

# Short-term clinical stability and lack of insight are associated with a negative attitude towards antipsychotic treatment at discharge in patients with schizophrenia and bipolar disorder

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**Purpose:** The primary aim of this study was to assess the range of attitudes towards antipsychotic treatment at hospital discharge in patients with schizophrenia and bipolar disorder. The secondary aim was to analyze the relationship between patients' attitudes and sociodemographic and clinical parameters.

**Patients and methods:** A cross-sectional study with a sample of patients admitted due to acute exacerbation of schizophrenia or a manic episode was conducted. Attitude towards pharmacological treatment at discharge was assessed with the 10-item Drug Attitude Inventory (DAI-10). Logistic regression was used to determine significant variables associated with attitude to medication.

**Results:** Eighty-six patients were included in the study. The mean age was 43.1 years (standard deviation [SD] 12.1), and 55.8% were males. Twenty-six percent of the patients presented a negative attitude towards antipsychotic treatment (mean DAI-10 score of  $-4.7$ , SD 2.7). Most of them had a diagnosis of schizophrenia. Multivariate analysis showed that poor insight into illness and a greater number of previous acute episodes was significantly associated with a negative attitude towards medication at discharge (odds ratio 1.68 and 1.18, respectively).

**Conclusion:** Insight and clinical stability prior to admission were related to patients' attitude towards antipsychotic treatment at hospital discharge among patients with schizophrenia and bipolar disorder. The identification of factors related to the attitude towards medication would offer an improved opportunity for clinicians to select patients eligible for prophylactic adherence-focused interventions.

**Keywords:** attitude towards treatment, schizophrenia, bipolar disorder, therapeutic adherence, discharge, insight

## Introduction

Nonadherence to medication remains a challenging problem in the management of patients suffering from schizophrenia and bipolar disorder.<sup>1</sup> Rates of adherence among patients with schizophrenia are between 50%–60%, and among those with bipolar affective disorder the rates are as low as 35%.<sup>2</sup> Up to 75% of all patients with schizophrenia discontinue treatment within 2 years of hospital discharge.<sup>1</sup>

Nonadherence to treatment is associated with poorer clinical and functional outcomes, increased use of emergency psychiatric services, and an increased number of hospital admissions.<sup>3,4</sup>

Medication adherence in schizophrenia is a multifactorial phenomenon involving four main groups of factors: sociodemographic variables (age, sex, occupation, level

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of education, and social status); illness-related variables (type and severity of symptoms, illness insight, course of illness); treatment-related variables (dosage schedule complexity, frequency and intensity of side effects, length of treatment); and patient general values and attitudes (illness attitudes).<sup>1,5</sup> In addition, patients' decisions to be adherent may be the result of interaction among different factors, such as the degree of global psychopathology, possible substance abuse, the side effects experienced or perceived subjective well-being.<sup>6-8</sup> Psychotic symptoms, poor insight, substance abuse/dependence, and work impairment are negatively related to medication adherence during maintenance in patients with bipolar disorder.<sup>9</sup> Thus, adherence problems may be determined by many factors that could contribute to maintain patients in this situation even after intervention for improving adherence.<sup>10</sup>

Although a factor shown by a series of studies to be related to adherence, little attention has been paid to the degree of patients' satisfaction with the prescribed medication.<sup>11-14</sup> It has been consistently observed after hospital admission that factors such as the level of insight into the patient's attitude towards medication can predict adherence to treatment.<sup>15</sup> Subjective perception of medication in outpatients has been widely studied, though not in the context of patients who are discharged after admission due to acute episodes.<sup>1</sup>

The primary aim of this study was to assess the range of attitudes towards antipsychotic treatment at hospital discharge in patients with schizophrenia and bipolar disorder. The secondary aim was to analyze the relationship between patients' attitudes and sociodemographic and clinical parameters.

## Material and methods

This was a cross-sectional study conducted in five community 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 Clinico San Carlos (Madrid, Spain).

## Subjects

The study included inpatients aged 18 years or older, with a *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision (DSM-IV-TR) diagnosis of schizophrenia or bipolar disorder, presenting acute exacerbation of schizophrenia or an acute manic episode, respectively, and receiving antipsychotic treatment for at least 7 days prior to enrollment.

Patients with a diagnosis of substance abuse or dependence, organic brain disorders or other diagnosis corresponding to

Axis I or II of the DSM-IV-TR were excluded. Written informed consent was obtained in all cases.

