Clinical Features Associated With Poor Pharmacologic Adherence in Bipolar Disorder: Results From the STEP-BD Study

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Background: Poor medication adherence is common among bipolar patients.

Method: We examined prospective data from 2 cohorts of individuals from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (1999–2005) with bipolar disorder. Clinical and sociodemographic features associated with missing at least 25% of doses of at least 1 medication were assessed using logistic regression, and a risk stratification model was developed and validated.

Results: Of 3,640 subjects with 48,287 follow-up visits, 871 (24%) reported nonadherence on 20% or more study visits. Clinical features significantly associated ($P < .05$) with poor adherence included rapid cycling, suicide attempts, earlier onset of illness, and current anxiety or alcohol use disorder. Nonadherence during the first 3 months of follow-up was associated with less improvement in functioning at 12-month follow-up ($P < .03$). A risk stratification model using clinical predictors accurately classified 80.6% of visits in an independent validation cohort.

Conclusion: Risk for poor medication adherence can be estimated and may be useful in targeting interventions.

J Clin Psychiatry 2010;71(3):296–303

Submitted: *July 7, 2009; accepted September 16, 2009 (doi:10.4088/JCP.09m05514yel).*
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Contemporary treatment guidelines underscore the central role of medication treatment in the management of bipolar disorder.[1–3] Still, multiple studies suggest that poor medication adherence is common among patients with bipolar disorder, with point prevalences of up to 50%.[4–7] Consequences of poor adherence are substantial and may include greater chronicity and risk of recurrence and hospitalization,[7] greater health care costs,[8,9] and risk for suicide.[10,11] Poorer adherence has also been suggested to account for the markedly poorer treatment outcomes in many naturalistic studies compared to randomized trials.[12]

A number of psychosocial interventions have been demonstrated to improve treatment adherence in bipolar disorder (for a review, see Sajatovic et al[13]). A better understanding of risk factors for poor adherence would allow better targeting of such interventions, as well as facilitate development of more specific interventions. Numerous previous studies have examined clinical features associated with poorer treatment adherence[4,5,7,14–19]; taken together, these studies suggest that features such as psychiatric comorbidity, history of suicide attempts, and earlier onset of illness are consistently associated with poorer adherence. However, the modest sample sizes, absence of direct replication, and variation in means of assessment have limited attempts to derive a set of generalizable predictors and establish their utility for risk stratification.

To better understand prevalence and predictors of poor medication adherence in a representative clinical sample, we utilized prospective data from the multicenter Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) observational study of bipolar disorder. Advantages of this cohort include its minimal inclusion and exclusion criteria, intended to maximize generalizability, as well as the availability of both a model development and a replication cohort because of the large number of participants. We identified clinical and sociodemographic predictors from among the initial 2,000 subjects to enter the STEP-BD study, then we attempted to replicate them and demonstrate their predictive validity among the subjects who subsequently entered that study.

METHOD

Study Overview

The STEP-BD study was a multicenter observational "effectiveness" study, conducted in the United States between 1999 and 2005, that evaluated prospective outcomes among individuals with bipolar disorder. Methods for the STEP-BD study as a whole are detailed elsewhere.[12,20]

Participants

Study participation was offered to all bipolar patients seeking outpatient treatment at any of the participating study sites. Entry criteria included meeting *DSM-IV* criteria for bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified (NOS); cyclothymia or schizoaffective disorder bipolar type; and ability to provide informed consent. For individuals aged 15–17 years, written assent was also required from parent or guardian. Hospitalized individuals were eligible to enter following discharge.

Assessments

Bipolar diagnosis was determined using mood and psychosis modules from the Structured Clinical Interview for *DSM-IV* as incorporated in the Affective Disorders Evaluation and confirmed by a second clinical rater using the Mini International Neuropsychiatric Interview (MINI).[21] Comorbid Axis I diagnoses were also determined using the MINI. At each visit, clinicians assigned current mood status based on the Clinical Monitoring Form,[22] which assesses *DSM-IV* criteria for depressive, manic, hypomanic, or mixed states in the prior 14 days. Each criterion was scored on a scale of 0–2, where 1 represents "threshold" by *DSM-IV* mood episode criteria; fractional scores were used to indicate subthreshold symptoms.

Additional details of patient retrospective course on entering the STEP-BD study were collected by the clinician on the Affective Disorders Evaluation, including proportion of time in the preceding year with depressive, manic, and anxious symptoms, as well as number of episodes of each type.

