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Testing for Clinical Inertia in Medication Treatment of Bipolar Disorder

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Abstract

Background—Clinical inertia has been defined as lack of change in medication treatment at visits where a medication adjustment appears to be indicated. This paper seeks to identify the extent of clinical inertia in medication treatment of bipolar disorder. A second goal is to identify patient characteristics that predict this treatment pattern.

Method—Data describe 23,406 visits made by 1,815 patients treated for bipolar disorder during the STEP-BD practical clinical trial. Visits were classified in terms of whether a medication adjustment appears to be indicated, and also whether or not one occurred. Multivariable regression analyses were conducted to find which patient characteristics were predictive of whether adjustment occurred.

Results—36% of visits showed at least 1 indication for adjustment. The most common indications were non-response to medication, side effects, and start of a new illness episode. Among visits with an indication for adjustment, no adjustment occurred 19% of the time, which may be suggestive of clinical inertia. In multivariable models, presence of any indication for medication adjustment was a predictor of receiving one (OR=1.125, 95% CI = 1.015, 1.246), although not as strong as clinical status measures.

Limitations—The associations observed are not necessarily causal, given the study design. The data also lack information about physician-patient communication.

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Presentations

This paper was presented at the 16th World Congress of Psychiatry, Madrid, September 18, 2014, and the Twelfth Workshop on Psychiatric Costs and Assessment, Venice, March 27, 2015.

Conclusions—Many patients remained on the same medication regimen despite indications of side effects or non-response to treatment. Although lack of adjustment does not necessarily reflect clinical inertia in all cases, the reasons for this treatment pattern merit further examination.

Keywords

Bipolar disorder; pharmaceuticals; prescribing decisions; clinical inertia

1. Introduction

Bipolar disorder (BD) is among the twenty leading causes of years lived with disability worldwide.(Vos et al. 2012) It is a severe, chronic disorder that impairs functioning in multiple life domains, in particular psychosocial and occupational,(Hirschfeld, Lewis and Vornik 2003; Judd et al. 2008; Keck, Kessler and Ross 2008; Kessler et al. 2006; Kessler, Merikangas and Wang 2007; Lee et al. 2010; Ruggero et al. 2007) imposing a total economic burden estimated at \$151.0 billion for the US in 2009.(Dilsaver 2011) In addition, individuals with bipolar disorders have an annual risk of suicide attempts that is 30 to 60-fold higher than the general population.(Gonda et al. 2012) Some of these poor outcomes may result from lack of treatment, with large numbers of individuals not receiving treatment, or not adhering enough to benefit. For example, in one national study, only 64% of people with bipolar I disorder who had had an active major depressive, manic, or hypomanic episode in the previous 12 months reported receiving medication.(Merikangas et al. 2007) However, another concern is that some bipolar patients are not receiving the right treatment to relieve their symptoms, in a context where different medications and dosages work for different patients. Pharmacological treatment for BD typically involves use of medications from multiple classes, and requires monitoring patients for side effects and nonresponse, in case medication adjustment is needed.(Yatham et al. 2013)

For several other chronic medical conditions, clinical inertia is increasingly discussed as a possible explanation for poor treatment outcomes. Clinical inertia has been defined as “failure of health care providers to initiate or intensify therapy when indicated.” (Phillips et al. 2001) Evidence for this phenomenon has been studied for a variety of diseases, as documented in a 2009 review by Faria et al.(Faria et al. 2009) For example, a study of hypertensive patients found that anti-hypertensive medications were intensified in only 13% of visits where an elevated blood pressure was recorded.(Okonofua et al. 2006) In the case of depression treatment, one study found that treatment adjustment was recommended in only one-third of observation periods that ended with less than a full response.(Henke et al. 2009) Other diseases for which clinical inertia has been studied include diabetes, renal disease and dyslipidemia.(Faria et al. 2009) However, no studies have yet evaluated the existence of clinical inertia in treatment of bipolar disorder.

This study attempts to measure the potential prevalence of clinical inertia in bipolar disorder treatment, based on rates of non-adjustment of medications where adjustment might appear to be indicated. We do not include psychosocial therapies in our definition of adjustment, as arranging psychotherapy typically takes considerably longer than changing the medication regimen, in the settings studied. We identify some demographic and clinical correlates of

this treatment pattern. However, since non-adjustment may result from factors other than clinical inertia (reviewed in the Discussion), our findings should be considered to be a 'high end' estimate which could be used as a reference for future research on this topic. Given the exploratory character of the study, formal hypotheses are not tested.