## Assessments

The diagnoses were established on the basis of the Structured Clinical Interview for DSM-IV-TR. Sociodemographic and course-related variables were collected on admission. Patients' attitude towards treatment was assessed with the 10-item Drug Attitude Inventory (DAI-10), which is a self-report instrument of true-false statements about the nature of patient experience with psychotropic drug use.<sup>16,17</sup> 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. Other subjective aspects related to treatment adherence were assessed using the Rating of Medication Influences (ROMI) scale.<sup>18</sup> This is a valid and reliable instrument used to assess subjective reasons for medication adherence or nonadherence. The total 20 patient-report items have three subscales related to adherence (prevention, influence of others, and medication affinity) and five subscales related to nonadherence (denial/dysphobia, logistical problems, rejection of label, family influence, and negative therapeutic alliance). The DAI focuses on rather global aspects of medication benefits, not drug-specific effects or side effects. ROMI yields additional information that can be more pertinent in certain patients. An example would be a nonadherent patient who scores high on the DAI, but simply cannot afford to buy medication.<sup>19,20</sup>

The Clinical Global Impression – Severity scale (CGI-S) was used to assess global clinical status. Insight was measured using the first three items of the Scale to Assess Unawareness of Mental Disorder (SUMD).<sup>21</sup> These items assess the subject's general insight into having a mental disorder, the effects of medication on the disorder, and general understanding of the consequences of the disorder, respectively. They are rated on a 5-point Likert scale (1 = "aware" to 5 = "unaware"), with higher scores indicating poorer awareness. Antipsychotic side effects were assessed using the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale (UKU).<sup>22</sup>

All ratings were performed at discharge.

## Statistical analysis

Categorical data were analyzed with a Chi-squared test and continuous data by means of the Student's *t*-test (both two-tailed). A correction of alpha for multiplicity of tests was conducted using Bonferroni's procedure. The results

on attitude towards medication obtained by the patients on the DAI-10 scale are reported for all patients and clinical subgroups. The result obtained from the scale was calculated as the total score with values in the range of  $-10$  to  $+10$ . In addition, patients were divided into two groups according to positive ( $\geq 0$ ) or negative ( $< 0$ ) scores on the 10-item DAI.<sup>17,23</sup> Spearman's rank correlation was used to assess the associations between patients' attitudes and other subjective factors associated with adherence. For this purpose, the result of the ROMI scale was taken as the scale total, and its two subscales (the Compliance and the Noncompliance subscales), as separate.<sup>18</sup> To qualitatively characterize patients with a negative result in the DAI-10, we compared these patients in terms of their sociodemographic and clinical variables, and the incidence of adverse effects versus patients who obtained a positive result. To estimate the average severity level of the adverse events experienced by the patient, the mean and SD of all recorded events were calculated in each case.

We included significant variables determined by univariate analysis ( $P \leq 0.2$ ) and confounding variables into the backward stepwise logistic regression model, aiming to identify factors associated with the sign of the attitude towards antipsychotic medication. The correlation matrix for the independent variables was examined to detect potential multicollinearity problems in model building and to select the final candidate predictors to be included in the model based on clinical criteria. The final model contained only the independent variables that maintained a significant association with the outcome after adjustment ( $P \leq 0.05$ ), according to the likelihood ratio test. The variables used to adjust the initial model were: age, sex, living status, diagnosis, number of previous acute episodes, time since the last hospitalization, CGI-S score, and severity of adverse events. "Time since the last acute episode" variable was not included due to collinearity.

All statistical tests were performed considering a significance level of 5%. The SAS statistical package (release 8.02; SAS Institute Inc, Cary, NC), was used throughout.

## Results

Of the 99 recruited patients, 86 were included in the analysis (45 with a diagnosis of schizophrenia and 41 with bipolar disorder). Deviations from protocol ( $n = 13$ ) were due to failure to meet the screening criteria, such as length of hospital stay ( $n = 7$ ). The mean age was 43.1 years (SD 12.1), with males comprising 55.8% of the sample. The mean CGI-S score was 3.4 (SD 1.1). Table 1 summarizes the main sociodemographic and clinical characteristics of the sample.

