribution close to normal, are presented as mean ± standard deviation.

Table 2 Differences between adherent and nonadherent patients in sociodemographic variables, clinical general variables and treatment-related variables

	Non adherent (N=28)	Adherent (N=48)	p
Sociodemographic variables			
Age during the study	46.5 ± 11.7	50.8 ± 10.9	0.11
Man	10 (35.7)	18 (37.5)	0.88
Higher education	4 (14.3)	9 (18.8)	0.76

Table 2 Continuation

	Non adherent (N=28)	Adherent (N=48)	p
Sociodemographic variables			
Marital status married or stable partner	12 (42.9)	17 (35.4)	0.52
Cohabitation with relatives or other	24 (85.7)	36 (75)	0.27
Employed	5 (17.9)	12 (25)	0.47
High socioeconomic status	2 (7.1)	0 (0)	0.13
Clinical general variables			
Onset age	28 (23.5-38)	32 (25-40)	0.34
Years of evolution since symptom onset	15.5 (4.5-22.5)	15 (10.5-21.5)	0.67
Any psychiatric admission	23 (82.1)	37 (77.1)	0.60
Time from last admission, months (n=60)	38 (23-84)	48 (18-120)	0.62
Any suicide attempt	16 (57.1)	18 (37.5)	0.097
Number of episodes (per 10 years of evolution)	7.2 (5.5-14.4)	4.3 (3.5-8.6)	0.005
Manic episodes (per 10 years of evolution)	2.2 (1.3-3.3)	1.8 (1.8-3.8)	0.35
Depressive episodes (per 10 years of evolution)	3.8 (2.3-7.5)	2.5 (1.1-4.2)	0.029
Any hypomanic episode	17 (60.7)	20 (41.7)	0.11
Any mixed episode	8 (28.6)	7 (14.6)	0.14
Other psychiatric disorders	12 (42.9)	8 (16.7)	0.012
Present or past harmful use or dependency of alcohol, cannabis or cocaine	17 (60.7)	11 (23.4)	0.001
Treatment-related variables			
Treatment used			0.74
Only mood stabilizer	3 (10.7)	6 (12.8)	
Mood stabilizer and antipsychotic	20 (71.4)	26 (55.3)	
Mood stabilizer and antidepressant	2 (7.1)	7 (14.9)	
Number of psychotropic tablets per day	6 (4-7)	5.5 (4-7)	0.74
Concomitant treatment for somatic chronic pathology	13 (46.4)	23 (47.9)	0.90

Qualitative variables are summarized as frequency (percentage), while quantitative variables with a distribution significantly far from normal are presented as median (percentile 25 - percentile 75) and those with a distribution close to normal, are presented as mean ± standard deviation.

Table 3 Differences between adherent and nonadherent patients in psychopathological, psychological and result variables

	Non adherent (N=28)	Adherent (N=48)	p
Pychopathologic variables			
Insight Scale			
Awareness of mental disorder	22 (78.2)	42 (87.5)	0.34
Awareness of medication effects	21 (75.0)	32 (66.7)	0.45
Awareness of the social consequences of the disease	21 (75.0)	38 (79.2)	0.67
Global score	4 (3-6)	3 (3-7)	0.51
Any episode with psychotic symptoms	23 (82.1)	29 (60.4)	0.049
Psychological variables and subjective aspects variables			
Questionnaire of beliefs on medication (BMQ)			
BMQ General	18.5 (17-23)	18 (15-23)	0.42
Harm	1.5 (1.3-2.4)	2 (1.5-2.3)	0.56
Abuse	3.1 (2.5-3.5)	2.8 (2-3.2)	0.071
BMQ Specific	36 (34-37)	33 (28-34)	<0.001
Need	4 (3.2-3.8)	2.2 (1.6-3)	0.73
Concern	3.0 ± 0.8	2.3 ± 0.8	<0.001
Drug attitude inventory (DAI)	17.5 (15.5-19)	18 (17-19)	0.087
Result variables			
FAST scale (total)	33.5 (27.5-43.5)	20.5 (12-39)	0.037
Autonomy	1 (0.8-1.5)	0.75 (0-2.5)	0.15
Occupational functioning	2.6 (2-3)	0.8 (0-2.4)	<0.001
Cognitive functioning	1.2 (0.5-2.1)	1 (0.2-1.8)	0.35
Financial status	1 (0-2)	0 (0-1.5)	0.11
Interpersonal relationships	0.7 (0.3-1.2)	0.7 (0.3-1.5)	0.79
Leisure	2 (1-2)	1 (0-2)	0.003

Qualitative variables are summarized as frequency (percentage), while quantitative variables with a distribution significantly far from normal are presented as median (percentile 25 - percentile 75) and those with a distribution close to normal, are presented as mean ± standard deviation.

chotic symptoms and psychiatric comorbidities. The relationship of symptoms and clinical severity with adherence seems to be complex, since it is probably bidirectional. On the one hand, nonadherence facilitates relapse[5]. On the other hand, the severity of the disease has been associated with nonadherence[15] and in particular, the presence of psychotic symptoms[33] and psychotic episodes[2]. Furthermore, comorbidity with personality disorder[9] and obsessive-compulsive disorder[34] has been associated with nonadherence. Our findings are in agreement with previous ones, but our design does not allow us to establish the direction of the association.