2. Method

Data

This paper used data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study. STEP-BD was a multisite study funded by the National Institute of Mental Health (NIMH) that was designed to evaluate the longitudinal outcome of patients with bipolar disorder. The overall design involved a large prospective naturalistic study, combined with specific randomized controlled trials, at 22 sites in the United States between November 1999 and July 2005. The sites were specialty clinics in academic medical settings.(Sachs et al. 2003) The present study involved no new data collection from the STEP-BD subjects, and was approved by the institutional review board of our institution.

To enroll in STEP-BD, patients were required to be at least 15 years of age and to meet DSM-IV criteria for bipolar I disorder, bipolar II disorder, cyclothymia, bipolar disorder not otherwise specified, or schizoaffective manic or bipolar disorder subtypes. Exclusion criteria were limited to the unwillingness or inability to comply with study assessments or the inability to give informed consent. Although the study included a few small, randomized trials, most patients were seen only in the naturalistic arm, in which clinicians were trained on expert consensus guidelines and other published treatment guidelines, and encouraged but not required to follow those guidelines.(Sachs et al. 2003) However, treatment decisions were based entirely on the preferences of the treating physicians in collaboration with their patients, and were not constrained in any way. This paper uses data from the naturalistic arm only. Details on subject recruitment and diagnostic methods are available in other papers from the study.(Sachs et al. 2003) (Ghaemi et al. 2006)

Over the course of the STEP-BD study, psychiatrists recorded data at each study visit on patients' medication treatment; adverse side effects; self-reported adherence to prescribed medications; clinical mood state (e.g. depressed, manic, mixed or hypomanic); social and role functioning; and self-reported comorbidities (e.g. substance use, eating disorders, medical conditions). These data were recorded on a Clinical Monitoring Form (CMF), a one-page assessment tool that consists of nine parts. Its subscales were constructed as a standardized assessment substitute for the narrative process note routinely used in clinical practice. The CMF also recorded information on laboratory data, stressors, selected mental status items, and the percent time and severity of depressive, anxious and/or elevated mood symptoms experienced in the prior 10 days.(Sachs, Guille and McMurrich 2002)

Analytic sample

There were 3,271 patients in the study for whom at least one CMF was available. For this paper, patients were excluded if they: 1) did not have a lifetime diagnosis of bipolar disorder (n=1,213), 2) had visits on the randomized pathways (n=252), 3) used a medication whose

name could not be determined from the study data (n=37), or 4) lacked demographic information (n=250). In addition, 136 patients who only had one visit during the study were excluded, as any adjustment they received would not be observable. Since the CMF reported on adjustments prior to the current visit, each patient's final visit was excluded, as we would not be able to observe any adjustments that occurred at that visit. This resulted in a sample of 23,406 study visits made by 1,815 patients, whose care was managed by 193 physicians.

Measures

This section describes how key measures used for this paper were constructed.

Clinical status—Current clinical assessments of depressed, manic, mixed, or hypomanic states and of euthymic or subsyndromal states were based on standard STEP-BD procedures that used the CMF and application of DSM-IV criteria to all depressive and manic mood symptoms. Patients who did not meet criteria for a current episode but had not recovered from their last episode were classified as either ‘continued symptomatic’ (if they had 3 or more moderate symptoms) or ‘recovering’ otherwise. Patients who did not meet criteria for a current episode and had recovered from their last episode were classified as either ‘roughening’ (if they had 3 or more moderate symptoms) or ‘recovered’ otherwise. All raters were trained during STEP-BD sessions in application of the CMF clinical mood status assessment, and adequate interrater reliability was ascertained.(Ghaemi et al. 2006) In addition, the Clinical Global Impression (CGI) Severity scale was collected at each visit, recording the patient's severity of psychopathology on a scale from 1 (not at all ill) to 7 (extremely ill).

Indications for adjustment—A set of indications was developed by the study team, based on the clinical and research experience of the clinician co-investigators. The definition of the indications was also informed by influential treatment guidelines.(Malhi et al. 2009; Suppes et al. 2005; Yatham et al. 2013) These guidelines advise physicians to modify the medication regimen over time in response to changes in the patient's mood (e.g. mania, depression) and treatment phase (e.g. acute, maintenance), and also if the patient is not responding or is experiencing side-effects. A visit was classified as having an indication for treatment adjustment if the patient met any of the following criteria:

- Presence of any severe side effects (rated 4 on a scale of 0-4) or at least 2 moderate side effects (rated 2 or 3) at both the current and previous visits.
- Non-response to treatment. This was judged to be present if: a) the patient's current episode had lasted more than 8 weeks, or b) the patient had been classified as ‘continued symptomatic’ for more than 8 consecutive weeks, or c) the patient had been classified as ‘continued symptomatic’ after an episode ended in the last 8 weeks.
- “Roughening”/increased symptoms for 3 consecutive weeks.
- New or more severe psychotic symptoms in the last week. This criterion was met if any of the four psychotic symptom variables showed an increase in severity, or if new symptoms appeared. The symptoms evaluated were paranoid

ideation, ideas of reference, hallucinations and delusions, and each was measured on a scale of 0-4.

