Non-Compliance and Related Factors in Patients With Bipolar I Disorder: A Six Month Follow-Up Study

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Abstract

Background: Medication treatment compliance among bipolar patients is quite widespread. Objectives: Treatment compliance depends on multiple factors. The aim of this study was to evaluate the predicting factors of noncompliance in patients with bipolar I disorder admitted to an Iranian hospital during a six-month follow up period. Materials and Methods: This cross-sectional study included 47 bipolar I disorder subjects who were admitted to the Iran psychiatric hospital and that were chosen using a non-randomized convenient sampling model. The patients were assessed at baseline, and at two and six months after admission. For evaluating the patients, we used the medication possession ratio (MPR), the drug attitude inventory (DIA-10), the young mania rating scale (YMRS) and the scale for the assessment of positive symptoms (SAPS). The data were analyzed using a general linear model by SPSS 16 software.

Results: The repeated measures analysis revealed that medication compliance increased successively (P = 0.045), and age, gender and symptom severity did not alter the pattern.

Conclusions: There is an increasing pattern in treatment compliance in bipolar I disorder patients, regardless of the known predicting factors for nonadherence.

Keywords: Bipolar Disorder, Non-Compliance, Treatment Compliance

1. Background

Medication treatment compliance among bipolar patients is quite widespread. Montoya et al. reported that 40% of bipolar patients are partially or completely nonadherent (1). Other studies have indicated that 20% - 70% of bipolar patients are poorly adherent (27). Guscott and Taylor (8) have noted that poor compliance is the principle reason for the discrepancy between efficacy and effectiveness in bipolar patients (8). Non-compliance is a frequent cause of relapse among patients (9, 10). Gonzalez-Pinto et al. observed rates of suicide that were 5.2 times greater in nonadherent patients than in patients on lithium (11). The effects of noncompliance include worsening symptoms, reduction in the quality of life, more hospital admissions and increased suicide behavior (12-49). Commonly encountered reasons for noncompliance in bipolar patients include negative attitudes toward the illness (3, 7, 20-26), poor insight (3, 20-30) severity of depression (3, 20-25), manic symptoms (3, 11, 20-25, 30, 31), younger age (9, 30, 32-34), male gender (9, 11, 30, 33-35), psychotic symptoms (21, 29, 30), loneliness (32), being unmarried (9, 11, 33, 34, 36, 37) and substance abuse (3, 11, 20-26, 30, 32). Colom et al. as well as Scott and Godwin, reported the major risk for nonadherence in teenagers and elderly (3) was the duration of treatment (34, 38).

2. Objectives

Although contradictory findings in adherence research have brought increased attention in other countries, researchers in Iran have not yet shown adequate interest. Based on "a scientometric analysis of studies on mood disorders in Iran" (1), only 75 articles on bipolar disorder were published up to January 2008 (39). Therefore, this paper aims to present the pattern of compliance and also evaluate some factors relating to adherence.

3. Materials and Methods

This study was a prospective longitudinal and naturalistic study of patients who were hospitalized in the Iran Psychiatric hospital, Tehran, Iran.
3.1. Sampling and Participants

All patients who were admitted were supervised by the attending psychiatrist and assessed regarding the inclusion and exclusion criteria.

The inclusion criteria were being 18 years or older; being able to speak Persian; living in Tehran, Karaj or the suburbs; being diagnosed as type one bipolar disorder by a board certified psychiatrist based on the diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV-TR) (40) and having the same diagnosis using the structured clinical interview for DSM-IV axis I disorders (SCID-I) performed by a trained resident of psychiatry; having at least one landline and one cell phone to facilitate contact; and providing informed written consent. The exclusion criteria included being mentally retarded or having any other permanent cognitive decline. The sampling was conducted in May 2008 and 50 patients were enrolled in the study. Three patients dropped out, and the assessment was repeated for the remaining 47 patients two and six months later.

3.2. Procedure

This study was conducted by five psychiatric residents who were trained to assess patients. Also, the inter-rater reliability for the rating scales were checked for reliability (39).

All participants had follow-up visits at two and six months after admission. The two follow up visits were free of charge and were held in an outpatient setting, unless the patient required admission due to any indication. The administrative assistant reminded the patients about their appointments (39).

3.3. Instruments

1) The demographic and clinical variables questionnaire included demographic characteristics and certain clinical features such as history of treatment and previous admissions (39).