**Table 1** Sociodemographic and clinical characteristics of the sample

|                                                             | N = 86      |
|-------------------------------------------------------------|-------------|
| Age (years), mean (SD)                                      | 43.1 (12.1) |
| Sex (male), N (%)                                           | 48 (55.8)   |
| Living status (alone), N (%)                                | 15 (17.4)   |
| Marital status (single), N (%)                              | 65 (78.3)   |
| Diagnosis, N (%)                                            |             |
| Schizophrenia                                               | 45 (52.3)   |
| Bipolar disorder                                            | 41 (47.7)   |
| Duration of illness (years), mean (SD)                      | 18.3 (13.4) |
| Number of acute episodes within the last 5 years, mean (SD) | 3.4 (4.7)   |
| Time since the last acute episode (years), mean (SD)        | 3.0 (5.4)   |
| Number of hospitalizations, mean (SD)                       | 5.0 (7.8)   |
| DAI-10 score, mean (SD)                                     | 2.1 (4.9)   |
| CGI-S score, mean (SD)                                      | 3.4 (1.1)   |
| SUMD score, mean (SD)                                       | 7.5 (3.3)   |
| ROMI, mean (SD)                                             |             |
| Total score                                                 | 44.3 (6.0)  |
| Compliance subscale score                                   | 19.4 (3.3)  |
| Noncompliance subscale score                                | 24.9 (5.2)  |

**Abbreviations:** DAI-10, 10-item Drug Attitude Inventory; CGI-S, Clinical Global Impression – Severity scale; SD, standard deviation; SUMD, Scale of Unawareness of Mental Disorders; ROMI, Rating of Medication Influences scale.

## Attitude towards medication

The mean DAI-10 score at discharge was 2.1 points (95% confidence interval [CI]: 1.0–3.2). A total of 74.4% ( $n = 64$ ) of the patients presented a positive attitude towards treatment. Most patients with a negative attitude had a diagnosis of schizophrenia ( $n = 16/22$ , 72.7%) (Table 2).

The mean ROMI total score was 44.3 (95% CI: 43.0–45.5), indicating a clear predominance of reasons for not complying with treatment. Analysis of the relationship between subjective attitude and reasons for compliance only revealed a direct relationship between the score obtained on the DAI-10 scale and the compliance subscale of the ROMI ( $r = 0.5$ ;  $P < 0.0001$ ).

We found a larger number of patients with a negative attitude towards treatment among those who had been clinically stable (event-free) for less time. Thus, patients who revealed a negative attitude had remained stable for a mean of 0.9 years (95% CI: 0.6–1.2), whereas patients with a positive attitude revealed a longer mean stability period of 3.7 years (95% CI: 2.2–5.2), with a mean difference between groups of 2.8 (95% CI: of 1.9–4.2;  $P = 0.0004$ ). This finding was also confirmed both in patients with schizophrenia and in patients with bipolar disorder separately: the mean difference in clinical stability time based on attitude was 3.1 years ( $P = 0.0218$ ) and 2.9 years ( $P = 0.0012$ ), respectively.

The mean SUMD score of patients with a positive attitude towards treatment was 6.6 (95% CI: 5.9–7.4), whereas