- New acute episode. True if at a given visit the patient's clinical state was depressed, manic, hypomanic or 'mixed', and at the previous visit the patient was not in one of these states.

Medication adjustment—A medication adjustment was deemed to have occurred if the physician recommended adding or discontinuing any medications, or recommended any changes in dosage.

Clinical inertia—Visits were defined as exhibiting clinical inertia if there was at least one indication for medication adjustment (as defined above), but no adjustment occurred. This visit-level measure was used in turn to construct a patient-level measure: whether a patient had experienced any visits with inertia.

Patient characteristics—These were collected at study intake using the study's Demographic Form. Patient characteristics used for this paper include the patient's age, gender, race/ethnicity, marital status, education, employment status, and income level.

Medication adherence—At each visit, clinicians recorded patients' self-reported adherence to each medication (mg. missed in past 7 days). From this we computed the mean adherence rate at each visit, across medications in the core classes used for bipolar treatment (mood stabilizers, antidepressants and antipsychotics). Mean visit-level adherence was defined as adequate if it was at least 75%.

Statistical analysis

For the subsample of visits where an indication for adjustment was present, associations between patient characteristics and the occurrence of adjustment were tested for statistical significance, using chi square tests for categorical characteristics and t-tests for continuous ones. All statistical tests were two-tailed. In addition, multivariable logistic regressions were estimated to predict the occurrence of adjustment as a function of whether any indication for adjustment was present (Model 1) or alternatively, which specific indications were present, with multiple indications included in a single model (Model 2). Both models included multiple observations per patient. To avoid the clustering bias that could have otherwise resulted, each model included patient fixed effects (an indicator variable for each patient). This removes the need to explicitly control for time-invariant patient characteristics such as gender, as their effects on the outcome are captured by the fixed effects. In addition, Model 2 does not include the adjustment indication for roughening, as this was highly correlated with having a clinical status of roughening. Both models controlled for time elapsed since the preceding visit, as greater elapsed time might make adjustment more likely.

3. Results

Sample characteristics

Characteristics of the 1,815 study subjects included in this analysis are reported in Table 1.

Prevalence of clinical inertia

Sample members made 25,221 study visits, for an average of 13.9 visits each. After excluding each patient's last visit, this left 23,406 visits for analysis (Table 2). A total of 36% of visits showed at least one indication for adjustment. The most common indications were start of a new illness episode (13.7%), nonresponse to medication (11.7% of visits), and side effects (10.3%). The most common type of adjustment was a change in dosage (30.9% of visits), followed by addition of a medication without dropping any (15.4%) and dropping a medication without adding any (13.4%). Among visits with an indication for adjustment, 18.8% did not result in any adjustment, which is suggestive of clinical inertia. 'Inertial' visits were 7% of all visits.

At the patient level, 37.9% of the 1,815 patients had one or more visits that exhibited clinical inertia. This proportion is much higher than the share of all visits that exhibited inertia (7%). One implication is that the 'inertial visits' were not concentrated among a handful of patients (in which case the share of patients would have been similar to or lower than the share of visits: 7%). Rather, a substantial number of patients appear to have experienced at least one inertial visit, along with other visits without inertia.

Since inertia could represent 'watchful waiting', we checked how often there was an adjustment at the visit following an inertial one. Among those inertial visits where there was a subsequent visit, 57% of those subsequent visits included an adjustment. The visits with an adjustment occurred 4.7 days sooner than those without an adjustment (33.3 compared to 38 days; $p < .05$; data not shown).

Correlates of clinical inertia

Among patients with an indication for medication adjustment, an adjustment was less likely to occur at visits where the patient was male, aged greater than 45, non-white race, divorced/widowed/separated, or received no psychosocial intervention (Table 3). In addition, given the presence of an indication, patients who received an adjustment had higher severity of illness than those who did not (CGI score of 2.96 compared to 2.34, $p < .01$). The other variables presented in Table 1 were not significantly associated with adjustment and are not shown in Table 3.

