Patient Preference and Adherence

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ORIGINAL RESEARCH

Suboptimal treatment adherence in bipolar disorder: impact on clinical outcomes and functioning

This article was published in the following Dove Press journal:
Patient Preference and Adherence
17 January 2013
Number of times this article has been viewed

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Background: The primary aim of this study was to assess drug treatment adherence in patients with bipolar disorder and to identify factors associated with adherence. The secondary aim was to analyze the impact of suboptimal adherence on clinical and functional outcomes.

Methods: A cross-sectional study was conducted in a sample of outpatients receiving an oral antipsychotic drug. Medication adherence was assessed combining the 10-item Drug Attitude Inventory, the Morisky Green Adherence Questionnaire, and the Compliance Rating Scale. Logistic regression was used to determine significant variables associated with suboptimal adherence to medication.

Results: Three hundred and three patients were enrolled into the study. The mean age was 45.9 ± 12.8 years, and 59.7% were females. Sixty-nine percent of patients showed suboptimal adherence. Disease severity and functioning were significantly worse in the suboptimal group than in the adherent group. Multivariate analysis showed depressive polarity of the last acute episode, presence of subsyndromal symptoms, and substance abuse/dependence to be significantly associated with suboptimal treatment adherence (odds ratios 3.41, 2.13, and 1.95, respectively).

Conclusion: A high prevalence of nonadherence was found in an outpatient sample with bipolar disorder. Identification of factors related to treatment adherence would give clinicians the opportunity to select more adequately patients who are eligible for potential adherence-focused interventions.

Keywords: bipolar disorder, treatment adherence, functioning, polarity, subsyndromal symptoms

Introduction

The estimated lifetime prevalence of bipolar disorder in Europe is approximately 1%.[1] In the population aged 15–44 years, bipolar disorder is among the leading causes of disability in the developed world, which partially explains the significant economic burden of the disease.[2] In addition, bipolar patients use health care services more than patients with other mental disorders.[2,3]

The presence of mood episodes in bipolar disorder has a strong association with poor functioning.[4] However, it is now recognized that symptomatic and functional outcomes in bipolar disorder are not synonymous.[5] Rosa et al reported that patients with depressive and manic episodes experience poor psychosocial functioning in distinct areas and that these deficits persist in an attenuated form even during remission periods.[5] The complex clinical nature of bipolar disorder may complicate measurement of functional impairment. The Functioning Assessment Short-Test (FAST) was recently

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developed and validated to assess specific life domains of functioning as well as overall functioning in patients with bipolar disorder.[6]

Nonadherence with medication remains a challenging problem in the management of patients with bipolar disorder.[7] Adherence rates are as low as 35%.[8] Scott et al reported that 30%–50% of patients receiving a mood stabilizer did not take treatment against medical advice at least once over the course of one year.[9] A recently published survey of psychiatrists from eight European countries estimated that 57% of bipolar patients were partially or nonadherent with medication.[10] Psychotic symptoms, poor insight, substance abuse/dependence, and work impairment are negatively related to medication adherence during maintenance in patients with bipolar disorder.[11–14] An irregular daily routine or life circumstances and feeling better were also considered as relevant reasons for patients discontinuing medication.[10]

Nonadherence with treatment is associated with poorer clinical and functional outcomes, increased use of emergency psychiatric services, and an increased number of hospital admissions.[15] The primary aim of this study was to assess treatment adherence in a sample of outpatients with bipolar disorder using a protocol with three different adherence scales. The secondary aim was to analyze the impact of suboptimal adherence with medication on clinical outcomes and functioning.

Materials and methods

This was a cross-sectional study conducted in 31 community-based mental health centers throughout Spain. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was reviewed and approved by the ethics committee of the Hospital Clínic (Barcelona, Spain).