A subset of patients also completed the NEO Five-Factor Inventory (NEO-FFI[23]), a 60-item self-report with each item rated on a 5-point scale. Twelve items assess each of the 5 personality dimensions (neuroticism, extraversion, conscientiousness, openness, and agreeableness). Scores were converted to sex-adjusted *t* scores with a (normative) mean of 50 and a standard deviation of 10 using adult normative data.[23] The NEO-FFI was administered at the initiation of the STEP-BD study but later eliminated from the assessment package, so it was available for only a subset of subjects.

Intervention

Study clinicians in the STEP-BD study were trained to use model practice procedures, which included published pharmacotherapy guidelines,[20] but they could prescribe any treatment that they felt to be indicated. Elsewhere, we have reported high concordance between treatment selection and guideline recommendations, indicating that patients received standard-of-care treatment when entering the STEP-BD study.[24] Patients could continue existing psychosocial interventions or be referred for psychosocial interventions, based on clinician and patient preference. All subjects also received a standard psychoeducation program including videotape and workbook at study entry.[25]

Outcomes

Because the STEP-BD study was intended to mimic clinical practice, participants were seen as frequently as clinically indicated. The Clinical Monitoring Form,[22] which includes a clinician-rated assessment of *DSM-IV* mood state criteria, was completed at each visit. At each visit, current medications and dosages were also recorded using the Clinical Monitoring Form. Patients were asked to report the total number of missed doses of each medication that they were prescribed in the preceding week, and this was recorded by the clinician as mg/wk missed. Patients were also asked systematically about categories of adverse effects, including tremor, dry mouth, sedation, constipation, diarrhea, headache, poor memory, sexual dysfunction, increased appetite, and extrapyramidal symptoms; severity in each category was rated on a scale from 0 (not present) to 4 (severe).

On a quarterly basis for the first 12 months and every 6 months thereafter, additional assessments were completed. These included quantification of depressive symptoms, using the Montgomery-Asberg Depression Rating Scale (MADRS[26]); manic symptoms, using the Young Mania Rating Scale (YMRS[27]); quality of life using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q[28]); and functioning using the Longitudinal Interval Follow-Up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT[29]).

Statistical Analysis

In total, 4,107 subjects entered the STEP-BD study, but only 3,640 completed at least 1 follow-up visit. This cohort was divided based on study protocol into the 1,771 subjects with at least 1 follow-up visit who were among the first 2,000 to enter STEP-BD (hereafter referred to as the STEP-2000), and the subsequent 1,869 subjects with at least 1 follow-up visit (hereafter referred to as the STEP-2 cohort).

Percent nonadherence was calculated for each medication based on number of milligrams missed in the past week and summarized as the maximum nonadherence at any given visit. Maximum percent nonadherence of at least 25% was defined a priori in the STEP-BD protocol as *poor adherence* at that visit, ie, missing at least 25% of total doses of any 1 medication was defined as poor adherence. Adverse effect reports were condensed into presence or absence of each adverse effect.

Associations with poor adherence at any given visit were examined with logistic regression using the robust clustering estimator of variance to account for clustering of visits within subjects and allow for the use of all subjects and all visits (rather than, for example, 1 visit per subject or a summary measure of all visits). Separate analyses were conducted for sociodemographic and clinical features, comorbidity, current mood symptoms, and adverse effects. Total number of medications and cumulative number of clinicians were also examined for association with poor adherence.

Analysis of association with nonadherence proceeded in 3 stages. First, individuals drawn from the STEP-2000 cohort were analyzed. Any features associated with $P < .05$ (uncorrected) in this cohort were then examined in the subsequent (STEP-2) cohort for purposes of replicating univariate associations. Finally, a multiple logistic regression model was derived using backward-elimination stepwise regression (requiring $P > .2$ for elimination) in the STEP-2000 cohort and validated in the STEP-2 cohort.

To examine potential longer-term implications of nonadherence, we also examined association between 3-month adherence, calculated as proportion of visits during this period with nonadherence, and 12-month measures, including LIFE-RIFT, Q-LES-Q, MADRS, and YMRS, using linear regression. All analyses were conducted using Stata 10.0 (StataCorp LP, College Station, Texas).

RESULTS

Among the full cohort of 3,640 patients, 1,690 subjects (46.4%) reported adherence at all visits; 503 (13.8%) subjects reported some nonadherence but on fewer than 10% of visits; 576 (15.8%) reported nonadherence on between 10% and 20% of visits; and 871 (23.9%) reported nonadherence on 20% or more visits. On average, subjects reported poor medication adherence on 12.8% of visits.

