# Adherence to Pharmacotherapy in Bipolar Disorder Patients With and Without Co-Occurring Substance Use Disorders

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***Objective:*** To examine patterns of adherence to mood stabilizers and reasons for nonadherence in patients with bipolar disorder, with and without substance use disorder (SUD).

***Method:*** From December 2003 to October 2004, 115 patients with DSM-IV–diagnosed bipolar disorder (58 with SUD and 57 without SUD) were administered a structured interview regarding their lifetime experience with mood stabilizers.

***Results:*** Lifetime adherence with mood stabilizers for the SUD group was 65.5%, versus 82.5% for the non-SUD group ($p < .05$). Lifetime lithium adherence for the SUD group was lower than for the non-SUD group (65.9% vs. 85.0%, $p < .05$). Substance-related reasons were more commonly cited by the SUD group than the non-SUD group. In contrast, pill- and dosage-related reasons were more frequently endorsed by the non-SUD group than the SUD group.

***Conclusion:*** In bipolar disorder patients, those with co-occurring SUD were less adherent than those without SUD. The SUD group was also less adherent to lithium than the non-SUD group. The reasons for nonadherence differed by presence or absence of a SUD. Physicians should be alert to these differences in their clinical practices while prescribing medications.

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Pharmacotherapy with mood stabilizers constitutes the mainstay of treatment for bipolar disorder.[1] In the past decade, a number of medications for bipolar disorder have surfaced. However, a gap exists between the efficacy of these medications and their effectiveness in a real-world setting.[2] Guscott and Taylor[2] have attributed much of this efficacy-effectiveness gap for lithium to poor medication adherence. A recent study reported that one third of patients with bipolar disorder fail to take at least 30% of their medication.[3] Nonadherence with medication is consistently associated with poor treatment outcomes in bipolar disorder patients, including relapse, hospitalization, social and occupational dysfunction, violence, and suicide.[4–8] Further, an episode of nonadherence may increase the risk of poor treatment response to a previously successful pharmacologic regimen.[9]

In the first systematic study of medication adherence in bipolar patients, Jamison et al.[10] found that the most common reasons for lithium nonadherence were feeling depressed, being bothered by the idea that one's moods are controlled by medication, and being bothered by having a long-term illness. In a study of anticonvulsant adherence in manic patients, Keck et al.[11] found that 64% of patients did not adhere to their medications fully; denial of illness and lack of control over one's life were the most common reasons for nonadherence.

A highly prevalent subgroup of bipolar disorder patients with a high likelihood of poor medication adherence is those individuals with a co-occurring substance use disorder (SUD).[12–14] The National Institute of Mental Health Epidemiologic Catchment Area study[15] found that 60% of patients with bipolar I disorder develop a SUD in their lifetime; this comorbidity rate is higher than for any other Axis I disorder. More recently, the National Epidemiologic Survey on Alcohol and Related Conditions[16] reported an adjusted odds ratio of 3.5 for bipolar I disorder and any alcohol use disorder, and an adjusted odds ratio of 4.5 for bipolar I disorder and drug use disorder.

Our group[17] conducted a study of medication adherence in patients with bipolar disorder and SUD. While over 60% of patients complied with each medication

  

Table 1. Categories of Reasons for Medication Nonadherence in 115 Patients With Bipolar Disorder

| Category | Common Sample Responses |
|---|---|
| Attitudes toward bipolar disorder | "I thought I was cured from bipolar disorder," pills did not help bipolar disorder |
| Substance-related | Was high, hungover, or intoxicated; did not want to mix medication with substances |
| Mood-related | Depressive or manic symptoms |
| Side effects | Nausea, diarrhea, sedation |
| Pill/dosage-related | Was a hassle to take pills, misunderstood prescription, thought there were too many pills to take |
| Increased dosage | Pills were not helping to decrease symptoms, so increased dosage; took more pills than prescribed to get high (intoxicated) |
| Forgetting | Forgot, ran out of pills, left pills at home |
| Other experiences | Wanted to try alternate approaches, did not like having blood taken |

more than two thirds of the time during their lives, the level and reasons for nonadherence varied by medication. For example, we found significantly greater lifetime adherence with valproate than with lithium. Lithium nonadherence was most commonly due to intolerable side effects, while valproate nonadherence was more likely related to "hassles" such as blood tests.

An interesting finding in our study was that no patients reported medication nonadherence because of concerns that their mood was being controlled by medications. This is in contrast to Jamison et al.,[10] who found this to be the most common reason for lithium nonadherence in bipolar patients who had not been selected for having a co-occurring SUD. This disparity suggests that the rates of medication adherence and the reasons for nonadherence may differ in bipolar patients with and without a SUD. However, this issue has not been systematically studied to date. Therefore, this report compares levels of adherence and reasons for nonadherence with mood stabilizers among bipolar disorder patients with and without a co-occurring SUD.