**Table 2** Sociodemographic and clinical characteristics according to attitude towards treatment

|                                                             | Positive DAI-10 score<br>(N = 64) | Negative DAI-10 score<br>(N = 22) | P-value                   |
|-------------------------------------------------------------|-----------------------------------|-----------------------------------|---------------------------|
| Age (years), mean (SD)                                      | 42.1 (11.7)                       | 45.9 (13.0)                       | 0.201 (T = 1.29)          |
| Sex (male), N (%)                                           | 39 (60.9)                         | 9 (40.9)                          | 0.103 ( $\chi^2 = 2.66$ ) |
| Living status (alone), N (%)                                | 9 (14.1)                          | 6 (27.3)                          | 0.159 ( $\chi^2 = 1.98$ ) |
| Marital status (single), N (%)                              | 48 (78.7)                         | 17 (87.3)                         | 0.527 ( $\chi^2 = 1.28$ ) |
| Diagnosis, N (%)                                            |                                   |                                   | 0.026 ( $\chi^2 = 4.93$ ) |
| Schizophrenia                                               | 29 (45.3)                         | 16 (72.7)                         |                           |
| Bipolar disorder                                            | 35 (54.7)                         | 6 (27.3)                          |                           |
| Duration of illness (years), mean (SD)                      | 18.1 (13.9)                       | 19.1 (12.3)                       | 0.773 (T = -0.29)         |
| Number of acute episodes within the last 5 years, mean (SD) | 2.9 (4.4)                         | 5.0 (5.7)                         | 0.084 (T = -1.74)         |
| Time since the last acute episode (years), mean (SD)        | 3.7 (5.7)                         | 0.9 (0.7)                         | 0.001 (T = 2.15)          |
| Number of hospitalizations, mean (SD)                       | 4.4 (7.9)                         | 6.6 (7.2)                         | 0.276 (T = -1.10)         |
| Time since the last hospitalization (years), mean (SD)      | 4.5 (6.8)                         | 0.9 (0.6)                         | 0.001 (T = 2.18)          |
| DAI-10 score, mean (SD)                                     | 4.5 (2.8)                         | -4.7 (2.7)                        | 0.001 (T = 13.66)         |
| CGI-S score, mean (SD)                                      | 3.3 (1.1)                         | 3.8 (0.7)                         | 0.045 (T = -2.03)         |
| SUMD score, mean (SD)                                       | 6.6 (2.8)                         | 10.1 (3.3)                        | 0.001 (T = -4.73)         |
| ROMI, mean (SD)                                             |                                   |                                   |                           |
| Total score                                                 | 44.5 (6.1)                        | 43.6 (5.5)                        | 0.534 (T = 0.56)          |
| Compliance subscale score                                   | 20.3 (2.8)                        | 16.7 (3.2)                        | 0.001 (T = 5.01)          |
| Non compliance subscale score                               | 24.2 (5.3)                        | 26.9 (4.3)                        | 0.021 (T = -2.21)         |
| UKU score                                                   | 4.1 (5.9)                         | 5.0 (6.9)                         | 0.517 (T = -0.28)         |

**Note:** Patients were grouped according to positive ( $\geq 0$ ) or negative ( $< 0$ ) scores on the 10-item DAI.<sup>23</sup>

**Abbreviations:** DAI-10, 10-item Drug Attitude Inventory; CGI-S, Clinical Global Impression – Severity scale; SD, standard deviation; SUMD, Scale of Unawareness of Mental Disorders; ROMI, Rating of Medication Influences scale; UKU, Udvalg for Kliniske Undersøgelser Side Effect Rating Scale; T, Student's t-test;  $\chi^2$ , Chi-squared test.

in patients with a negative attitude the score was 10.1 (95% CI: 8.8–11.3). The difference between both groups was 3.5 (95% CI: 2.0–4.9;  $P < 0.0001$ ). An inverse relationship was observed between attitude towards treatment and patient insight at discharge: patients with a negative attitude obtained insight scores indicative of poorer disease awareness ( $r = -0.31$ ;  $P = 0.0039$ ). The subsequent analysis by subgroups only confirmed this result among patients with schizophrenia with a mean difference between groups based on attitude of 3.7 (95% CI: 1.9–5.6).

Multivariate analysis showed insight into illness and the number of previous acute episodes to be related to patient attitude towards treatment at discharge. Patients with poorer insight revealed a 68% greater likelihood of having a negative attitude towards medication (odds ratio [OR] 1.68;  $P = 0.0086$ ). In addition, a greater number of acute episodes during the previous 5 years was associated with a greater likelihood of having a negative attitude (OR 1.18;  $P < 0.0001$ ). The model explained 43% of the variation in the dependent variable ( $R^2$  Nagelkerke) (Table 3).

**Table 3** Logistic regression analysis

| Step                                   | Effect removed                                   | DF | Number in         | Wald Chi-square | Pr > ChiSq     |
|----------------------------------------|--------------------------------------------------|----|-------------------|-----------------|----------------|
| <b>Summary of backward elimination</b> |                                                  |    |                   |                 |                |
| 1                                      | Living status                                    | 1  | 8                 | 0.0608          | 0.8052         |
| 2                                      | Age                                              | 1  | 7                 | 0.1411          | 0.7071         |
| 3                                      | CGI-S                                            | 1  | 6                 | 0.5582          | 0.4550         |
| 4                                      | Diagnosis                                        | 1  | 5                 | 1.6883          | 0.1938         |
| 5                                      | UKU score                                        | 1  | 4                 | 2.0652          | 0.1507         |
| 6                                      | Sex                                              | 1  | 3                 | 3.4863          | 0.0619         |
| 7                                      | Time since the last hospitalization              | 1  | 2                 | 3.8353          | 0.0502         |
|                                        |                                                  |    | <b>Odds ratio</b> | <b>95% CI</b>   | <b>P-value</b> |
|                                        | SUMD score                                       |    | 1.68              | (1.29; 2.17)    | 0.0086         |
|                                        | Number of acute episodes within the last 5 years |    | 1.18              | (1.04; 1.33)    | <0.0001        |

**Abbreviations:** CGI-S, Clinical Global Impression – Severity scale; CI, confidence interval; SUMD, Scale of Unawareness of Mental Disorders; UKU, Udvalg for Kliniske Undersøgelser Side Effect Rating Scale.