The STEP-2000 cohort included 28,672 visits for 1,771 subjects (mean 16.2 visits; median 13 visits; range, 1–102). The STEP-2 (replication) cohort included 19,615 visits for 1,869 subjects (mean 10.5 visits; median 8 visits; range, 1–98). Basic features of the 2 cohorts individually and in combination are available in eTable 1 (available at PSYCHIATRIST.COM) and are similar to prior reports.[12,30] Table 1A shows results of logistic regression examining association of sociodemographic and clinical features with poor adherence visits, both unadjusted and adjusted for depressive and manic symptom severity at each visit. Results are sorted by descending magnitude of odds ratio. Sociodemographic features significantly associated with poor adherence in both the initial cohort and the replication cohort included younger age, being Hispanic, being unemployed, and having household income less than $50,000/y. Lifetime clinical features associated with poor adherence included rapid cycling, suicide attempts, earlier onset of illness age, and current anxiety or alcohol use disorder at study entry. Depressive, irritable, manic, and anxious symptoms at each visit were also associated with greater likelihood of nonadherence. Among adverse effects (Table 1B), only self-reported memory impairment was associated with greater nonadherence. Among personality measures, only a greater NEO-FFI openness score was significantly associated with nonadherence.

To examine the predictive utility of the sociodemographic and clinical features identified, we utilized a backward-elimination stepwise logistic regression model in which terms with $P > .2$ were eliminated (including all terms yielded little substantive change). NEO-FFI scores were excluded from these models to confine them to clinical features obtained in routine clinical practice. The resulting model is summarized in Table 2; the formula for risk calculation is available from the authors on request. Receiver operating characteristic curves for the full model are in eFigure 1A and 1B. We selected a cut-point of 0.15 to achieve a negative predictive value greater than 90% in the STEP-2000 (discovery) cohort. At this threshold, classification accuracy was 83.6%. In the STEP-2 (validation) cohort, accuracy was 80.6%; sensitivity, specificity, negative predictive value, and positive predictive value were 19.4%, 89.5%, 88.5%, and 21.0%, respectively. Risk of nonadherence in the replication cohort is illustrated in Figure 1 for each quintile of risk score. While the model systematically underestimates risk in the validation cohort (Hosmer-Lemeshow goodness-of-fit $\times 2({}_5df) = 100.11$; $P < .001$), its calibration remains good in that higher risk scores predict greater risk.

Finally, Table 3 shows association between 3-month adherence and 1-year outcomes for all STEP-BD subjects, adjusted for 3-month measures using linear regression. Improvement in functional status, as measured by the LIFE-RIFT, was significantly less among individuals with more nonadherence in the first 3 months. Reduction in manic symptoms, as measured by the YMRS, was likewise significantly lower among individuals with more nonadherence while change in depressive symptoms (via MADRS) was not.

DISCUSSION

This prospective investigation of adherence among more than 3,600 bipolar patients seen for over 48,000 visits confirms the prevalence of poor adherence suggested by previous studies. Consistent with previous reports, we find sociodemographic features including younger age and single marital status to be reproducibly associated with nonadherence. The STEP-BD study enrolled few nonwhites, but Hispanic ethnicity (regardless of primary language) was associated with poorer adherence, consistent with greater attrition observed in major depressive disorder.[31] (The subsequent stepwise regression further suggests that the association with ethnicity is not confounded by differences in household income or education, a result confirmed by subsequent logistic regression [results not shown]). Illness features including earlier onset, history of suicide attempts, rapid cycling, and alcohol use comorbidity were also predictive of nonadherence. Among personality measures, greater openness, as measured by the NEO-FFI, was associated with greater risk for nonadherence.

Conversely, while adverse effects are often cited as a reason for nonadherence, we find only weak evidence of association between specific adverse effects and nonadherence. Notably, memory impairment/cognitive effects were the only significant predictor of nonadherence, which might suggest that

Table 1A. Clinical Features Associated With Poor Adherence at Any Given Follow-Up Visit in 2 Cohorts of Individuals With Bipolar Disorder