## METHOD

We recruited 115 patients with bipolar disorder (58 with SUD and 57 without SUD) from inpatient, partial hospital, residential, and outpatient treatment programs at McLean Hospital, a psychiatric hospital near Boston, Mass. In accordance with HIPAA and Institutional Review Board (IRB) regulations, we sought permission from treating physicians who asked inpatients whether they could be approached by the research team for the study. All other patients were recruited through IRB-approved fliers posted throughout the hospital.

All potentially eligible participants gave written informed consent after having the study explained to them. Eligible patients had to have a lifetime diagnosis of bipolar disorder and had to have taken a mood stabilizer at some point in their lifetime. Participants were administered the substance use disorders, mood disorders, and psychotic disorders modules of the Structured Clinical Interview for DSM-IV (SCID)[18] by the first author (S.G.M.) to confirm the diagnosis of bipolar disorder and to evaluate whether they met criteria for a lifetime diagnosis of SUD.

From December 2003 to October 2004, study participants were given a structured interview to review their lifetime experience with mood stabilizers. United States Food and Drug Administration (FDA)–approved treatments for bipolar disorder (valproate, lithium, olanzapine, lamotrigine, risperidone, quetiapine, ziprasidone, aripiprazole, and carbamazepine extended-release) as well as those that are commonly used off-label (gabapentin, topiramate, oxcarbazepine, levetiracetam, zonisamide, carbamazepine, and omega-3 fatty acids) were included.

For each medication, data for lifetime use were gathered, including dose, frequency, and duration of each medication. To assess adherence, we used a structured interview that we had utilized in a previous study[17]; this was a modified version of an instrument developed by Jamison et al.[10] Patients were asked about their level of adherence, i.e., whether they took the medication all of the time, more than two thirds of the time but not all the time, one third to two thirds of the time, or less than one third of the time. They were also asked whether they took more than the prescribed dose. Nonadherence was defined as taking two thirds or less of the prescribed dose over one's lifetime, or any use of more than the prescribed dose.[17] Overall adherence was defined as adherence to two thirds or more of the prescribed medications.

Patients who were not fully adherent were asked to identify reasons for nonadherence. These were categorized as attitudes towards bipolar disorder, substance-related reasons, mood-related reasons, side effects, increased dosage, forgetting, pill and dosage, and other experiences (see Table 1). Each patient was allowed to endorse more than one category as a reason for nonadherence.

Data analyses were conducted using Stata version 8.2 (StataCorp LP, College Station, Tex.). Chi-square tests and Fisher exact tests were used for the analyses.

## RESULTS

### Clinical and Sociodemographic Characteristics

The mean ± SD age of the overall sample was 39.0 ± 11.7 years; 94 (81.7%) had bipolar I disorder, 20 (17.4%)

Table 2. Rates of Lifetime Medication Adherence in 115 Patients With Bipolar Disorder

| | SUD | | No SUD | |
|---|---|---|---|---|
| Drug | Adherent, % (N) | Taking Medication, N | Adherent, % (N) | Taking Medication, N |
| Lithium[a] | 65.9 (27) | 41 | 85.0 (34) | 40 |
| Valproate | 66.7 (28) | 42 | 77.1 (27) | 35 |
| Risperidone | 95.5 (21) | 22 | 92.6 (25) | 27 |
| Quetiapine | 63.3 (19) | 30 | 80.0 (24) | 30 |
| Gabapentin | 75.0 (24) | 32 | 77.3 (17) | 22 |
| Lamotrigine | 82.1 (23) | 28 | 86.4 (19) | 22 |
| Olanzapine | 74.2 (23) | 31 | 75.0 (18) | 24 |
| Topiramate | 82.4 (14) | 17 | 73.7 (14) | 19 |
| Omega-3 fatty acids | 100.0 (12) | 12 | 90.0 (9) | 10 |
| Carbamazepine | 53.3 (8) | 15 | 83.3 (10) | 12 |
| Aripiprazole | 81.8 (9) | 11 | 81.8 (9) | 11 |
| Ziprasidone | 100.0 (9) | 9 | 100.0 (4) | 4 |
| Oxcarbazepine | 50.0 (4) | 8 | 71.4 (5) | 7 |
| Other | 50.0 (1) | 2 | 90.0 (9) | 10 |
| Overall[b] | 65.5 (38) | 58 | 82.5 (47) | 57 |

[a] $\chi^2 = 3.99$, df = 1, $p < .05$.
[b] $\chi^2 = 4.28$, df = 1, $p < .05$.
Abbreviation: SUD = substance use disorder.

had bipolar II disorder, and 1 (0.9%) had bipolar disorder not otherwise specified. There were no significant differences between the SUD and non-SUD groups in these characteristics. However, the non-SUD group had a higher proportion of women (73.7% [42/57] vs. 51.7% [30/58] in the SUD group; $\chi^2 = 5.92$, df = 1, p = .015).