Subjects

Outpatients aged 18 years or older with a documented clinical diagnosis of bipolar I or II disorder and receiving an oral antipsychotic drug were enrolled into the study. Patients with organic brain disorders or other diagnosis corresponding to Axis I or II of the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision), except for substance abuse/dependence disorder, were excluded. Written informed consent was obtained from all subjects.

Assessments

The diagnosis was established using the Structured Clinical Interview for DSM-IV-TR. Sociodemographic data and disease history were collected from medical records and clinical interviews. To assess treatment adherence, three different scales were used in order to provide a broad description of this parameter: the 10-item Drug Attitude Inventory (DAI-10), the Morisky-Green Adherence questionnaire (MAQ), and the Compliance Rating Scale (CRS, Table 1).[16–20] The DAI-10 is a self-administered instrument of true-false statements about the nature of patient experience with use of psychotropic drugs.[16,17] Scores range from −10 to +10, with higher scores indicating a more positive attitude towards medication. The DAI correlates with both clinician-rated adherence and biochemical measures of adherence.[21] The MAQ addresses how patients may fail to take medication as prescribed due to forgetfulness, carelessness, stopping the drug when they feel better, or stopping treatment because they believe it makes them feel worse.[18] It is a self-rated questionnaire consisting of four questions with yes/no answers. When the answer indicates a negative adherence issue, a score of 1 is recorded. Total score ranges from 0 (good adherence) to 4 (poor adherence).[18] MAQ score at a threshold of ≥ 1 may be a valuable tool for identifying nonadherent patients in a cohort where adherence is low.[22] The scale has good validity and reliability, and was initially developed to assess compliance in patients with arterial hypertension and occasionally in the context of psychiatric disorders.[23,24] The CRS uses a 1–7 ordinal scale to quantify the clinician's assessment of the adherence level shown by the patient.[19,20] Higher scores represent greater adherence. The CRS has demonstrated sensitivity for detecting differences in outcomes among patients receiving compliance therapy versus nonspecific counseling.[19,20] Patients with a score ≤ 4 were labeled nonadherent.[25] Several methods for measuring adherence are available, each with its own set of limitations. The use of multiple measures of adherence is encouraged to balance the limitations of individual instruments.[7]

The Young Mania Rating Scale (YMRS) and the Montgomery-Åsberg Depression Rating Scale (MADRS) are used to assess manic and depressive symptoms, respectively.[26,27] The modified Clinical Global Impression-Bipolar Disorder severity of illness scale (CGI-BP) was used

Table 1 Measures of medication adherence

Name of scale	Items (n)	Administration	Suboptimal adherence
DAI-10	10	Self-report	Negative score
MAQ	4	Self-report	Score ≥ 1
CRS	7	Clinician-report	Score ≤ 4

Abbreviations: DAI-10, 10-item Drug Attitude Inventory; MAQ, Morisky Green Adherence Questionnaire; CRS, Compliance Rating Scale.

to evaluate global clinical status.[28] Finally, FAST was used to assess functional impairment.[6] This is a valid and reliable 24-item instrument that reviews the main functioning problems experienced by psychiatric patients in six specific domains, ie, autonomy, occupational and cognitive functioning, financial issues, interpersonal relationships, and leisure time. The overall score ranges from 0 to 72, with higher scores indicating greater disability. The authors suggest a cutoff value of <11 as indicating functional remission.[6]

Statistical analysis

Categorical data were analyzed using the Chi-squared test, and continuous data using the Student's *t*-test (both two-sided). Treatment adherence was categorized as optimal/suboptimal using a combination of cutoff scores on the following three scales: DAI-10 ≥ 0 plus MAQ = 0 plus CRS > 4 versus DAI-10 < 0 plus MAQ ≥ 1 plus CRS ≤ 4.