	STEP-2000[a]				STEP-2[b]	
Variable	Crude Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI
Socioeconomic						
Ethnicity: Hispanic	1.48	1.00–2.19*	1.51	1.01–2.24*	1.79	1.36–2.36*
Household income < $50,000/y	1.45	1.23–1.71*	1.43	1.22–1.68*	1.47	1.25–1.72*
Currently married	0.80	0.68–0.95*	0.80	0.68–0.94*	0.81	0.70–0.95*
Male sex	0.83	0.71–0.97*	0.86	0.73–1.00	0.91	0.79–1.05
White (vs all others)	0.88	0.66–1.17	0.87	0.66–1.15	NA	
Age (per 10 y)	0.89	0.84–0.94*	0.89	0.84–0.95*	0.86	0.82–0.91*
At least some college (vs none)	0.95	0.78–1.17	0.99	0.81–1.21	NA	
Currently unemployed	1.01	0.83–1.23	0.99	0.82–1.20	NA	
Clinical (study entry)						
Alcohol use disorder (current)	1.68	1.35–2.09*	1.63	1.32–2.03*	1.42	1.17–1.73*
Anxiety disorder (current)	1.47	1.26–1.72*	1.35	1.16–1.57*	1.31	1.13–1.51*
Rapid cycling, lifetime	1.40	1.17–1.68*	1.32	1.11–1.58*	1.34	1.14–1.57*
Rapid cycling, year prior to entry	1.37	1.17–1.60*	1.30	1.11–1.51*	1.26	1.09–1.45*
History of suicide attempt, lifetime	1.32	1.12–1.54*	1.21	1.04–1.42*	1.20	1.03–1.39*
Onset age (per 10 y)	0.77	0.70–0.83*	0.78	0.72–0.85*	0.84	0.77–0.92*
Manic symptoms (*DSM-IV*), count	1.23	1.18–1.27*	1.17	1.13–1.22*	1.22	1.18–1.27*
History of psychosis, lifetime	0.90	0.77–1.06	0.93	0.79–1.10	NA	
Bipolar I disorder (vs bipolar II disorder or NOS)	1.11	0.94–1.30	1.11	0.95–1.31	NA	
Depressive symptoms (*DSM-IV*), count	1.10	1.08–1.12*	1.07	1.05–1.10*	1.07	1.05–1.10*
Bipolar II disorder (vs bipolar I disorder or NOS)	0.93	0.79–1.09	0.92	0.78–1.08	NA	
Days depressed, past year (per 105)	1.06	1.03–1.08*	1.04	1.01–1.07*	1.06	1.03–1.08*
Days irritable, past year (per 10%)	1.05	1.03–1.07*	1.03	1.01–1.06*	1.04	1.01–1.06*
Days elevated, past year (10%)	1.05	1.01–1.08*	1.03	1.00–1.07	NA	
Days anxious, past year (per 10%)	1.03	1.01–1.05*	1.01	0.99–1.03	NA	
Clinical (each visit)						
Days irritable, past 2 weeks (per 10%)	1.09	1.07–1.10*	1.06	1.03–1.08*	1.04	1.01–1.06*
Days elevated, past 2 weeks (per 10%)	1.05	1.01–1.08*	1.03	1.00–1.06	NA	
Days depressed, past 2 weeks (per 10%)	1.04	1.02–1.05*	1.00	0.98–1.01	NA	
Days anxious, past 2 weeks (per 10%)	1.04	1.02–1.05*	1.01	0.99–1.02	NA	
Personality (NEO-FFI)						
Agreeableness (*t* score)	0.98	0.97–0.99*	0.98	0.97–0.99*	1.00	0.98–1.02
Openness (*t* score)	1.02	1.01–1.03*	1.02	1.01–1.03*	1.02	1.00–1.04*
Conscientiousness (*t* score)	1.02	1.01–1.03*	1.02	1.01–1.02*	1.00	0.99–1.02
Neuroticism (*t* score)	1.01	0.99–1.02	1.00	0.99–1.02	NA	
Extraversion (*t* score)	1.00	0.99–1.01	1.00	0.99–1.01	NA	

Table 1B. Adverse Effects and Other Aspects of Treatment Associated With Poor Adherence

Adverse Effect						
Memory impairment	1.21	10.02–1.44*	1.08	0.90–1.29	NA	
Extrapyramidal symptoms	1.20	0.83–1.73	1.11	0.77–1.60	NA	
Increase in appetite	1.12	0.96–1.31	1.04	0.89–1.21	NA	
Sexual dysfunction	1.11	0.88–1.39	1.05	0.83–1.33	NA	
Dry mouth	1.10	0.93–1.29	1.00	0.85–1.17	NA	
Constipation	1.10	0.83–1.45	1.00	0.76–1.33	NA	
Sedation	1.02	0.88–1.18	0.94	0.80–1.09	NA	
Tremors	1.00	0.86–1.16	0.93	0.80–1.09	NA	
Cumulative no. of clinicians	0.98	0.95–1.01	0.99	0.96–1.02	NA	
No. of psychotropic medications	1.04	1.01–1.07*	1.02	0.99–1.06	NA	

[a]The STEP-2000 subsample was derived from the 3,640 completing the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study with at least 1 follow-up visit being divided based on study protocol into the 1,771 subjects with at least 1 follow-up visit who were among the first 2,000 to enter the STEP-BD study.
[b]STEP-2 refers to the 1,869 subjects remaining from the cohort of 3,640 completing the STEP-BD study with at least 1 follow-up visit.
*Nominal $P < .05$ (ie, 95% CI excludes 1).
Abbreviations: NA = not applicable, NOS = not otherwise specified.

nonadherence is more likely to be a result of the cognitive deficits that are increasingly recognized in bipolar disorder.[32] Alternatively, this adverse effect may be a proxy for specific medications associated with poorer adherence, although incorporating terms for individual medication classes into logistic regression models (antipsychotic, anticonvulsant, lithium, benzodiazepine) did not meaningfully change the magnitude of association (results not shown).