### Use of Multiple Mood-Stabilizing Medications

Many of the subjects had been prescribed multiple mood-stabilizing medications, both serially and concurrently. On average, the 115 subjects had been prescribed a mean ± SD of 4.9 ± 2.6 mood-stabilizing agents in their lifetime. These counts did not differ significantly between SUD (5.2 ± 2.5) and non-SUD (4.7 ± 2.7) patients. Medication adherence rates did not differ between subjects taking several (3 or more) mood-stabilizing agents currently compared with those who were taking 1 or 2 agents. This held true when analyzed across SUD and non-SUD groups.

### Medication Adherence

Overall, the patients in the non-SUD group (N = 47/57, 82.5%) were more likely to meet our criteria for lifetime adherence (i.e., adherent with two thirds or more of total number of medications) with mood stabilizers than the SUD group (N = 38/58, 65.5%; $\chi^2 = 4.28$, df = 1, $p < .05$).

When we examined adherence to specific medications in the 2 groups, we found differences only in lithium. The non-SUD group (N = 34/40, 85.0%) had a higher rate of lifetime lithium adherence than did the SUD group (N = 27/41, 65.9%; $\chi^2 = 3.99$, df = 1, $p < .05$).

Since more women were in the non-SUD group than the SUD group, we analyzed the data controlling for SUD and found that gender is not related to overall adherence or to lithium adherence.

Levels of adherence for medications are summarized in Table 2.

### Reasons for Nonadherence

Overall, the most frequent reasons for nonadherence in this sample of patients were attitudes towards bipolar disorder (32 of 141 reasons, 22.7%) and side effects (29 of 141 reasons, 20.6%). Not surprisingly, substance-related reasons were more commonly endorsed by the SUD group than by the non-SUD group (22.0% vs. 3.0% reasons given; $\chi^2 = 6.83$, df = 1, $p < .01$). In contrast, pill- and dosage-related reasons for nonadherence were more frequently endorsed by the non-SUD group than by the SUD group (23.0% vs. 10.0%; $\chi^2 = 4.86$, df = 1, $p < .05$). There were no other significant differences in reasons for nonadherence between the 2 groups. Table 3 presents a detailed analysis comparing reasons for nonadherence between the 2 groups.

Participants who gave 1 category of reasons were significantly more adherent than those that gave multiple categories of reasons (89.3% [25/28] vs. 69.0% [60/87], p = .046); however, they did not differ in age, gender, and SUD status significantly.

## DISCUSSION

Our data showed a significantly higher rate of lifetime nonadherence to mood stabilizers among bipolar disorder patients with SUD than those with no SUD.

When we examined specific medications, the level of adherence between SUD and non-SUD patients differed significantly only for lithium. While several mood stabilizers (quetiapine, carbamazepine, and oxcarbazepine) showed lower rates of adherence in the SUD group, these differences were not significant, most likely due to the small number of patients taking these medications. In

  

**Table 3. Lifetime Reasons for Nonadherence With Medication in Bipolar Disorder Patients With and Without Substance Use Disorder (SUD)[a]**

| Reasons for not Taking Medication—Lifetime | No SUD, % (N) | SUD, % (N) |
|---|---|---|
| Side effects | 25 (10) | 19 (19) |
| Attitudes toward bipolar disorder | 28 (11) | 21 (21) |
| Pill/dosage-related[b] | 23 (9) | 10 (10) |
| Substance-related[c] | 3 (1) | 22 (22) |
| Mood-related | 10 (4) | 17 (17) |
| Forgot | 8 (3) | 9 (9) |

[a]All patients were asked to list the most important reasons for nonadherence but were allowed to endorse more than 1 reason for nonadherence to each mood stabilizer they were prescribed.
[b]$\chi^2 = 4.86$, df = 1, $p < .05$.
[c]$\chi^2 = 6.83$, df = 1, $p < .01$.

contrast, the rates of adherence were very similar in SUD and non-SUD patients for valproate, lamotrigine, gabapentin, olanzapine, topiramate, risperidone, aripiprazole, ziprasidone, and omega-3 fatty acids. The relatively poor rate of lithium adherence in bipolar patients with SUD is notable, especially when contrasted with the high adherence rate in those without SUD; this corroborates our previous findings of poor adherence to lithium in bipolar patients with SUD.[17]

Not surprisingly, just as adherence rates differed, the reasons for nonadherence differed between bipolar patients with and without SUD. In the SUD group, substance-related reasons were the most frequently cited reason for nonadherence; these included not taking medication either because of intoxication or a hangover or a desire to avoid combining medications with substances. This finding suggests that clinicians treating bipolar patients with SUD should inquire about how their substance use affects medication adherence.

