Clinical Factors Associated With Treatment Noncompliance in Euthymic Bipolar Patients

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Background: Noncompliance with medication is a very common feature among bipolar patients. Rates of poor compliance may reach 64% for bipolar disorders, and noncompliance is the most frequent cause of recurrence. Knowledge of the clinical factors associated with noncompliance would enhance clinical management and the design of strategies to achieve a better outcome for bipolar patients. Although most patients withdraw from medication during maintenance treatment, compliance studies in euthymic bipolar samples are scarce.

Method: Compliance treatment and its clinical correlates were assessed at the end of 2-year follow-up in 200 patients meeting Research Diagnostic Criteria for bipolar I or bipolar II disorder by means of compliance-focused interviews, measurements of plasma concentrations of mood stabilizers, and 2 structured interviews: the Schedule for Affective Disorders and Schizophrenia and the Structured Clinical Interview for DSM-III-R Axis II disorders. Well-compliant patients and poorly compliant patients were compared with respect to several clinical and treatment variables.

Results: The rate of mildly and poorly compliant patients was close to 40%. Comorbidity with personality disorders was strongly associated with poor compliance. Poorly compliant patients had a higher number of previous hospitalizations, but reported fewer previous episodes. The type of treatment was not associated with compliance.

Conclusion: Clinical factors, especially comorbidity with personality disorders, are more relevant for treatment compliance than other issues such as the nature of pharmacologic treatment. Compliant patients may have a better outcome in terms of number of hospitalizations, but not necessarily with respect to the number of episodes. Bipolar patients, especially those with personality disorders, should be monitored for treatment compliance.

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Noncompliance to medication regimens has been reported to range from 15% to 85% in medical illnesses,[1] and it is especially common in patients with chronic relapsing disorders. Noncompliance with pharmacologic treatment is a very frequent feature among bipolar patients, with rates reaching 64%.[2] For example, incomplete compliance may be the rule rather than the exception among patients receiving lithium.[3] Treatment discontinuation is the most important predictor of relapse and poor outcome for these patients.[4–6] Compliance issues may explain the discrepancies in the effectiveness of prophylactic lithium between clinical trials and naturalistic studies. Some studies also suggest the possibility of lithium refractoriness after discontinuation in patients with an initial good response,[7–9] but this finding is still largely questioned by other authors.[10,11] On the other hand, optimal serum lithium levels (0.8–1.0 mmol/L) may enhance psychosocial outcome.[12] Mortality rates among noncompliant bipolar patients are much higher than among compliant patients.[13,14] Furthermore, lithium may have antisuicidal effects.[15]

A review of several studies of lithium noncompliance shows a surprisingly wide range of discontinuation rates (12%–64%), a range that could be caused by assessment variability or large differences concerning the definition of noncompliance. According to Boyd et al.,"medication noncompliance is the failure to comply (intentional or accidental) with the physician's directions (expressed or implied) in the self-administration of any medication."[16(p362)]

Factors associated with pharmacologic noncompliance in bipolar disorders were divided by Jamison and colleagues[17] into 4 categories: patient related, illness related, drug related, and physician related. Patients' bad feelings about "being under drug control" and illness denial appear to be the most common reasons for noncompliance.[2,17]

Some patients have a poor compliance because they miss their "high" periods.[18] Jamison and Akiskal[18] also reported cultural factors as potential reasons for medication withdrawal. Moreover, noncompliance may be a more complex phenomenon with a large number of causes such as being bothered by side effects or patients' environmental pressure against medication. For instance, Weiss et al.[19] reported that 14% of bipolar patients are noncompliant with pharmacologic treatment. Side effects were the most commonly cited reason for medication noncompliance. Comorbid substance use is another factor related to poor compliance.[20,21]

Some studies have found differences in compliance depending on the medication. Weiss and colleagues[19] reported a worse compliance pattern with lithium than with valproate.