Prior reports have generally examined adherence in more select bipolar populations. In one of the largest studies to date to examine predictors, among 306 predominantly male veterans, less intensive treatment regimens, more obstacles

Table 2. Variables in Nonadherence Risk Prediction Model[a]

Variable	Odds Ratio	95% CI
% days depressed, past year (per 10%)	1.039	1.009–1.070
% days anxious, past year (per 10%)	0.979	0.955–1.004
Household income < $50k	1.278	1.083–1.508
Any comorbid Axis I anxiety disorder	1.334	1.118–1.591
Age at study entry (per 10 years)	0.928	0.868–0.993
Male sex	0.854	0.721–1.013
Current alcohol use disorder	1.358	1.055–1.748
Hispanic (versus non–Hispanic)	1.698	1.132–2.547
Rapid cycling, past year	1.229	1.037–1.457
Age at onset (per 10 years)	0.839	0.757–0.930

[a]Variables significantly and independently associated with risk for poor medication adherence.

Figure 1. Observed Versus Predicted Risk for Poor Medication Adherence in a Second (Validation) Cohort

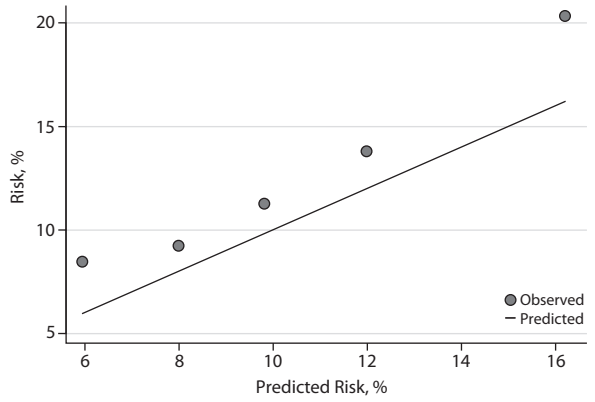

Table 3. One-Year Outcomes, Based on 3-Month Nonadherence

Outcome	β	SE	*P* Value	β (95% CI)	
Quality of Life Enjoyment and Satisfaction Questionnaire	−1.92	1.81	.288	−5.48	1.63
LIFE-RIFT	0.94	0.44	.032	0.08	1.80
Montgomery-Asberg Depression Rating Scale	1.73	1.20	.149	−0.62	4.08
Young Mania Rating Scale	1.74	0.71	.014	0.35	3.14

Abbreviation: LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation-Range of Impaired Functioning Tool.

to health care, and prior suicide attempts were associated with greater nonadherence.[14] In another cohort, associations were reported between nonadherence and younger age, minority ethnicity, and comorbid substance abuse.[5] In a questionnaire-based study of 429 bipolar patients, risk factors for nonadherence included alcohol dependence, younger age, greater degree of affective symptoms, and adverse effects.[15] A fourth study found an association between current substance use disorders and poorer adherence,[16] while another report highlighted shorter illness duration and earlier age at onset.[17] Finally, a Web-based questionnaire suggested that effects of socioeconomic status, severity of depressive symptoms, and selected adverse effects, including weight gain and cognitive effects, impact adherence as well.[18] Our results are consistent with many of these findings.

Many of the predictors we identify cannot be modified but may still be useful in targeting interventions to improve adherence by finding high-risk individuals. For example, the association with Hispanic ethnicity may suggest the importance of greater sensitivity to cultural or linguistic differences. More generally, the development and validation of risk stratification models has become common across medicine as a means of translating research findings into clinical practice,[33] but this approach remains relatively rare in psychiatry.[34] Here, we illustrate the potential application of such a risk score, demonstrating that the assessment of several basic clinical features allows stratification of nonadherence risk. We emphasize that a prediction tool can be useful in stratifying risk even where its absolute discrimination is not high, if it is well-calibrated, as in the present case. In other words, while this tool cannot reliably identify who will or will not be poorly adherent, those in the higher-risk categories are substantially more likely to be poorly adherent than those in the lower-risk categories.[35,36] So, for example, one could imagine calculating a nonadherence risk score in every patient entering a clinic and making an intervention such as a follow-up phone call or use of a Medication Event Monitoring System (MEMS) cap only in those in the highest quartile.