Pill- and dosage-related reasons (e.g., a misunderstood prescription, too many pills to take) were endorsed more frequently by the non-SUD group than by the SUD group. It could be that SUD patients are less bothered by these issues because their illicit substance use may also involve complicated regimens.

These differences in adherence point out the importance of screening SUD in patients with bipolar disorder and addressing the substance use issues when present. Recent advances in both pharmacotherapy[19] and behavioral integrated treatments[20] of these 2 diagnoses suggest that attending to these issues simultaneously can improve outcome in bipolar patients.

Limitations of the study include the reliability of the patients' self-reports, which may have been influenced by recall bias and poor recall. Secondly, interviewers were not blinded to the SUD status of the subjects and may have expected greater nonadherence in the SUD patients. To minimize interviewer bias, interviewers were trained to administer the interview in a highly structured manner without prompting or giving suggestions to the participants. We also did not collect collateral information from family or treaters. However, patients' perceptions of why they do not take their medications as prescribed ultimately guide their decision-making process about adherence and are thus critical to assess. Finally, the higher proportion of women in the non-SUD group may have affected our findings. Although we found no gender-based differences in adherence, this study was designed with adequate statistical power to detect only large gender differences.

## CONCLUSION

Medication adherence is a crucial and understudied problem in patients with bipolar disorder. It appears from this study that bipolar patients with and without SUD differ in their rates and patterns of adherence. Physicians should be alert to these differences in clinical practice when prescribing medications.

*Drug names:* aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), levetiracetam (Keppra), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax and others), ziprasidone (Geodon), zonisamide (Zonegran and others).

## REFERENCES


1. American Psychiatric Association. Practice Guidelines for the Treatment of Patients with Bipolar Disorder. Rev ed. Washington, DC: American Psychiatric Association; 2002
2. Guscott R, Taylor L. Lithium prophylaxis in recurrent affective illness: efficacy, effectiveness and efficiency. Br J Psychiatry 1994;164:741–746
3. Scott J, Pope M. Self-reported adherence to treatment with mood stabilizers, plasma levels and psychiatric hospitalization. Am J Psychiatry 2002;159:1927–1929
4. Colom F, Vieta E. Treatment adherence in bipolar patients. Clin Approaches Bipolar Disord 2002;1:49–56
5. Scott J. Predicting medication non-adherence in severe affective disorders. Acta Neuropsychiatrica 2000;12:128–130
6. Goodwin FK, Jamison KR. Manic Depressive Illness. New York, NY: Oxford University Press; 1990
7. Swartz MS, Swanson JW, Hiday VA, et al. Violence and severe mental illness: the effects of substance abuse and non-adherence to medication. Am J Psychiatry 1998;155:226–231
8. Mueller-Oerlinghausen B, Muser-Causemann B, Volk J. Suicides and parasuicides in a high-risk patient group on and off lithium long-term medication. J Affect Disord 1992;25:261–269
9. Post RM, Leverich GS, Altshuler L, et al. Lithium-discontinuation-induced refractoriness: preliminary observations. Am J Psychiatry 1992;149:1727–1729
10. Jamison KR, Gerner RH, Goodwin FK. Patient and physician attitudes toward lithium. Arch Gen Psychiatry 1979;36:866–869
11. Keck PE Jr, McElroy SL, Strakowski SM, et al. Factors associated with pharmacologic noncompliance in patients with mania. J Clin Psychiatry 1996;57:292–297
12. Keck PE Jr, McElroy SL, Strakowski SM, et al. Compliance with maintenance treatment in bipolar disorder. Psychopharmacol Bull 1997; 33:87–91
13. Aagaard J, Vestergaard P, Maarbjerg K. Adherence to lithium prophylaxis, 2: multivariate analysis of clinical and psychosocial predictors of non-adherence. Pharmacopsychiatry 1988;21:166–170
14. Danion JM, Neunruther C, Krieger-Finance F, et al. Compliance with long-term lithium treatment in major affective disorders.

Pharmacopsychiatry 1987;20:230–231
15. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990;264:2511–2518
16. Grant BF, Stinson FS, Hasin DS, et al. Prevalence, correlates and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2005;66:1205–1215
17. Weiss RD, Greenfield SF, Najavits LM, et al. Medication compliance among patients with bipolar disorder and substance use disorder. J Clin Psychiatry 1998;59:172–174
18. Spitzer RL, Gibbon M. Structured Clinical Interview for DSM-IV. New York, NY: New York State Psychiatric Institute; 1996
19. Salloum IM, Cornelius JR, Daley DC, et al. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism. Arch Gen Psychiatry 2005;62:37–45
20. Weiss R, Griffin M, Kolodziej M, et al. A randomized trial of integrated group therapy versus group drug counseling for patients with bipolar disorder and substance dependence. Am J Psychiatry 2007;164:100–107

  