Multivariable regression results indicate that presence of any indication for medication adjustment was a statistically significant predictor of receiving one (OR=1.125, 95% CI = 1.015, 1.246), after controlling for other variables (Table 4). However, the likelihood of adjustment was more strongly associated with various specific clinical status variables. For example, adjustment was more likely at visits where the patient exhibited mania (OR=3.078, 95% CI=2.136, 4.435). To test the importance of specific indications for adjustment, an alternative specification (Model 2) was estimated in which the single variable measuring 'any indication' was replaced by a set of four indicators for the presence of specific adjustment indications (e.g. nonresponse). Adjustment is more likely in the presence of an adjustment-indication for side effects (OR=1.211, CI=1.052, 1.393) or for psychotic symptom increase (OR=1.273, CI=1.078, 1.504). Contrary to expectations, adjustment is less likely in the presence of nonresponse (OR=0.849, CI=0.726, 0.995), and starting a new

episode was not predictive of adjustment. Associations were stronger for most of the clinical status variables than for the adjustment-indication variables. However, only four variables had an odds ratio larger than 2, which is often considered a threshold for clinical (as opposed to statistical) significance.

In addition, we estimated separate models in which low adherence was included as a predictor, which required dropping 1,418 visits for which adherence information was missing. Low adherence was not a statistically significant predictor of adjustment, nor did its inclusion in models change the sign or statistical significance of the indication variables. (Data not shown.)

In terms of other explanatory variables, patients with a higher CGI score were also more likely to receive an adjustment. Given the use of patient fixed effects, control for time-invariant patient characteristics was neither necessary nor feasible, and these were omitted from the models presented in Table 4. Models which did include patient demographics instead of fixed effects found that adjustment was more likely for patients who were younger (15-25), female, white, college-educated, or on disability benefits. (Data not shown).

Finally, we examined the distribution of ‘inertial’ visits across physicians. (Data not shown.) Of the 193 physicians observed, 34% had no visits with inertia, 47% had 1-10% of their visits classified as inertial, and most of the rest (16%) had 11-30%. Only 2% had a rate over 30%. However, it is worth noting that 18% of these physicians had 5 or fewer visits, which is a small sample from which to draw any conclusions.

Limitations

Several limitations of this research should be noted. First, the correlations observed are not necessarily causal in nature, since they could reflect confounding by other unobserved variables. However, to the extent that these other variables are time-invariant within patient, they are controlled for by the patient fixed effects. Second, the data include little information about the physicians who provided treatment, such as their training, years of experience, or the clinics where they practice. Also, the data do not report on the nature of any communication between patients and physicians about prescribing. Third, our measure of inertia assumes an expectation of adjustment at the first visit after an indication appears, but this may not be realistic, for reasons reviewed in the Discussion, below. Finally, the data come from a study encouraging use of guideline care, occurring in academic medical settings, features which are not representative of all treatment of bipolar disorder. However, one could speculate that the extent and impact of clinical inertia may in fact be higher in other settings, implying that these estimates would be conservative.

4. Discussion

This study finds widespread prevalence of the indications that we had identified as being suggestive of a need for medication adjustment, with at least one indication being found at 36% of visits. In turn, medication adjustment occurred at 69% of visits, and among those adjustments, changes in dosage were twice as common as changes in medications. Few other studies have measured the prevalence of indications and of adjustments. During another

pragmatic trial for bipolar disorder, Nierenberg et al identified necessary clinical adjustments as those undertaken to respond to clinical need, and found that there were between 0.5 and 1.0 such adjustments per patient month, over a 24-week period.(Nierenberg et al. 2013) In an observational study using insurance claims, McCombs et al found that many more regimen changes involved augmentation than mere switching (discontinuation of original medication within 60 days).(McCombs, Ganapathy and Zolfaghari 2011) However, given their different measures and definitions, it is not straightforward to compare these studies' findings to ours.

Turning to the intersection of indication and adjustment, the results are suggestive of some degree of clinical inertia, with no medication adjustment occurring in 19% of visits where adjustment appears to be indicated. This is a relatively low proportion. However, there are probably millions of individuals receiving treatment for bipolar disorder in the US alone, given a nationwide 12-month prevalence of bipolar I disorder estimated at 0.6%, (Merikangas et al. 2007) and given that one third of those with bipolar I receive any specialty mental health treatment in a year.(Wang et al. 2005) Nineteen percent of that population would represent a sizeable number of patients undergoing distress which could potentially have been relieved by a more active approach to medication management.