Some of the predictors identified might allow for further refinement and personalization of psychosocial interventions to improve adherence. For example, the association with memory impairment would suggest that behavioral strategies to ensure proper medication dosing and timing would be useful. An abundant literature from other medical disorders, such as diabetes and human immunodeficiency virus (HIV), supports the use of tools such as diaries, reminder telephone calls, and pagers.[37–39]

Our results also underscore the importance of addressing nonadherence in pharmacotherapy. We found that poor medication adherence in the first 3 months was associated with poorer outcomes at 1 year (ie, 9 months later). This result is consistent with common sense as well as prior reports, including a recent analysis of medical claims data which found an association with greater health care costs.[8] On the other hand, establishing a causal link between nonadherence and outcome is difficult: an alternative hypothesis is that nonadherence is simply a marker of more severe or chronic illness. In either case, these results underscore the importance of interventions targeting nonadherent individuals as a means of improving outcomes, including psychosocial interventions.[13,30,40,41]

One notable limitation in interpreting the present results is the reliance on a self-report measure of adherence, as blood levels of medication were not consistently applied to monitor adherence. While the self-report approach is the same as that taken by most previous investigations, objective

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assessments, such as pill counts or electronic monitoring, suggest that patients may intentionally or unintentionally overreport their adherence. (For a review of the methodological limitations of self-report and electronic monitoring, see Berg and Arnsten.[42]) However, this distinction should simply decrease our power to detect associations between nonadherence and outcome rather than introducing bias per se. Reliance on self-report may account for the association between *greater* conscientiousness and poorer adherence in the STEP-2000 cohort (although not the STEP-2 cohort) if these individuals are more likely to recall and acknowledge missed medication doses.

A second limitation is the paucity of detailed assessment of patient attitudes, which multiple prior reports indicate plays a key role in influencing adherence.[43–47] This report therefore should be considered to complement those investigations, and the optimal assessment of nonadherence risk might combine a quantitative assessment of risk with an assessment of patient attitudes.

By design, the STEP-BD study included 2 cohorts to enable replication. Therefore, in the univariate analyses presented here, we elected not to correct for multiple comparisons because we were not testing hypotheses per se but rather trying to estimate the relative impact of individual features on risk for nonadherence. To minimize risk of type I error, we then attempted to replicate any associations nominally significant in the STEP-2000 cohort. Likewise, for the prediction analysis, we elected to use a split sample to guard against overfitting arising from spurious association.

We chose not to examine nonadherence risk associated with individual medications here because of the substantial risk of confounding by indication. Treatments were not randomly assigned, and thus some interventions might have been selected or avoided based on nonadherence. For example, if lithium treatment was initiated in patients with poorer adherence, it would appear that lithium was associated with poorer adherence, a relationship which could be misconstrued as causal. In sensitivity analyses, we did examine the effect of including medication types as time-dependent covariates, as these did not meaningfully change univariate associations or model results (those analyses not presented here). Not surprisingly, a greater number of psychotropic medications were associated with greater risk of nonadherence (Table 1B).

A final consideration is the generalizability of our results. The STEP-BD study was intended to be an effectiveness study, with broad inclusion criteria (in terms of comorbidity, for example) and naturalistic follow-up. Because subjects agreed to participate in the study and comply with study protocol, overall adherence may well be higher than might be seen in a general ambulatory mental health setting. While the associations identified were replicated in a second large cohort, further investigation of our risk criteria in other clinical populations would be worthwhile before they are applied more broadly.

Drug name: lithium (Eskalith, Lithobid, and others).