## Discussion

Medication adherence plays a key role for patients with schizophrenia and bipolar disorder. Poor insight and negative attitude towards medication are risk factors for adherence problems. Beck et al described a direct negative relationship between concerns regarding antipsychotic drugs and adherence and an indirect negative effect of a general distrust regarding pharmacotherapy and adherence.<sup>24</sup> The authors showed a mediation effect between awareness of illness and perceived necessity of antipsychotic medication on adherence.<sup>24</sup> The heterogeneity of factors involved in adherence problems calls for appropriate matching of interventions to the selected population.<sup>1,25</sup>

We investigated attitude towards medication at discharge in a sample of patients with acute exacerbation of schizophrenia or an acute manic episode. After an acute episode and once stabilized, most patients showed scant motivation to continue psychiatric treatment. Twenty-six percent of the sample, with a predominance of patients with schizophrenia, even showed a negative attitude indicating a subjective response of nonadherence to the prescribed antipsychotic treatment.

Patients with a negative attitude towards antipsychotic medication were characterized as those revealing shorter clinical stability (event-free) prior to admission and those with a poorer level of insight. This is consistent with previous publications demonstrating the relationship between patient attitude towards treatment and level of insight using a range of assessment, in the context of both out- and inpatients.<sup>7,19,26–29</sup> An inverse relationship was found between attitude and degree of insight using the Birchwood Insight Scale ( $r = -0.54$ ;  $P < 0.001$ ) and the insight item (G12) of the Positive and Negative Syndrome Scale ( $r = -0.49$ ;  $P < 0.001$ ).<sup>27,30</sup>

The DAI is one of the most common measures used to assess attitude or adherence rating scales.<sup>20,31</sup> Positive attitude towards medication, as measured by the DAI-10, is associated with significantly higher adherence rates.<sup>32,33</sup> The attitude towards treatment in outpatients has been additionally related to factors, such as employment status, duration of untreated psychosis (DUP), disease severity, treatment response, hospital profile, and therapeutic alliance with the medical staff.<sup>7,26,27,34,35</sup> Moreover, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study found that the degree of clinical improvement due to treatment and patient quality of life are factors also related to the attitude towards medication.<sup>36</sup>

No significant differences in the mean UKU side effect scale score between the positive and negative attitude towards

medication group were observed. Although many studies link the adverse event profile of antipsychotic drugs to attitude and adherence, the results are not always consistent. A number of studies confirm this link while others do not.<sup>19,34,37,38</sup> Some authors even highlight the fact that giving patients adequate information on the possible incidence of adverse effects can mitigate their negative impact on attitude.<sup>39</sup>

This study has some limitations. First, a cross-sectional study cannot confirm associations between the factors studied and must be limited to their descriptive and exploratory value or for generating hypotheses that should be confirmed in prospective follow-up studies. Second, we did not assess participants' capacity to consent to participate in the study using specific instruments. Third, attitude towards adherence was measured solely on the basis of subjective assessments and was not controlled through objective methods. Fourth, the categorical approach to analyze DAI-10 scores could limit the finding of additional correlations. Fifth, lack of homogeneity in our study sample, including schizophrenic and bipolar patients, could also bias the factors associated with medication attitude. Finally, another limitation was the lack of assessment of additional factors related to attitude towards medication, such as therapeutic alliance, DUP, and type of pharmacological class.<sup>1,35</sup>

The relationship between patients' attitude towards medication and sociodemographic and clinical variables has been previously analyzed in different studies.<sup>7,19,33–37</sup> Our study has addressed this issue focusing on specific characteristics of patients with a negative attitude at the time of an acute episode. Insight into illness has been reported in different studies as a key factor in treatment adherence.<sup>24,40</sup> The length of clinical stability prior to admission due to an acute episode is an interesting aspect identified in our study with a limited sample of patients. In this context, our results underscore the importance of identifying patients with poor clinical stability and/or a lack of insight at discharge to involve them in adherence-focused psychotherapy and psychoeducational programs.<sup>41–43</sup>

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## Disclosure

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