Noncompliance has frequently been associated with young age,[22] male gender,[23] being unmarried,[24] multiple medication regimens,[25] fewer episodes, first year of lithium treatment, history of manic episodes,[26] and comorbid psychiatric illness,[24] especially substance abuse.[27]

There is an obvious relationship between insight and compliance. Some recent studies show differences in insight between manic patients and bipolar depressive patients. These differences are maintained once the episode has remitted.[28] Hence, it can be hypothesized that bipolar patients with more manic features would have a worse compliance pattern.

To provide further data on the rates of pharmacologic compliance and the clinical features associated with it in euthymic bipolar outpatients, we assessed compliance in a large sample of bipolar I and II patients. We hypothesized that some clinical factors such as the presence of psychotic features, predominance of manic episodes, and comorbidity would be associated with poor compliance.

Available studies of compliance with euthymic patients are very scarce, and previous studies were focused on psychological issues for withdrawal[18] rather than on clinical correlates of noncompliance. Most previous studies contained several biases such as studying patients during an acute episode or focusing only on bipolar patients with comorbid substance abuse, and some were burdened by small sample size. Clarifying the clinical factors associated with compliance without having symptom interference may give us a clear idea of the patterns of use and misuse of medication in bipolar patients, enhancing the design of improved psychoeducational programs. To the best of our knowledge, this is the first study to examine clinical factors associated with poor compliance in a large sample of euthymic bipolar outpatients.

METHOD

Pharmacologic treatment compliance was assessed in 200 consecutive bipolar outpatients fulfilling Research Diagnostic Criteria for bipolar I disorder (N = 144) or bipolar II disorder (N = 56) enrolled in the 2-year naturalistic follow-up of the Bipolar Disorders Program at the Hospital Clinic and University of Barcelona (Spain). After complete description of the study to the subjects, written informed consent for the collection of demographic, clinical, compliance, and personality data was obtained at the beginning of the follow-up.

All patients were assessed with the Schedule for Affective Disorders and Schizophrenia, lifetime version (SADS)[29] by 2 independent raters (A.B., E.V.) conducting separate interviews and were entered in the study only when diagnostic concordance occurred (κ index > 0.8). Patients with Hamilton Rating Scale for Depression[30] scores higher than 8 or Young Mania Rating Scale[31] scores higher than 6 at the time of the compliance interview were excluded from the study to ensure that compliance-related behavior would not be a mere consequence of clinical state. Clinical and demographic data were obtained from the structured interviews with the patient and at least 1 first-degree relative or partner.

Compliance was assessed by a clinical and compliance-focused interview (available on request) with the patient, a compliance-focused interview (available on request) with first-degree significant relatives or partner, and plasma concentrations of mood stabilizers assessed during the last 2 years; the last is an objective parameter, not always valid as a poor compliance marker but very useful when noncompliance is denied by the patient and ignored by his or her family. The interview administered to the patient included questions relative to the patient's attitude toward medication, illness denial, number of medication neglects per month (a quantitative measure in response to the question, "How many times have you forgotten to take your medication?"), information about voluntary withdrawal, selective medication neglects (a measure of when patients selectively did not take individual medications), motivation, the patient's behavior toward a lost dose, and past history of treatment withdrawal. This interview was inspired by other similar questionnaires such as the Lithium Attitudes Questionnaire,[32] but referred to all kinds of psychiatric medication, not only mood stabilizers. The interview administered to the family or partner included questions related to familial attitude toward medication and observed signs of poor compliance. "Good compliance" was considered when the 3 criteria (2 interviews and plasma levels) coincided in suggesting it. "Poor compliance" was considered when none of the criteria suggested good compliance. Finally, "medium compliance" was considered when 2 criteria suggested good compliance and the other 1 suggested poor compliance, or, on the contrary, 2 suggested poor compliance and the third criteria suggested good compliance or when the patient admitted noncompliance with part of the medication regimen.