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Potential conflicts of interest: **Dr Perlis** has received research support from Eli Lilly and Elan/Eisai; advisory/consulting fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Pfizer, and Proteus Biomedical; and speaking fees or honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, and Pfizer and has equity holdings and patents for Concordant Rater Systems, LLC. **Dr Ostacher** reports receiving research support from the National Institute on Alcohol Abuse and Alcoholism and Pfizer; advisory/consulting fees from Pfizer and Concordant Rater Systems; speaker's fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Pfizer, and Massachusetts General Psychiatry Academy (MGHPA) (MGHPA talks were supported through Independent Medical Education grants from the following pharmaceutical companies in 2008: AstraZeneca, Eli Lilly, and Janssen Pharmaceuticals). **Dr Thase** has served as an advisor or consultant to AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, MedAvante, Neuronetics, Novartis, Organon, Schering-Plough, Sepracor, Shire, Supernus, Transcept, and Wyeth; has served on the speakers' bureaus of AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly, GlaxoSmithKline, Organon, Sanofi-Aventis, and Wyeth; has provided expert testimony for Jones Day (Wyeth litigation) and Phillips Lytle (GlaxoSmithKline litigation); is a shareholder with MedAvante; and receives income from royalties and/or patents with American Psychiatric Publishing, Guilford Publications, Herald House, and WW Norton; his wife is the senior medical director for Advogent (formerly Cardinal Health). **Dr Sachs** has received research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Memory Pharmaceuticals, the National Institute of Mental Health (NIMH), Novartis, Pfizer, Repligen, Shire, and Wyeth; has served on the speaker bureaus of Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Memory Pharmaceuticals, Novartis, Otsuka, Pfizer, Sanofi-Aventis, Takeda, and Wyeth; has served as an advisory board member or consultant for Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, CNS Response, Elan Pharmaceuticals, Eli Lilly, GlaxoSmithKline, Janssen, Memory Pharmaceuticals, Merck, Novartis, Organon, Pfizer, Repligen, Sanofi-Aventis, Shire, Sigma-Tau, Solvay, and Wyeth; and his spouse is a shareholder with Concordant Rater Systems. **Dr Nierenberg** has served in the past 3 years as a consultant/advisor to Abbott, Appliance Computing, BrainCells, Bristol-Myers Squibb, Eli Lilly, EpiQ, GHenaissance, Forest, GlaxoSmithKline, Innapharma, Janssen, Jazz, Merck, Novartis, Pam Labs, Pfizer, PGX Health, Schering-Plough, Sepracor, Shire, Somerset, Takeda, and Targacept; has received research/grant support from Bristol-Myers Squibb, Cederroth, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Lichtwer Pharma, Medtronics, NARSAD, NIMH, Pfizer, Stanley Foundation through Broad Institute, Ortho-McNeil-Janssen, Pfizer, Pam Labs, Shire, and Wyeth-Ayerst; and has received honoraria from Bristol-Myers Squibb, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, the MGH Psychiatry Academy (MGHPA activities in 2008 and 2009 were supported through Independent Medical Education grants from AstraZeneca, Eli Lilly, and Janssen), and Wyeth-Ayerst; earns fees for editorial functions for *CNS Spectrums* through MBL Publishing and *Psychiatric Annals* through Slack, honoraria as a CME Executive Director for *The Journal of Clinical Psychiatry* through Physicians Postgraduate Press, and royalties from Cambridge University Press and Belvoir Publishing; owns stock options in Appliance Computing and Brain Cells; and, through MGH, owns copyrights to the Clinical Positive Affect Scale and the MGH Structured Clinical Interview for the Montgomery Asberg Depression Scale exclusively licensed to the MGH Clinical Trials Network and Institute. **Dr Miklowitz** and **Ms Hay** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: The study was supported by a NARSAD Young Investigator Award (R. H. P.); a Sydney L. Baer Foundation Award (R. H. P.); and a Bowman Family Foundation Award (R. H. P.). The STEP-BD project was funded in whole or in part with federal funds from the NIMH,

National Institutes of Health, under contract N01MH80001 to Gary S. Sachs, MD (Principal Investigator [PI]), Michael E. Thase, MD (Co-PI), and Mark S. Bauer, MD (Co-PI).

Disclaimer: Any opinions, findings, and conclusions or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the National Institute of Mental Health.

Acknowledgments: Active STEP-BD sites and PIs included Baylor College of Medicine (Lauren B. Marangell, MD); Case University (Joseph R. Calabrese, MD); Massachusetts General Hospital and Harvard Medical School (Andrew A. Nierenberg, MD); Portland VA Medical Center (Peter Hauser, MD); Stanford University School of Medicine (Terence A. Ketter, MD); University of Colorado Health Sciences Center (Marshall Thomas, MD); University of Massachusetts Medical Center (Jayendra Patel, MD); University of Oklahoma College of Medicine (Mark D. Fossey, MD); University of Pennsylvania Medical Center (Laszlo Gyulai, MD); University of Pittsburgh Western Psychiatric Institute and Clinic (Michael E. Thase, MD); and University of Texas Health Science Center at San Antonio (Charles L. Bowden, MD). We thank the patients and families who have contributed their time to this study.

