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Complex Polypharmacy in Bipolar Disorder: Side effect burden, adherence, and response predictors

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Abstract

Background: Complex polypharmacy (CP) is common in bipolar disorder (BD). We assessed the associations between CP, adherence, and side effect burden, and patient traits associated with clinical improvement in relationship to CP.

Methods: We conducted a secondary analysis of 482 adult BD participants in the Bipolar CHOICE trial. We examined the associations between CP (use of ≥3 BD medications) and non-adherence (missing >30% of BD medication doses in the last 30 days) and side effect burden (Frequency, Intensity and Burden of Side Effects Rating scale) using multivariate models with patient random effects. We used logistic regression to assess the patient traits associated with remission among those with majority CP use (Clinical Global Impression-Severity for BD score ≤2 for 8+ weeks).

Results: 43% of patients had any CP and 25% had CP for the majority of the study. CP was associated with non-adherence (OR=2.51, 95% CI [1.81, 3.50]), but not worse side effect burden. Among those with CP, 16% achieved remission; those with non-adherence, comorbid social or generalized anxiety disorder, or BD I vs. II were less likely to achieve remission among those with CP.

Limitations: There could be unmeasured confounding between use of CP and side effect burden or adherence. Adherence was measured by self-report, which could be subject to reporting error.

Conclusions: BD patients with CP were less likely to adhere to therapy, and those with worse adherence to CP were less likely to clinically respond. Clinicians should assess medication adherence prior to adding another agent to medication regimens.

Keywords

complex polypharmacy; polypharmacy; bipolar disorder; medication adherence

INTRODUCTION

Bipolar disorder is a chronic and recurrent illness associated with disability, poor functional outcomes, and high levels of health care use and spending. The use of combination drug therapies, such as two mood stabilizers or a mood stabilizer plus an atypical antipsychotic drug, has become standard care in the treatment of bipolar disorder.[1–3] Numerous studies further demonstrate that complex polypharmacy (CP), that includes 3 or more medications for the treatment of bipolar disorder, has increased over time across a range of populations and settings.[4] Moreover, compared with other mental illnesses, bipolar disorder is more likely to be accompanied by co-occurring anxiety, substance use, and other medical conditions, which can add substantially to treatment complexity and patients' total drug burdens.[5,6]

Despite the prevalence of CP in bipolar disorder, evidence on its effect is mixed. Some trials find that certain two-drug combinations are more efficacious than monotherapy,[7–17] and a

single trial found the addition of topiramate to three-drug combination therapy in bipolar disorder improved obsessive compulsive symptoms. [18] Other studies, however, find limited benefit of certain adjunctive combination therapies in bipolar disorder.[19–23] While case reports suggest that some patients benefit from complex drug treatment, it is also common for patient to not improve, yet remain on CP.[24]

There could be risks associated with CP, such as increasing the probability of experiencing side effects, including weight gain, sedation, poor motor coordination, or adverse drug interactions,[25,26] all of which could reduce adherence.[27] Increased complexity and cost of medication management for patients could also adversely affect adherence for patients with CP.[28] However, the evidence on the direct association between complex regimens and adherence is limited.[29–31] Minimizing drug burdens for patients who do not benefit clinically from complex regimens could reduce unintended adverse effects. Prior studies have found that CP is more common among patients with greater depressive symptoms, prior suicide attempts, and comorbid anxiety. However, there is little information about the traits of patients that are more likely to positively respond to CP. Better targeting of CP to patients most likely to benefit could improve outcomes, while mitigating the potential unintended consequences of CP among those less likely to respond.

We used longitudinal data from a large comparative effectiveness trial to investigate how CP use is associated with side effect burden and adherence. We also examined the patient sociodemographic and clinical characteristics associated with response to CP.