Table 1. Relevant Differential Qualitative Features Between Bipolar Patients With Good, Medium, and Poor Compliance

	Good Compliance (N = 121)		Medium Compliance (N = 54)		Poor Compliance (N = 25)			
Variable	N	%	N	%	N	%	χ^2	p Value
Axis II comorbidity	21	17.4	20	37.0	11	44.0	13.53	.00
Substance abuse	23	19.0	9	16.7	10	40.0	5.62	.06

To assess the influence of the predominance of the type of acute episodes, the sample was split into 3 groups: "manic type" was considered when the total number of manic and hypomanic episodes was higher than the number of depressive and mixed episodes. On the contrary, "depressive type" was considered when episodes of depression were the majority. Finally, "mixed type" was considered when there was a predominance of mixed episodes over others.

All psychiatric medication (neuroleptics, antidepressants, mood stabilizers, and benzodiazepines) prescribed to the patients in the last 2 years was accounted for to measure the influence of each medication. Drugs were grouped according to therapeutic profile into the following categories: mood-stabilizers (also separating lithium from carbamazepine and valproate), antipsychotics (subdividing into conventional and atypical), antidepressants, benzodiazepines, and others. The number of drugs that the patient was taking was also introduced as a variable in the multivariate analysis.

Axis II comorbidity was assessed through the Spanish version of the Structured Clinical Interview for DSM-III-R Axis II disorders (SCID-II),[33,34] administered by a single clinician (F.C.) trained in its use to achieve a more accurate diagnosis of personality disorders. Preliminary partial results of this specific assessment in 40 bipolar II patients have been published elsewhere.[35] Since they theoretically could be relevant, schizotypal features were also registered even when they did not reach the threshold for the diagnosis of schizotypal personality disorder. The assessment of compliance was made by 1 rater who administered neither the SCID-II nor the SADS and thus was blind to the clinical features and diagnostic conditions of the patients.

The 3 compliance groups were compared using several statistical techniques, including the chi-square statistic with Yates correction or Fisher exact test for the comparison of qualitative data. A simple factorial analysis-of-variance model was used for dimensional variables. After a preliminary data analysis, the sample was divided in 2 groups (good compliance [N = 121] vs. poor/medium compliance [N = 79]), putting together mildly and poorly compliant patients, and a multiple stepwise linear regression was applied to obtain further information about sources of variability. The variables included in the regression analysis were compliance; age at onset; current age; number of depressive, mixed, hypomanic, and manic episodes; number of hospitalizations; illness duration; and total number of medications prescribed. All statistics were 2-tailed, and significance was set at $p < .05$.

Table 2. Differential Qualitative Features Between Bipolar Patients With Good Compliance and Poor Compliance[a]

	Good Compliance (N = 121)		Poor Compliance (N = 79)			
Variable	N	%	N	%	χ^2	p Value
Female	67	55.4	45	57.0	0.04	NS
Bipolar I diagnosis	87	71.9	57	72.7	0.22	NS
Family history of affective disorder	60	49.9	34	43.0	0.91	NS
Presence of psychotic symptoms	83	68.6	59	74.7	0.97	NS
Axis II comorbidity	21	17.4	31	39.2	13.33	.00
Substance abuse	23	19.0	19	24.1	0.71	NS
Schizotypal features	19	15.7	17	21.5	4.10	.04
Physical illness	37	30.6	18	22.8	1.25	NS
Rapid cycling	16	9.9	9	11.4	0.05	NS
Living alone	16	9.9	15	19.0	1.31	NS
Married	46	38.0	28	35.4	0.15	NS
Active work status	67	55.4	46	58.2	0.05	NS
Attempted suicide	32	26.4	22	27.8	0.03	NS
Drug treatment						
Monotherapy with mood stabilizer	42	34.7	21	26.6	1.11	NS
Lithium	99	81.8	63	79.7	0.13	NS
Carbamazepine	48	39.7	35	44.3	0.42	NS
Valproate	10	8.3	7	8.9	0.02	NS
Antipsychotics						
Typical	88	72.7	59	74.7	0.30	NS
Atypical	28	23.1	23	29.1	1.06	NS
Antidepressants	78	64.5	54	68.4	0.37	NS
Benzodiazepines	55	45.5	37	46.8	0.24	NS
Episode predominance					0.91	NS
Manic type	44	36.4	34	43.0	...	...
Depressive type	64	52.9	37	46.8	...	...
Mixed type	13	10.7	8	10.1	...	...