Multivariate logistic regression was performed to evaluate the potential influence of different factors on suboptimal treatment adherence. The analysis was carried out using suboptimal adherence as the dependent variable and gender (male versus female), age (continuous variable), substance abuse/dependence (alcohol, cannabis, cocaine, with one variable, yes versus no), polarity of the last episode (manic, hypomanic, depressive, or mixed), presence of an acute episode at enrolment (yes versus no), presence of subsyndromal symptoms (yes versus no), YMRS score (≤20 versus >20), MADRS score (≤10 versus >10), FAST score (≤11 versus >11), and participation in psychoeducational programs (no versus yes) by means of a backward stepwise procedure; interactions with no evidence of association ($P > 0.20$) were eliminated from the models, except when based on a priori clinical considerations. All statistical tests were performed considering a significance level of 5%. SAS statistical software release 8.02 (SAS Institute Inc, Cary, NC), was used throughout.

Results

A total of 303 patients were included in the analysis. Their mean age was 45.9 ± 12.8 years, and females represented 59.7% of the sample. Table 2 summarizes the main sociodemographic and clinical characteristics of the sample. According to the definition of treatment adherence used in the study, combining the DAI, MAQ, and CRS scales, 69.3% of patients (n = 210) were classified as having suboptimal medication adherence.

No significant differences were seen in terms of gender, living status, type of bipolar disorder, or disease duration between patients with optimal and suboptimal adherence. However, patients with adherence problems were significantly younger, were more likely to be unemployed, more frequently experienced depressive polarity of the most recent acute episode, and had a greater prevalence of substance abuse/dependence disorder and higher MADRS and YMRS total scores. Only 37% of patients with suboptimal adherence were euthymic, as compared with 63.4% in the adherent group. In addition, subsyndromal symptoms were found in 40% of poorly adherent patients. Finally, the population with suboptimal adherence also showed worse functioning than adherent patients, with total FAST scores of 27.1 (95% confidence interval 24.4–29.9) and 18.5 (95% confidence interval 17.5–23.9), respectively ($P = 0.0002$). Table 3 shows the main sociodemographic and clinical characteristics of the sample according to treatment adherence criteria.

Table 2 Sociodemographic and clinical characteristics of sample

	n = 303
Age (years), mean (SD)	45.9 (12.8)
Gender (female), n (%)	181 (59.7)
Living status (alone), n (%)	50 (16.5)
Working status (unemployed), n (%)	44 (14.5)
DSM-IV-TR diagnosis, n (%)	
Bipolar I disorder	228 (75.2)
Rapid cycling, n (%)	45 (14.8)
Duration of illness (years), mean (SD)	12.6 (9.8)
Number of hospitalizations, mean (SD)	2.8 (3.8)
MADRS score, mean (SD)	8.3 (8.2)
YMRS score, mean (SD)	5.6 (7.2)
CGI-BP overall score, mean (SD)	2.01 (1.2)
DAI-10 score, mean (SD)	4.8 (4.8)
MAQ (score ≥ 1), n (%)	203 (67.0)
CRS score, mean (SD)	5.3 (1.7)
FAST score, mean (SD)	24.4 (17.8)

Abbreviations: DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; MADRS, Montgomery-Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale; CGI-BP, Clinical Global Impression-Bipolar Disorder Severity Scale; DAI-10, 10-item Drug Attitude Inventory; MAQ, Morisky Green Adherence Questionnaire; CRS, Compliance Rating Scale; FAST, Functioning Assessment Short Test; SD, standard deviation.

Multivariate analysis showed that the main variables associated with suboptimal treatment adherence were depressive polarity of the last episode (odds ratio [OR] 3.41), current acute episode (OR 2.67), presence of subsyndromal symptoms (OR 2.13), and substance abuse/dependence (OR 1.95, Table 4).