The role of awareness of the disease in adherence in bipolar disorder has been scarcely studied and more studies are needed[3,35]. Two prospective studies[12,33] and an expert consensus[2] pointed out to deficient awareness of the disease as a risk factor for nonadherence. However, no differences were found between the two established groups in our study. Such a lack of association might be accounted for by two main reasons: on the one hand, the awareness of the disease in our sample was high, probably because of clinical stability. The awareness of the disease is worse during episodes than in remission[35]. On the other hand, it has been pointed out that there are two types of nonadherence: intentional and unintentional. While the former one is related with the awareness of the disease, the latter one is related with cognitive and other factors[2,36]. All of this means heterogeneity in nonadherent patients, which may in turn entail higher complexity in the identification of causative factors, which might be different for every one of the subgroups.

Nonadherent patients showed higher "concern" levels in the scale of beliefs on medication and, furthermore, it was one of the two variables that remained in the model after multivariate analysis. Patients with chronic diseases establish a benefit-risks evaluation of their medication (need versus concern) that influences adherence[21]. Other authors have also found an association between nonadherence and higher concern on the adverse effects and doubts on the need for medication[37,38]. The fear of suffering adverse effects and concern about that, especially weight gain, has been considered a major risk factor[2]. These findings support the above recommendations of questioning the patients on their beliefs and feelings on medication, actively listening and evaluating them[2] for a better understanding of patients' points of view and of helping them reevaluate their beliefs on medication[39].

The possible consequences of nonadherence on functioning has been scarcely studied. In this study, we found an association with worse global functioning, specifically in the areas of occupational functioning and leisure time. Our findings are in line with those of a European survey with bipolar disorder patients: 44.6% referred difficulties in their

Table 4 Multivariate model (n=76)

Predictor variables	B	Wald (z)	P	Odds Ratio [CI 95%]
BMQ concerns	1.3	7.01	0.008	3.7 (1.4-9.8)
Cannabis, cocaine or alcohol	1.38	4.52	0.032	4.0 (1.1-14.0)
Total episodes per decade	0.08	2.5	0.11	1.1 (0.98-1.20)
Other psychiatric diagnoses	0.96	1.96	0.16	2.6 (0.68-9.9)
Suicide attempts	0.42	0.39	0.53	1.4 (0.41-5.6)
Psychotic episodes	0.78	0.98	0.32	2.2 (0.46-10.4)
DAI	0.25	1.66	0.20	1.3 (0.88-1.90)
Constant	-5.2	12.8	<0.001	

The dependent variable is "nonadherence to therapy".

occupational activity and 41% difficulties for leisure activities, among other difficulties[40]. In a recent study, where the FAST scale was also used, an association was found between nonadherence and worse functioning[29]. In the same line, an association was found between subtherapeutic serum levels of lithium and worse psychosocial functioning, as compared with the adequate serum levels[41]. Probably, nonadherence impairs funcioning[42]. The possible role of cognitive functioning is more uncertain and complex. In that case, it could be bidirectional since a worse cognitive function could also be a *cause* of unintentional nonadherence[2,43]. Cognitive deficiencies – also scarcely studied – are more important than traditionally considered and, although most symptoms tend to remission in euthymia, some of them persist, in a third of patients[43]. Although we failed to find an association between cognitive functioning and adherence, like in a recent study conducted with objective and subjective measures of neurocognition and a large sample[11], our results should be interpreted with caution, since the situation of clinical stability could have determined lower intensity and prevalence, thus making identification of possible differences more difficult; and we did not use specific tools for evaluating neurocognition.

This study had certain limitation as well as strong points. Since it was not prospective, the cause-effect relationships that have been hypothesized cannot be offered with the strength of prospective studies, but as a function of their plausibility. No structured tool was used for the diagnosis of bipolar disorder, but the medical record and the clinical interview. The situation of clinical stability is a strong point, since interferences by clinical symptoms in the evaluation of the different subjective areas are prevented, and a better evaluation of areas directly influenced by clinical symptoms is possible. Furthermore, the attention, concentration and memory necessary for the evaluation interview are more preserved. However, it may reduce the external validity since those patients with severe disease may not be equally represented in the sample.