[a]Abbreviation: NS = not significant. The poor compliance group comprised patients with poor or medium compliance.

RESULTS

One hundred twenty-one patients (60.5%) were considered to have good compliance, 54 (27.0%) were only partially compliant (medium compliance group), and 25 patients (12.5%) were included in the poor compliance group. Table 1 shows the most relevant results obtained when dividing the sample into these 3 groups. After verifying that medium compliance and poor compliance groups showed no differences, we split our sample into 2 groups (good compliance vs. poor/medium compliance). The demographic and clinical characteristics of the sample divided in 2 groups according to compliance are shown in Tables 2 and 3.

No differences of age and sex were found among the 3 groups. As expected, Axis II comorbidity was strongly associated with poor or medium compliance ($p = .00$). Spe-

Table 3. Differential Quantitative Features Between Bipolar Patients With Good Compliance and Poor Compliance[a]

	Good Compliance (N = 121)		Poor Compliance (N = 79)			
Variable	Mean	SD	Mean	SD	t	p Value
Age, y	44.71	16.87	41.58	12.29	1.52	NS
Age at onset, y	28.04	13.29	26.42	9.95	0.97	NS
Age at first hospitalization, y	31.69	13.55	32.02	13.65	–0.12	NS
Illness duration, y	16.49	12.55	15.05	10.43	0.84	NS
No. of previous episodes						
Total	15.87	22.83	10.90	9.19	2.13	.03
Manic	2.42	4.11	2.96	3.68	–0.94	NS
Hypomanic	4.92	9.55	2.29	3.74	2.73	.00
Mixed	0.68	2.05	0.67	1.46	0.06	NS
Depressive	7.47	12.71	4.54	5.10	2.27	.02
No. of hospitalizations	1.55	2.18	2.94	3.44	–3.20	.00
No. of suicide attempts	0.44	0.97	0.58	1.31	–0.77	NS

[a]The poor compliance group comprised patients with poor or medium compliance. Abbreviation: NS = not significant.

cific types of Axis II comorbidity are presented in Table 4. Forty-two patients received a single diagnosis of comorbid personality disorder. Five patients received 2 diagnoses of personality disorder (histrionic personality disorder and paranoid personality disorder [N = 2], histrionic personality disorder and borderline personality disorder [N = 2], and histrionic personality disorder and obsessive-compulsive personality disorder [N = 1]). Three patients received 3 comorbid personality disorder diagnoses (borderline personality disorder, histrionic personality disorder, and schizotypal personality disorder; borderline personality disorder, antisocial personality disorder, and narcissistic personality disorder; and avoidant personality disorder, dependent personality disorder, and obsessive-compulsive personality disorder). Finally, 2 patients met criteria for 4 personality disorders (histrionic personality disorder, borderline personality disorder, paranoid personality disorder, and narcissistic personality disorder; and obsessive-compulsive personality disorder, schizoid personality disorder, paranoid personality disorder, and avoidant personality disorder). The mean number of diagnoses per comorbid patient was 1.51.

We found no specific association between substance abuse or dependence and treatment compliance. For Axis II disorders, histrionic personality disorder appeared to be clearly associated with poor compliance. Schizotypal features were related to poor compliance, but this association disappeared when comorbidity with personality disorders was excluded. The presence of physical illness was not associated with poor compliance. No clinical variable, such as seasonal pattern, rapid cycling, melancholia, catatonia, psychotic features, or atypical depressive symptoms, appeared to be relevant. Similar rates of manic and depressive illness types were found in each group. Unemployment and job invalidity were linked to medium compliance, but these results should be taken with caution because of the small size of some of the groups.

Table 4. Personality Disorder Comorbidity in Bipolar Patients[a]

Comorbid Personality Disorder	N	%
Without personality disorder	148	74
Histrionic	16	8
Borderline	11	5.5
Obsessive-compulsive	8	4
Schizotypal	8	4
Paranoid	6	3
Schizoid	5	2.5
Narcissistic	4	2
Avoidant	4	2
Dependent	3	1.5
Antisocial	3	1.5
Nonspecific	1	0.5

[a]Numbers do not add up to 200 because 10 patients had more than 1 personality disorder.