Discussion

Medication adherence plays a key role in patients with bipolar disorder.[7] Several specific factors associated with nonadherence in bipolar disorder have been reported, including young age, male gender, lower education level,

Table 3 Sociodemographic and clinical characteristics of patients with optimal and suboptimal treatment adherence

	Optimal adherence (n = 93)	Suboptimal adherence (n = 210)	*P* value
Age (years), mean (SD)	48.5 (12.1)	44.9 (11.9)	0.015
Gender (female), n (%)	53 (57.0)	128 (60.9)	0.516
Living status (alone), n (%)	14 (15.1)	36 (17.1)	0.651
Working status (unemployed), n (%)	8 (8.6)	36 (17.1)	0.003
DSM-IV-TR diagnosis, n (%)			
Bipolar I disorder	75 (80.6)	153 (72.9)	0.147
Duration of illness (years), mean (SD)	14.0 (11.6)	12.0 (9.0)	0.112
Number of hospitalizations, mean (SD)	2.2 (2.7)	3.3 (4.4)	
Polarity of last episode, n (%)			0.002
Mania	20 (21.5)	60 (28.6)	
Hypomania	21 (22.6)	33 (15.7)	
Depression	22 (23.6)	79 (37.6)	
Mixed	9 (9.7)	19 (9.0)	
Current clinical status, n (%)			0.001
Euthymia	59 (63.4)	78 (37.1)	
Acute episode	8 (8.6)	47 (22.4)	
Subsyndromal symptoms	26 (28.0)	85 (40.5)	
Suicidal ideation, n (%)	7 (7.5)	23 (11.0)	0.358
Substance abuse/dependence, n (%)			
Alcohol	17 (18.3)	62 (29.5)	0.040
Cocaine	3 (3.2)	31 (14.8)	0.003
Cannabis	9 (9.7)	50 (23.8)	0.004
MADRS score, mean (SD)	5.6 (7.1)	8.0 (7.8)	0.016
YMRS score, mean (SD)	2.6 (4.2)	5.7 (7.4)	0.0003
CGI-BP overall score, mean (SD)	2.6 (1.3)	2.7 (1.4)	0.570
CGI-BP depression score, mean (SD)	1.7 (1.1)	2.1 (1.2)	0.009
CGI-BP mania score, mean (SD)	1.5 (1.0)	2.0 (1.3)	0.0008
FAST score, mean (SD)	18.5 (16.8)	27.1 (17.6)	0.0002
Receiving psychoeducation, n (%)	11 (11.8)	28 (13.3)	0.718

Note: Suboptimal adherence was defined according to cutoff scores of DAI-10 < 0, MAQ ≥ 1, and CRS ≤ 4.

Abbreviations: DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; MADRS, Montgomery-Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale; CGI-BP, Clinical Global Impression-Bipolar Disorder Severity Scale; FAST, Functioning Assessment Short Test; SD, standard deviation.

being single, comorbid alcohol and drug abuse, psychotic symptoms during mania or mixed episodes, cognitive impairment, lack of insight, poor attitude towards medication, and work impairment.[11–14,29,30] Better understanding of the factors involved in suboptimal adherence with medication for bipolar disorder is crucial because modifiable risk factors could become targets for future interventions.

Table 4 Logistic regression analysis

	OR	95% CI	*P* value
Gender	1.18	0.66–2.13	0.571
Age	1.03	1.01–1.06	0.009
Substance abuse/dependence disorder	1.95	1.01–3.78	0.048
Polarity of the last episode			
Mania	2.11	0.86–5.16	0.101
Hypomania	1.59	0.63–4.00	0.326
Depression	3.41	1.43–8.11	0.016
Mixed	1.79	0.59–5.43	0.302
Current acute episode	2.67	1.02–7.00	0.045
Presence of subsyndromal symptoms	2.13	1.09–4.17	0.027
YMRS score > 20	1.81	0.60–5.44	0.290
MADRS score > 10	1.23	0.59–2.57	0.588
FAST score > 11	1.24	0.65–2.36	0.522
No psychoeducation	1.03	0.45–2.36	0.951

Abbreviations: CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale; OR, odds ratio; YMRS, Young Mania Rating Scale; FAST, Functioning Assessment Short Test.