Supplementary material: eTable 1 and eFigure 1A and 1B are available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: **Clinical Features Associated With Poor Pharmacologic Adherence in Bipolar Disorder: Results From the STEP-BD Study**

Authors: **Perlis RH, Ostacher MJ, Miklowitz DJ, Hay A, Nierenberg AA, Thase ME, Sachs GS**

Citation: **J Clin Psychiatry 2010;71**

doi Number: **10.4088/JCP.09m05514yel**

List of Supplementary Material for the article

1. **eTable1** Baseline sociodemographic and clinical features of the cohorts used for adherence analyses

2. **eFigure 1A and 1B** Receiver operating characteristic curves for nonadherence risk score in model development (STEP-2000; eFigure 1A) and validation (STEP-2; eFigure 1B) cohorts

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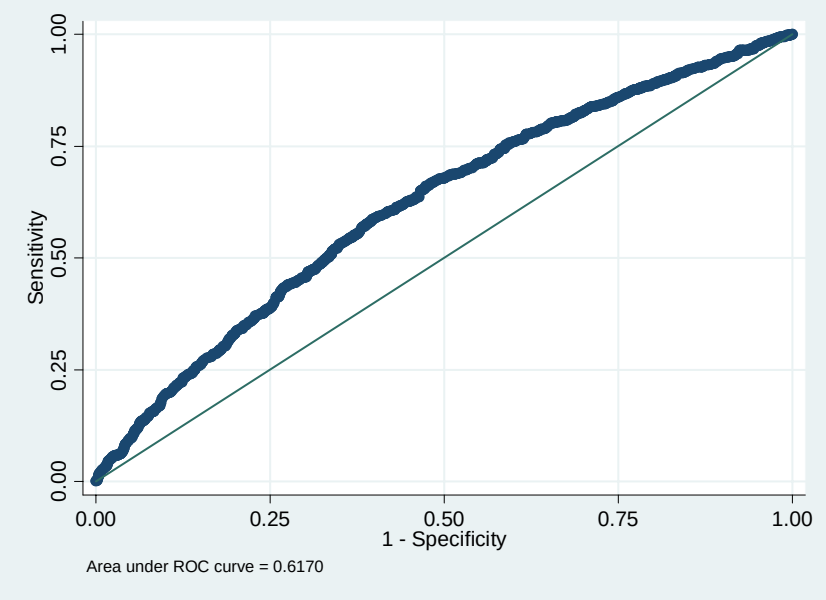
eTable 1. Baseline Sociodemographic and Clinical Features of the Cohorts Used for Adherence Analyses

	STEP-2000		STEP2		STEP (combined)	
	No.	%	No.	%	No.	%
Sex (male)	738	41.7	803	43.0	1,541	42.3
Race (Caucasian)	1,637	92.4	1,649	88.2	3,286	90.3
Ethnicity (Hispanic)	75	4.2	112	6.0	187	5.1
Married	648	38.3	621	35.3	1,269	36.8
Employed	792	46.8	746	42.4	1,538	44.6
Graduated high school	1,644	97.2	1,689	96.1	3,333	96.6
Completed some college	1,409	83.3	1,427	81.2	2,836	82.2
Household income < $50k	873	56.2	963	61.1	1,836	58.7
Bipolar 1	1,227	69.3	1,144	61.2	2,371	65.1
Bipolar 2	430	24.3	536	28.7	966	26.5
Current alcohol use d.o.	182	10.3	221	11.8	403	11.1
Current drug use d.o.	116	6.5	169	9.0	285	7.8
Current anxiety d.o.	597	33.7	696	37.2	1,293	35.5
History of suicide attempt	632	36.3	666	37.4	1,298	36.9
History of psychosis	658	38.5	676	37.9	1,334	38.2
Manic episodes (5+)	1,244	70.4	1,367	73.8	2,611	72.1
Depressive episodes (5+)	1,315	75.8	1,432	78.7	2,747	77.3
Rapid cycling (ever)	1,181	66.7	1,286	68.8	2,467	67.8
Rapid cycling (past year)	780	44.0	901	48.2	1,681	46.2
	Mean	SD	Mean	SD	Mean	SD
Age at entry	40.63	12.81	39.64	12.78	40.13	12.80
Age at onset	17.43	8.83	16.93	8.67	17.18	8.76
Age at first mania	21.81	10.07	21.34	9.94	21.58	10.01
Age at first depression	18.59	9.54	17.66	9.27	18.12	9.41
Days depressed, past yr	40.34	29.84	46.17	29.59	43.25	29.85
Days anxious, past yr	29.95	32.11	40.08	34.37	34.97	33.63
Days irritable, past yr	28.39	30.10	35.09	30.34	31.73	30.40
Days elevated, past yr	18.93	21.62	19.82	20.58	19.37	21.12

Baseline sociodemographic and clinical features of the STEP2000 and STEP2 cohorts.

eFigure 1. Receiver operating characteristic curves for nonadherence risk score in model development (STEP2000; eFigure 1A) and validation (STEP2; eFigure 1B) cohorts.

eFigure 1A.



eFigure 1B.