2) The structured clinical interview for DSM-IV axis I disorders (SCID-I) is a semi-structured interview used to diagnose the axis I disorders of DSM-IV (41, 42). The Persian clinical version of the SCID-I has been standardized for the Iranian population (43).

3) The Hamilton depressive rating scale-7 (HDRS-7) (44) is widely used in psychiatric research with favorable reliability and validity (45). It has been standardized for the Iranian population (46). McIntyre et al. reported that the 7-item HDRS had as much effectiveness as the 17-item scale and the total score of the HDRS-7 ranges from 0 to 26 (44).

4) The young mania rating scale (YMRS) is an 11-item clinician-administered scale used to measure the severity of manic symptoms. The total score of the YMRS ranges from 0 to 60, and the Persian version proved to be reliable and valid (47, 48).

5) The scale for the assessment of positive symptoms (SAPS) is a 35-item, five section clinician-administered scale used to measure the severity of psychiatric symptoms. The Persian version proved to be reliable as well (49-51).

6) The drug attitude inventory-10 (DAI-10) (shortened version) is a self-report inventory rating the patient’s attitude to the drugs taken. This inventory has previously been used on Iranian bipolar patients (39, 48). Hogan et al. confirmed the reliability and discriminative validity of the DAI-10. This instrument includes questions with true or false options. Complete compliance is shown by a score of six or more true answers (15, 52, 53).

7) The medication possession ratio (MPR) is defined as subtraction from the numbers of days’ supply the patients should have received to take their medication as prescribed. The MPR was calculated for study patients at the two and six-month follow-up visits after admission: MPR calculations were limited to individuals who were taking at least 75% of the prescribed drug doses. The MPR method has been used to quantify treatment adherence in a number of earlier studies (32, 54-57). Using the MPR scores, the patients were categorized as good adherence (MPR score ≥ 80), moderate adherence (MPR score 50 - 80) and poor adherence (MPR score ≤ 50) (54, 55, 58).

3.4. Data Analysis

The data were analyzed with SPSS 16 software and the chi-square, one-way ANOVA, Kruskal-Wallis and general linear models were used. A one-sample Kolmogorov-Smirnov test showed the number of previous episodes that led to hospitalization, and the symptom severity at the end of the follow-up did not have a normal distribution. A P value < 0.05 was considered as significant.

4. Results

In this study, 47 patients, with type one bipolar disorder were examined. The average age (mean ± SE) of the studied patients was 33.7 ± 1.8. Regarding gender, 32 patients (68.1%) were males and 15 (31.9%) were females. The mean number of previous episodes leading to hospitalization was 3.1 ± 0.3. The mean age of illness onset was 25.8 ± 10. The average period of their disorder was 8.1 ± 10 years. Considering the marital status, this study included 24 single patients (51.1%), 7 divorced or widow/widower patients (14.9%) and 16 married patients (34.0%).

In this study, the severity of the symptoms of mania and depression were measured by applying the YMRS.
and HDRS questionnaires at the beginning and end of the follow-up course. Based on this, the severity of the symptoms of mania was 20.4 ± 1.7 in the beginning and 4.0 ± 1.0 at the end. The severity indicated a significant statistical decline (Wilcoxon, P < 0.001).

Depression severity was 4.3 ± 0.57 in the beginning and 2.9 ± 0.47 at the end, which also shows a significant decline (P = 0.008).

Based on the SAPS questionnaire, 31 patients (66%) had psychotic symptoms in the beginning of study.

The level of medical compliance of all patients was calculated by the MPR formula. Accordingly, two people (4.3%) had a low level of drug compliance, 15 people (31.9%) had a medium level, and 30 (63.8%) had a high level.

The average grade of the DAI was 2.1 ± 0.75 in the beginning of the study, and this grade changed to 2.7 ± 0.8 at the end of the six-month period. This indicates that there was no increase in 0.85 ± 1.1 of the DAI in the course in the follow-up period (Wilcoxon, P = 0.27).

There was no significant statistical correlation between the MPR at the end of the research and the grade of the primary and final DAI (coefficient correlation was 0.16 and 0.06 in the two subjects, respectively; P < 0.05). MPR was also unrelated to the severity of mania and psychosis.

In the bivariate analysis, there was no significant relationship between primary depression and compliance (Table 1). However, in the multi-variable analysis, there was a small inverse relationship (Table 2). Moreover, there was no significant relationship between the primary or final DAI scores and compliance (r = 0.12, P = 0.46).