Comparing bipolar I patients (N = 144) with bipolar II patients (N = 56), we found no significant differences. Number of hospitalizations emerged from the stepwise linear regression as the quantitative factor explaining the majority of variability. The worse compliance the patients had in taking their medication, the higher their number of hospitalizations. When including the medium-compliance group with the poor-compliance group, number of previous episodes was higher for the patients considered to have good compliance. The same result was found with respect to hypomanic and depressive episodes, but no differences were found between the 2 groups in the number of manic and mixed episodes.

Patients receiving monotherapy (those who were taking a single mood stabilizer as unique treatment) were distributed in terms of compliance exactly as were the patients receiving multiple types of medication (mood stabilizer plus antidepressants or antipsychotic agents). Finally, we found no association between type of medication and compliance.

DISCUSSION

The most important findings of this study on clinical factors associated with treatment compliance in euthymic bipolar patients are that poor compliance with medication is strongly associated with the presence of an added diagnosis of personality disorder, not with medication itself, and that the most compliant patients have suffered from more episodes but, probably as a consequence of their better adherence to treatment, have been hospitalized less frequently. These findings could be interpreted as showing that patients may learn from the experience of subsequent relapses and be more prone to contact their psychiatrist when they notice any change in their mood. Patients with personality disorders may have more difficulties in recognizing prodromal symptoms and following medical advice.

Our rate of good compliance in patients is strikingly higher than those rates reported in other similar studies.[2] This difference may be due to 3 main reasons: (1) We included only euthymic patients, whereas the study by Keck et al.[2] included only manic patients. Euthymic patients have better insight than manic patients,[28] which may enhance compliance. (2) The sample in the study by Keck et al.[27] was composed in part of schizoaffective patients, who may have lower compliance rates, although this point was not confirmed by their own work. (3) Our sample was recruited from our Bipolar Disorders Program, a fact that may affect the described disparity in 2 different ways: we predominantly treat severely ill patients with many years of bipolar history, and lengthy illness may enhance patient insight and compliance. In addition, the program includes standard interventions to improve compliance.[36]

Noncompliance is related more to illness factors such as number of hospitalizations or comorbidity with personality disorders than to drug factors such as type of medication or polypharmacy. The prescription of a multiple-medication regimen or monotherapy apparently has nothing to do with compliance issues. This finding is at odds with some previous work[25] and is clinically relevant in that treatment possibilities should not be limited owing to concern about compliance. In our sample, compliance with lithium was not worse than with other drugs, but data are inconclusive because patients receiving lithium are overrepresented in our sample, whereas the valproate group was small, probably owing to the fact that valproate is not specifically marketed for the treatment of bipolar disorder in Spain.

Personality disorder comorbidity may be the strongest factor in predicting poor compliance, as was reported by Aagaard and colleagues[24] and Keck et al.[27] This phenomenon is not due to the higher number of medications that comorbid patients may take, which is irrelevant.

When dividing the sample into 3 groups according to treatment compliance, we found a trend toward an association between substance abuse and the least compliant group, which is consistent with the findings of previous studies.[19] The results probably did not reach significance because of the small size of the least-compliant subgroup (N = 25). Our rates of substance abusers are lower than those of the Epidemiologic Catchment Area study.[37,38] This disparity may be explained by the fact that most of our patients were engaged in a psychoeducative program partially focused on the treatment of substance abuse.

We found no differences between manic patients and depressive patients in terms of compliance, as could be suggested by the reported worse insight of the former.[28] This finding may be due to environmental factors such as the care received from family members who are mindful of the possibility of a new manic relapse, which can improve compliance without changing insight.