However, one must also consider possible alternative explanations for lack of medication adjustments, other than clinical inertia. First, physicians may be taking note of potential indications such as worsening side effects, but deliberately following a policy of 'watchful waiting', which may result in adjustment at a later visit. This could reflect concern about how the patient would handle the disruption associated with a medication switch, or alternatively, the physician may be waiting for results of blood tests needed for decision-making.(Musenga et al. 2009) If this were the case, it would not be correct to label such behavior as clinical inertia. A second possible reason for non-adjustment at a visit where it appears indicated could be that the physician realizes the patient is not adhering to the current regimen. In that case, a logical response might well be to encourage greater adherence rather than changing the regimen. This explanation appears less relevant to the current study, where self-reported adherence was high, and patients reporting non-adherence were no less likely than others to receive a medication adjustment. Finally, the patient may not want an adjustment despite the indication, and the physician may accommodate that preference.

In a wider context, even if all the visits in question were classified as clinical inertia, the 19% rate found here is much lower than the 87% rate of clinical inertia found by Okonofua et al in their study of medication adjustments for hypertensive patients with elevated blood pressure.(Okonofua et al. 2006) It is also considerably lower than the finding for depression treatment reported by Henke et al, that among observation periods that ended with less than a full response, one third did not result in a recommendation for treatment adjustment. (Henke et al. 2009) In any case, it may not be straightforward to compare clinical inertia rates across different diseases. For various other chronic diseases, physicians can observe clinical features which do not trouble the patient as symptoms – and researchers can assess the physicians' response to those clinical features. For bipolar disorder, by contrast, physicians often have to place some (although not complete) reliance on symptoms and side-

effects reported by the patient herself. As a result, treatment may be more dependent for BD than for many other diseases on the quality of physician-patient communication, and more vulnerable to clinical inertia when communication is poor. However, these features are also characteristic of depression care, and therefore less likely to explain the difference in inertia rates between bipolar disorder and depression. Differences in the populations studied and measurement approaches may play a role.

It is interesting that various socio-demographic characteristics are significantly associated with receipt of a medication adjustment when indicated. Those less likely to receive an adjustment included patients who were male, aged greater than 45, non-white race, divorced/widowed/separated, or received no psychosocial intervention. These differences could relate to poorer quality of physician-patient communication for some groups, differing patient preferences, or other issues. This could be something to explore in future studies.

It appears noteworthy that having at least one indication for adjustment increases the odds of adjustment at that visit by only 12%, after controlling for patient fixed effects and several clinical variables. One might have expected this effect to be larger, since the indication measures used here are derived from items that the physician herself observed and recorded. On the other hand, these models included current clinical status in addition to indications for adjustment. It is possible that physicians are paying more attention to the current clinical status and less to what has changed since the last visit, a finding that was also reported in Henke et al's study of adjustments in depression treatment.(Henke et al. 2009) This contrasts with an earlier finding from the same dataset that clinical status was not a strong predictor of the choice among medication classes for a new treatment episode.(Hodgkin et al. 2011) These two findings are compatible if most adjustments involve dose changes or switching drugs within the same class.

More generally, it would help to achieve better understanding of physician decision-making around medication adjustment. Future work on this topic would benefit most from matching detailed data on medication choices and patient presentation with surveys of physicians about their decision-making for those same patients. Future research may also employ more refined measures of indication and adjustment, if it uses data where these are feasible.

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HIGHLIGHTS

- A study of patients treated for bipolar disorder in a practical clinical trial
- At 36% of visits there was at least 1 indication for a medication adjustment
- No adjustment occurred for 19% of visits where one appeared indicated
- This suggests some clinical inertia, although other explanations could apply.

Table 1

Baseline characteristics of the study sample

	Percent	Standard Error
Gender:		
Female	55.6%	1.2%
Male	44.4%	1.2%
Age group:		
15-25	15.8%	0.9%
26-35	22.5%	1.0%
36-45	25.8%	1.0%
46-55	22.7%	1.0%
56 or older	13.1%	0.8%
Race:		
White	90.1%	0.7%
Other	9.9%	0.7%
Latino ethnicity:		
Yes	5.5%	0.5%
No	94.6%	0.5%
Marital status:		
Married	36.0%	1.1%
Never married	37.2%	1.1%
Other	26.8%	1.0%
Education:		
Completed college	53.7%	1.2%
Some college	26.7%	1.0%
High school or less	19.6%	0.9%
Employment status		
Employed full-time	29.6%	1.2%
Employed part-time	13.8%	0.8%
Disabled	18.8%	0.9%
Other ^a	37.8%	1.1%
Annual personal income from earnings		
Less than \$10,000	52.5%	1.2%
\$10,000-29,999	22.6%	1.0%
\$30,000 or more	24.9%	1.0%
Sample size (patients)	1,815	-

^a‘Other’ employment status includes retired, unemployed, homemaker, etc.