In the binary analysis, it was shown that there was no significant relation between compliance and age of admission, age at disease onset, disease duration, sex, marital status, number of episodes leading to hospitalization, symptom severity and the presence of psychosis at the beginning and the end of study (in all cases P > 0.1) (Table 1).

It is worth mentioning that in the analysis model, in order to avoid the multiple collinearity confounding variable effect, the variable named “present age of patient” was not entered due to its high linear correlation with the other variable named “age in the beginning of disorder” (r = 0.37, P < 0.001) (Table 2). Furthermore, based on the results of the general linear model analysis, it is shown that a significant relation could not be determined between the background elements being studied and drug compliance.

5. Discussion

This study was conducted over a six-month period in order to assess the risk factors that affect treatment compliance in type one bipolar disorder. After analyzing the data, no significant relation was found between drug compliance (MPR) and age, sex, marital status, psychosis and the severity of mania in bipolar patients. Additionally, the relation between treatment attitude and MPR was not significant.

However, the increase in treatment compliance was significant during the six months. Meanwhile, there was significant relation between drug use during the period one month before admission and the patient’s attitude.

The results of our study were consistent with those of Sajatovic et al. (26, 57, 58), Keck et al. (31), and Zeber et al. (59) in terms of an absence of any significant relation between treatment adherence and the patient’s age. However, Baldessarini et al. (60), Sajatovic et al. (32, 57), Shabani and Eftekhar (61) and Berk et al. (30) showed a significant relation between noncompliance and younger age. Conversely, some research reports that patients with an older age have better adherence (60). One of the reasons for the relation in the Baldessarini study may be the high number of samples, compared to this study, which had a small sample size.

Considering the absence of a relation between the patient’s sex and treatment adherence, our study result is consistent with that of Baldessarini et al. (60), Sharifi et al. (56), Sajatovic et al. (26, 32, 57, 58, 62), and also of other research such as Yen et al. (29), Colom et al. (3) and Scott and Pope (38). In the studies of Berk et al. (30), Lingam and Scott (63) and Gonzalez-Pinto et al. (11) adherence was less in men, while in the study of Ghorayshizadeh et al. (64) it was less in women, however, this could be because the study sample had the same number of men and women. In Sajatovic et al. research (26), 88.7% of research samples were men and this could be the reason for the relation between treatment nonadherence and the male gender. Furthermore, the low number of samples in this study may be a reason for the lack of correlation.

Considering the absence of a relation between marital status and treatment adherence, the results of this study are consistent with that of Yen et al. (29), Sajatovic et al. (32, 57), Colom et al. (3) Scott and Pope (38), Alagband-Rad et al. (51), Sharifi et al. (56) and Zeber et al. (59), however, Berk et al. (30), Ghorayshizadeh et al. (64), Gonzalez-Pinto et al. (11), Frank et al. (36) and Aagaard et al. (37). One of the reasons for noncompliance is being divorced or widowed. In the current study, 51.1% of the participants were never married and most of them lived within a family and under their control. This can be the reason for the absence of a relation between marital status and adherence, so it is recommended that the participants in future studies be divided based on whether they live alone or with others.

The lack of a significant relationship between the severity of mania and adherence, is consistent with Sajatovic...
et al. (32, 57) and Zeber et al. (59) and inconsistent with Gonzalez-Pinto et al. (11) and Keck et al. (31).

Considering the lack of a significant relationship between psychosis and adherence, this study was consistent with Sajatovic et al. (26, 32, 57, 58) and Zeber et al. (59) and inconsistent with Rosa (65) and Berk et al. (30). Berk et al. report a significant relation between the existence of psychosis and the severity of manic symptoms with treatment adherence. The reason for this may be more aggressive treatment and the improvement of symptoms, which leads to a better acceptance of treatment (30).

The significant relationship found between depression and adherence was inconsistent with Sajatovic et al. 2009 (26) and Sajatovic et al. 2008 (58).

In this study, there was no relationship found between drug attitude and treatment adherence, and this result was inconsistent with Sharifi et al. research (56). In Sharifi et al. study, there was no relation in a two-week period. However, in the 4th, 6th and 8th weeks, they report a positive relationship between a good attitude and treatment adherence. The relation between treatment attitude and drug consumption during the period one month before admission was significant in this study (56).