Poorly compliant patients had a significantly higher number of previous hospitalizations (poor compliance > medium compliance > good compliance), but not more previous episodes. In fact, the numbers of total previous episodes, depressions, and hypomanic episodes are higher for the good-compliance group. This finding could appear difficult to explain, since several studies have reported a worse course for noncompliant patients, but the explanation may well lie in the fact that episodes in noncompliant patients are not more frequent but are more serious, leading more frequently to hospitalization. Compliant patients may more easily report previous episodes and be more prone to admit the recurrent nature of their illness, even for minor recurrences. The reliability of some data, including number of episodes not leading to hospital admission, could therefore be questioned. We tried to avoid this bias by using multiple sources of information, such as interviewing not only the patient but also the family and partner, whenever possible. In view of the results, it seems likely that such bias existed, and episodes were probably better collected in the good-compliance group. On the other hand, we controlled medication to ensure that this difference would not merely be caused by a higher use of antidepressants, which might induce more hypomanic episodes, or, on the contrary, an overrepresentation of neuroleptic-enhanced depressions. A possible explanation for the higher number of hypomanic episodes would be, paradoxically, better insight allowing patients in the good-compliance group to notice hypomania better than other patients and thus reporting so to their psychiatrist. Other authors find no differences in the number of episodes or hospitalizations.[2]

Although in our sample we found no data suggesting better compliance with antidepressants than with other medications, the higher number of previous depressive episodes among the good-compliance group may only reflect a learned effect of the patients in being highly motivated for receiving treatment while depressed. This managing style would be maintained when patients were euthymic. Hence, the idea of taking medication to avoid depressive suffering may be causing better compliance than other possible motivations for compliance such as avoiding manic episodes or keeping stable. This issue needs to be confirmed by further investigation focused on psychological motivation for compliance.

Patient-related factors such as socioeconomic and marital status and educational level were not related to treatment compliance in our sample. We found no significant differences in demographic variables such as sex or age, coinciding with some recent works[2,19] but not with others.[22,23] Some authors argued that age could be relevant to compliance only in extreme ages, i.e., adolescents or the elderly[26]; we found a certain tendency ($p < .1$) toward this distribution in our sample in that patients aged 60 years or older were associated with good compliance and young

people (18–25 years) were more prevalent in the poor compliance group.

These results cannot be completely generalized to the whole bipolar population because of the special characteristics of the patients included in the Bipolar Disorders Program, described above. Moreover, we considered neither dimensional personality features (except for schizotypal traits) nor subjective and psychological factors, such as health beliefs (perceived seriousness of illness and perceived efficacy of treatment) and social supports that may play a certain role in compliance, as reported by other groups.[18,39] Aspects of the treatment regimen that may also be predictive, such as its complexity, side effects, cost, route, and ease of administration, should be more deeply studied in further studies. Finally, cognitive dysfunctions and neuropsychological deficits may also be related to compliance and should be studied as well.[40]

In summary, using the proposal of Jamison et al.[17] for the understanding of compliance patterns—dividing factors attached to compliance into 4 groups (patient related, illness related, drug related, and physician related)—we found a significant relevance of illness-related factors. Patient-related factors may have some weight, with a certain tendency to improve compliance with the passing of time. A study that focuses on psychological factors should be performed in the future to clarify issues such as fear of dependence or missing "highs" associated with mania and hypomania. Drug factors do not seem to be especially relevant in our sample, although we used no specific questionnaire to address the relevance of side effects on compliance, according to patient opinion. Our results, however, support the hypothesis that although some patients may blame drugs as the main cause of their noncompliant behavior, the real reason for such behavior is related to other issues, such as personality disorders and denial of illness. Physician-related factors are difficult to determine, because all patients were treated by 1 of the 3 psychiatrists (E.V., A.B., C.G.) of our team, allowing for a consistent attitude toward the patients, and were treated according to a prescribing pattern based on consensus and guidelines.

The results of this study have clinical implications in the management of euthymic bipolar patients. Compliant patients can expect a reduction of the number of hospitalizations, although this may not mean that they will suffer fewer episodes. Bipolar patients with personality disorders should be carefully monitored for treatment compliance.

Drug name: carbamazepine (Tegretol and others).

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