However, many problems arise when conducting research in this area. Medication adherence is difficult to define and measure. Most methods used to measure adherence are considered to be indirect, such as self-reporting by patients, medication measurements, use of electronic monitoring devices, and prescription record review. Unfortunately, no measure can be accepted as the "gold standard", because all methods have inherent limitations.[7] Therefore, we decided to assess treatment adherence using a combination of three different, well known indirect scales, ie, DAI-10, MAQ, and CRS. Finally, the results of this study show a high prevalence of suboptimal treatment adherence in a sample of outpatients with bipolar disorder treated with at least one antipsychotic drug (n = 210, 69.3%).

An interesting finding in our study was that depressive polarity of the most recent episode predicted treatment non-adherence (OR 3.41, $P = 0.016$). Linke et al recently reported that patients with bipolar disorder who last experienced a depressive episode learned better from negative feedback than from positive reinforcement.[31] These authors suggested that, in addition to cognitive impairment, motivational vulnerability depending on polarity of the last episode is present in euthymic patients.

Disease severity (YMRS, MADRS, CGI-BP Mania and Depression) was significantly worse in patients with suboptimal adherence as compared with the adherent group. De Dios et al found that patients with bipolar disorder were in an episode one third of the time, and were symptomatic (in an episode or with subsyndromal symptoms) in one third of visits during 72 weeks of follow-up.[32] Persistent subsyndromal symptoms increase the risk of and shorten the

time to affective relapse in bipolar disorder.[33] In our study, the presence of subthreshold symptoms was a predictor for suboptimal adherence (OR 2.13, $P = 0.027$).

Patient outcomes had traditionally been more focused on symptomatic remission. However, patient functioning is now considered to be one of the essential objectives when bipolar patients are treated.[2] In our study, patients with suboptimal adherence had greater functional impairment, as measured by FAST, than patients with optimal adherence. Because patients with suboptimal adherence were also more symptomatic, only an association between adherence and functioning can be suggested. Further research is needed to establish the role of treatment adherence in functionality of patients with bipolar disorder.

Our study has several limitations. First, a cross-sectional study cannot confirm associations between the factors studied and must be limited to their descriptive and exploratory value or to generate hypotheses that should be confirmed in prospective follow-up studies. Second, treatment adherence was measured using indirect scales (two patient-rated and one physician-rated). Several methods for measuring adherence are available, each with its own set of limitations.[34] Although Jonsdottir et al reported agreement between subjective and objective assessments of adherence, it is conceivable that we may have overestimated actual adherence.[35] It has recently been suggested that a mixed method, incorporating both objective and subjective methods to assess adherence, may be the most reliable option.[36] Third, the categorical approach to analysis of DAI-10 scores could limit the finding of additional correlations. Fourth, the sample population comprised patients taking an oral antipsychotic drug, so the results may not be generalized to include patients receiving treatment based only on mood stabilizers. Finally, neither insight into illness nor prior experience with psychopharmacological treatments and side effects were assessed as factors associated with treatment adherence.[7]

This study found a high prevalence of suboptimal adherence with treatment by bipolar outpatients seen in real-life practice. In this context, our results emphasize the importance of identifying patients with potentially modifiable risk factors for adherence-focused psychoeducational interventions.[37,38]

Disclosure

This study was sponsored by AstraZeneca Spain. JMM has received grants from and served as a consultant, advisor, or continuing medical education speaker for AstraZeneca, Boehringer Ingelheim, Bristol-Myers-Squibb, Otsuka, Lundbeck, Pfizer, Rovi, and Servier. CdD has received grant support or given presentations for AstraZeneca, Bristol-Myers-Squibb, Eli Lilly, Janssen-Cilag, Pfizer, GlaxoSmithKline, Cephalon, and Lundbeck. EM and JM are employees of AstraZeneca Spain.

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