Table 2

Prevalence of indications and adjustments

	Number of visits	Percent
Total visits	23,406	100.0%
Type of indication for adjustment: ^a		
Nonresponse to treatment	2,732	11.7%
Roughening	635	2.7%
Side effects	2,402	10.3%
New acute episode	3,207	13.7%
Psychotic symptom increase	1,374	5.9%
Tremor	334	1.4%
Extrapyramidal symptoms	52	0.2%
Any of the above indications	8,474	36.2%
Type of adjustment:		
Add new medication (only)	3,602	15.4%
Drop a medication (only)	3,147	13.4%
Add and drop medications	2,169	9.3%
Dosage adjustment (only)	7,236	30.9%
Any adjustment	16,154	69.0%
Among visits with any indication for adjustment:		
Adjustment occurred	6,882	81.2%
No adjustment ('inertia')	1,592	18.8%
Patient-level measures:		
Patient had any visits with inertia:		
Yes	688	37.9%
No	1,127	62.1%
Total patients	1,815	100%
	Mean	Standard deviation
Clinical Global Impression score (at baseline)	2.9	1.2
Study visits per patient	13.9	12.3
Days since previous visit	40.8	43.8

^aIndications are not mutually exclusive.

Table 3

Association of medication adjustment with selected patient characteristics

	<u>Among visits with indication for adjustment, % receiving:</u>	
	Adjustment	No Adjustment
Gender:	**	
Female	82.2	17.8
Male	79.6	20.4
Age group:	***	
15-25	83.9	16.1
26-35	84.5	15.5
36-45	80.8	19.2
46-55	79.1	20.9
56 or older	78.1	21.9
Race:	***	
White	81.8	18.2
Other	74.7	25.3
Marital status:	**	
Married	82.7	17.3
Never married	80.9	19.1
Divorced/separated/widowed	79.4	20.6
Any psychosocial interventions	*	
Yes	82.6	17.4
No	80.4	19.6
Clinical Global Impression (mean)	2.96	2.34
Medication adherence (mean) ^a	95.0%	95.0%
Days since previous visit (mean)	37.94	39.69
Number of visits	6882	1592

Note: Statistical significance of differences is denoted by:

All significance levels were ascertained using chi-squared test, except for CGI, where a t-test was used.

p<.0001.**
p<.01.*
p<.05.^aMissing for 1418 visits.

Table 4

Predictors of medication adjustment

	Model 1		Model 2	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Any indication for adjustment	1.125 *	1.015, 1.246	-	-
Specific indications:				
Nonresponse to treatment	-	-	0.849 *	0.726, 0.995
Side effects	-	-	1.211 **	1.052, 1.393
New acute episode	-	-	1.021	0.839, 1.243
Psychotic symptom increase	-	-	1.273 **	1.078, 1.504
Clinical Global Impression score (1-7)	1.227 ***	1.175, 1.282	1.264 ***	1.211, 1.319
Clinical status (reference=Recovered)				
Depression	2.256 ***	1.910, 2.665	2.158 ***	1.764, 2.640
Mania	3.078 ***	2.136, 4.435	2.911 ***	1.970, 4.300
Mixed	2.760 ***	1.812, 4.204	2.536 ***	1.865, 4.575
Hypomania	2.292 ***	1.692, 3.105	2.217 ***	1.578, 3.116
Continued symptomatic	1.846 ***	1.594, 2.139	1.899 ***	1.617, 2.230
Roughening	1.911 ***	1.611, 2.267	1.688 ***	1.357, 2.099
Recovering	1.226 ***	1.114, 1.348	1.139 ***	1.038, 1.249
Psychosocial interventions (n in past month)	0.993	0.972, 1.014	0.993	0.972, 1.015
Days since previous visit / 100	0.961	0.882, 1.047	0.958	0.879, 1.043
Number of observations (visits)	23,406		23,406	

Note: results are from multivariable logistic regression models with fixed patient effects.

For definitions of each indication, see Measures section.

p<.0001.

**
p<.01.

*
p<.05.