Considering the increase in adherence during the six-month follow-up, the result was inconsistent with Scott and Pope (38), Goodwin and Jamison (34), Colom et al. (66) and Sharifi et al. (56). In Sharifi et al. study, the follow-up duration was two months and treatment acceptance decreased during the two months, therefore, a longer follow-up period and intermittent visits in the two and six months may be the reasons for the increasing adherence in the current study (56).

| Table 1. Demographic Factors in Patients With Bipolar Disorder and Their Relationship With Drug Compliance\(^a\) |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Current age, y                                  | 33.7 ± 1.8      | 27.5 ± 6.5      | 34.6 ± 2.6      | 33.7 ± 1.8      | 0.67\(^b\)      |
| Onset of disease, y                             | 25.8 ± 1        | 26.5 ± 6.5      | 26.9 ± 1.7      | 25.2 ± 1.3      | 0.95\(^b\)      |
| Duration of disease, y                         | 8.1 ± 1         | 1               | 7.7 ± 1.5       | 8.8 ± 1.4       | 0.29\(^b\)      |
| Manic symptom severity in beginning, No.\(^c\) | 20.4 ± 1.7      | 18              | 21.7 ± 2.9      | 19.8 ± 2.2      | 0.86\(^b\)      |
| Manic symptom severity at end, No.\(^c\)       | 4 ± 1           | 7.5 ± 1.5       | 4.7 ± 2         | 3.4 ± 0.9       | 0.18\(^d\)      |
| Depression symptom severity in beginning, No.\(^c\) | 4.3 ± 0.57     | 3 ± 3           | 5 ± 1.1         | 4.1 ± 0.7       | 0.68\(^d\)      |
| Depression symptom severity at end, No.\(^c\)  | 2.9 ± 0.47      | 3 ± 3           | 2.7 ± 0.9       | 2.96 ± 0.56     | 0.87\(^d\)      |
| Sex                                             | Male            | 32 (68.1)       | NA              | 10 (33.3)       | 22 (68.7)       |
| Marital status                                  | Female          | 15 (31.9)       | 2 (31.3)        | 5 (33.3)        | 8 (53.3)        |
| Number of previous episodes, No.                | 3.1 ± 0.5       | 0.5 ± 0.5       | 3.3 ± 0.88      | 2.2 ± 0.7       | 0.36\(^d\)      |
| Psychotic symptom in beginning\(^d\)            | 31 (66)         | 2 (6.5)         | 21 (35.5)       | 18 (58.1)       | 0.48\(^b\)      |
| Psychotic symptom free in beginning\(^d\)      | 16 (34)         | NA              | 4 (25)          | 12 (75)         | 0.48            |

Abbreviation: NA, not available.
\(a\) Values are expressed as mean ± SE or No. (%).
\(b\) One-way ANOVA test.
\(c\) According to YMRS.
\(d\) Kruskal-Wallis test.
\(e\) Fisher’s Exact test.
\(f\) According to SAPS.
Table 2. Linear Relationship Model Independent of the Underlying Factors Associated With Medication Adoption Rate (in Percent) at the end of Follow-Up in Patients With Bipolar I Disorder

|                           | Correlation Coefficient | Power | P Value |
|---------------------------|-------------------------|-------|---------|
| Duration of disease       | 0.007                   | 0.093 | 0.535   |
| Onset of disease          | 0.002                   | 0.061 | 0.748   |
| Disease severity (YMRS) at the beginning of follow up | 0.005 | 0.081 | 0.599   |
| Disease severity (YMRS) at the end of follow up  | 0.005                   | 0.080 | 0.603   |
| Severity of depression (HDRS-7) at the beginning of follow up | 0.018 | 0.511 | 0.049   |
| Severity of depression (HDRS-7) at the end of follow up | 0.009 | 0.187 | 0.278   |
| Sex                       | 0.001                   | 0.053 | 0.859   |
| Marital Status            | 0.003                   | 0.062 | 0.916   |
| Psychotic symptoms at the beginning of the follow up | 0.032 | 0.240 | 0.026   |

Note: The current age of the patients had a high linear correlation with the age of onset variable (Pearson r = 0.73, P < 0.001), therefore, to avoid the confounding effect of multiple collinearity it was not entered into the model analysis.

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Footnotes
Authors’ Contribution: Sanaz Azadforouz collected the clinical data and drafted the manuscript. Amir Shabani conceived and designed the evaluation and drafted the manuscript. Shabnam Nohesara re-evaluated the clinical data and revised the manuscript. Masoud Ahmadzad-Asl analyzed the clinical and statistical data and revised the manuscript. All authors read and approved the final manuscript.

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