Additionally, although adherence evaluation methods have certain disadvantages[2], the use of two complementary methods to evaluate adherence in this study, one objective and the other one subjective, is rare in the available literature and is in agreement with current recommendations to use two evaluation methods whenever possible[19]. Assumedly, it minimized the disadvantages of every method used separately.

In conclusion, an important proportion of patients are nonadherent. Such patients presented a profile of present or past substance abuse, psychiatric comorbidities, concerns about medication and worse functioning. Clinicians should explore patients' beliefs and attitudes towards medication and help patients reevaluate them from a more realistic point of view. Interventions to prevent substance abuse should be made.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

REFERENCES

1. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487-97.
2. Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry. 2009;70(Suppl 4)1-46; quiz 47-8.
3. Leclerc E, Mansur RB, Brietzke E. Determinants of adherence to treatment in bipolar disorder: a comprehensive review. J Affect

Disord. 2013;149(1-3):247-52.
4. Lingam R, Scott J. Treatment non-adherence in affective disorders. Acta Psychiatr Scand. 2002;105(3):164-72.
5. Simhandl C, König B, Amann BL. A prospective 4-year naturalistic follow-up of treatment and outcome of 300 bipolar I and II patients. J Clin Psychiatry. 2014;75(3):254-62; quiz 263.
6. Gónzalez-Pinto A, Mosquera F, Alonso M, López P, Ramírez F, Vieta E, et al. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. Bipolar Disord. 2006;8:618-24.
7. Adams J, Scott J. Predicting medication adherence in severe mental disorders. Acta Psychiatr Scand. 2000;101:119-24.
8. Eaddy M, Grogg A, Locklear J. Assessment of compliance with antipsyshotic treatment and resource utilization in a Medicaid population. Clin Ther. 2005;27:263-72.
9. Colom F, Vieta E, Martínez-Arán A, Reinares M, Benabarre A, Gastó C. Clinical factors associated to treatment no compliance in euthymic bipolar patients. J Clinic Psychiatry. 2000;61:549-54.
10. Svarstad BL, Shiermana TI, Sweeney JK, Using Drug claims data to asses the relationship of medication adherence with hospitalisation and costs. Psychiatr Serv. 2001;52:805-11.
11. Jónsdóttir H, Opjordsmoen S, Birkenaes AB, Simonsen C, Engh JA, Ringen PA, et al. Predictors of medication adherence in patients with schizophrenia and bipolar disorder. Acta Psychiatr Scand. 2013;127(1):23-33.
12. Yen CF, Chen CS, Ko CH, Yeh ML, Yang SJ, Yen JY, et al. Relationships between insight and medication adherence in outpatients with schizophrenia and bipolar disorder: Prospective study. Psychiatry Clin Neurosci. 2005;59:403-9.
13. Hou R, Cleak V, Peveler R. Do treatment and illness beliefs influence adherence to medication in patients with bipolar affective disorder? A preliminary cross-sectional study. Eur Psychiatry. 2010;25(4):216-9.
14. Sajatovic M, Ignacio RV, West JA, Cassidy KA, Safavi R, Kilbourne AM, et al. Predictors of nonadherence among individuals with bipolar disorder receiving treatment in a community mental health clinic. Compr Psychiatry. 2009;50(2):100-7.
15. Pompili M, Venturini P, Palermo M, Stefani H, Seretti ME, Lamis DA, et al. Mood disorders medications: predictors of nonadherence – review of the current literature. Expert Rev Neurother. 2013;13(7):809-25.
16. Amador XF, Strauss DH, Yale SA, Flaum MM, Endicott J, Gorman JM. Assessment of insight in Psychosis. Am J Psychiatry. 1993;150:873-9.
17. Ruiz A, Pousa E, Duñó R, Crosas J, Cuppa S, García C. Spanish adaptation of the Scale to Asses Unawareness of Mental Disorder (SUMD). Actas Esp Psiquiatr. 2008;36(2):111-9.
18. Hogan TP, Awad AG, Eastwood MR. A self-report scale predictive of drug compliance in schizophrenics: Reliability and discriminative validity. Psychol Med. 1983;13:177-83.
19. Sajatovic M, Velligan DI, Weiden PJ, Valenstein MA, Ogedegbe G. Measurement of psychiatric treatment adherence. J Psychosom Res. 2010;69(6):591-9.
20. Robles García R, Salazar Alvarado V, Páez Agraz F, Ramírez Barreto F. Assessment of drug attitudes in patients with schizophrenia: psychometric properties of the DAI Spanish version. Actas Esp Psiquiatr. 2004;32(3):138-42.
21. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology & Health. 1999;14:1-24.
22. Beléndez-Vázquez M, Hernández-Mijares A, Horne R, Weinman J. Evaluación de las creencias sobre el tratamiento: validez y fiabilidad de la versión española del Beliefs about Medicines Questionnaire. Int J Clin Hlth Psyc. 2007;7(3):767-79.
23. Rosa AR, Sánchez-Moreno J, Martinez-Aran A, Salamero M, Torrent C, Reinares M, et al. Validity and Reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin Pract Epidemiol Ment Health. 2007;3:5.
24. Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res. 1997;73(3):159-71.
25. Vieta Pascual E, Torrent Font C, Martínez-Arán A, Colom Victoriano F, Reinares Gabnepen M, Benabarre Hernández A, et al. A user-friendly scale for the short and long term outcome of bipolar disorder: the CGI-BP-M. Actas Esp Psiquiatr. 2002;30(5):301-4.
26. Vieta E, de Arce R, Jiménez-Arriero MA, Rodriguez A, Balanzá V, Cobaleda S. Detection of subclinical depression in bipolar disorder: a cross-sectional, 4-month prospective follow-up study at community mental health services (SIN-DEPRES). J Clin Psychiatry. 2010;71(11):1465-74.
27. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24:67-74.
28. Val A, Amorós G, Martínez P, Ferández ML, León M. Estudio descriptivo del cumplimiento del tratamiento farmacológico antihipertensivo y validación del test Morisky y Green. Aten Primaria. 1992;10:767-70.
29. Montes JM, Maurino J, de Dios C, Medina E. Suboptimal treatment adherence in bipolar disorder: impact on clinical outcomes and functioning. Patient Prefer Adherence. 2013;7:89-94.
30. Teter CJ, Falone AE, Bakaian AM, Tu C, Ongür D, Weiss RD. Medication adherence and attitudes in patients with bipolar disorder and current versus past substance use disorder. Psychiatry Res. 2011;190(2-3):253-8.
31. Gaudiano BA, Weinstock LM, Miller IW. Improving treatment adherence in patients with bipolar disorder and substance abuse: rationale and initial development of a novel psychosocial approach. J Psychiatr Pract. 2011;17(1):5-20.
32. Laakso LJ. Motivational interviewing: addressing ambivalence to improve medication adherence in patients with bipolar disorder. Issues Ment Health Nurs. 2012;33(1):8-14.
33. González-Pinto A, Reed C, Novick D, Bertsch J, Haro JM. Assessment of medication adherence in a cohort of patients with bipolar disorder. Pharmacopsychiatry. 2010;43(7):263-70.
34. Baldessarini RJ, Perry R, Pike J. Factors associated with treatment nonadherence among US bipolar disorder patients. Hum Psychopharmacol. 2008;23(2):95-105.
35. Látalová K. Insight in bipolar disorder. Psychiatr Q. 2012; 83(3):293-310.
36. Furniss D, Barber N, Lyons I, Eliasson L, Blandford A. Unintentional non-adherence: can a spoon full of resilience help the medicine go down? BMJ Qual Saf. 2014;23(2):95-8.
37. Clatworthy J, Bowskill R, Parham R, Rank T, Scott J, Horne R. Understanding medication non-adherence in bipolar disorders using a Necessity-Concerns Framework. J Affect Disord. 2009; 116(1-2):51-5.
38. Sajatovic M, Levin J, Fuentes-Casiano E, Cassidy KA, Tatsuoka C, Jenkins JH. Illness experience and reasons for nonadherence among individuals with bipolar disorder who are poorly adherent with medication. Compr Psychiatry. 2011;52(3):280-7.
39. Julius RJ, Novitsky MA Jr, Dubin WR. Medication adherence: a review of the literature and implications for clinical practice. J Psychiatr Pract. 2009;15(1):34-44.
40. Morselli PL, Elgie R; GAMIAN-Europe. GAMIAN-Europe/BEAM survey I–global analysis of a patient questionnaire circulated to

3450 members of 12 European advocacy groups operating in the field of mood disorders. Bipolar Disord. 2003;5(4):265-78.
41. Solomon DA, Ristow WR, Keller MB, Kane JM, Gelenberg AJ, Rosenbaum JF, et al. Serum lithium levels and psychosocial function in patients with bipolar I disorder. Am J Psychiatry. 1996;153:1301-7.
42. Sanchez-Moreno J, Martinez-Aran A, Tabarés-Seisdedos R, Torrent C, Vieta E, Ayuso-Mateos JL. Functioning and disability in bipolar disorder: an extensive review. Psychother Psychosom. 2009;78(5):285-97.
43. Martínez-Arán A, Scott J, Colom F, Torrent C, Tabares-Seisdedos R, Daban C, et al. Treatment nonadherence and neurocognitive impairment in bipolar disorder. J Clin Psychiatry. 2009;70(7):1017-23.