METHODS

Study data and participants

We used data from a multi-center, randomized, open-label, rater-blinded, comparative effectiveness trial. The CHOICE trial (Clinical Health Outcomes Initiative in Comparative Effectiveness) compared lithium plus adjunctive personalized medication therapy (APT) vs. quetiapine plus APT.[32] (*Comparative Effectiveness Study for Bipolar Disorder*, https://clinicaltrials.gov/ct2/show/NCT01331304. Clinical Trials Registration Number: .) APT medications were allowed to change in both study groups over the course of the six-month study based on the clinical needs of the participants.[33] The trials were open-label, but outcome assessment was blind to randomization status.

The study included patients who met DSM-IV criteria for bipolar disorder I or II who were able to give written informed consent, were age 18 years or older and younger than 69 years old, were at least mildly ill at the time of enrollment (i.e., CGI-BP-S score ≥3), and willing to be randomized to each study arm. The study excluded those in crisis at the time of enrollment who required inpatient hospitalization, those with a contraindication to lithium or quetiapine (e.g., prior hypersensitivity, severe cardiovascular or renal disease), those pregnant or breastfeeding, those with acute or recent (past 30 days) drug or alcohol dependence, and those with a history of non-response to lithium at a serum level ≥1.0 mEq/L for ≥8 weeks, or quetiapine at ≥600mg for ≥8 weeks. A total of 692 patients were consented/screened for the study, out of which 482 participants were randomized to a study arm and followed for up to 9 study visits over six months (at weeks 0, 2, 4, 6, 8, 12, 16, 20 and 24)

over the time period from September 2010 through September 2013. Additional details on the CHOICE trial are available elsewhere.[32]

Complex Polypharmacy

We defined the key explanatory variable, CP use, as concurrently taking ≥3 drugs among the following bipolar disorder (BD) drug classes for the majority of study visits: lithium, antipsychotics, antidepressants, anticonvulsants, and anxiolytics. Data on drug use were captured at each study visit using the Medication Recommendation Tracking Form, which was developed by the Bipolar Trials Network to comprehensively capture physician prescribing behavior and clinical decision-making.[34]

Adherence and side effect burden

Self-reported adherence was measured using a validated instrument, the revised Tablets Routine Questionnaire (TRQ), which was assessed at each visit.[35] We defined non-adherence as reporting missing >30% of any prescribed BD treatment in the past month, which was developed as a clinically relevant measure of poor adherence in bipolar disorder.[36,37] In sensitivity analyses we also examined the association between CP and reports of missing any doses of BD drugs in the last 30 days.

We measured side effect burden using the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) Scale, as assessed for the bipolar drug regimen as a whole.[32,38] The FIBSER is a three-item self-rated measure of side effect burden that was collected at each visit. It assesses the frequency of side effects within the past week (none, 10%, 25%, 50%, 75%, 90%, 100% of the time), the side effect intensity (none, trivial, mild, moderate, marked, severe, intolerable), and the degree of interference with day-to-day functions (none, minimal, mild, moderate, marked, severe, unable to function); all sub-item scores range from 0–6. The total FIBSER score is the sum of each sub-item and ranges from 0–18, with lower numbers indicating lower side effect burden.[38]

Clinical remission

The Clinical Global Impression-Bipolar Severity (CGI-BP-S) score is a modified version of the CGI designed specifically for use in assessing global illness severity and change in patients with bipolar disorder. The scale was clinician-rated and assessed at each study visit. Among patients with a majority of visits with CP, we defined clinically meaningful response to treatment as a change of at least one point on the CGI-BP-S between the first visit with CP use and the final score of the study, or achieving remission, defined as a CGI-BP-S score ≤2 for 8 or more weeks.[39] We present findings using remission as the main outcome variable in analyses of patient traits associated with clinical response to CP, as well as sensitivity analyses examining the traits associated with clinical improvement.

Statistical Analysis

In multivariate analyses of adherence and side effect burden, the unit of analysis was the patient-visit, with each patient contributing multiple observations with time-varying measures of symptom severity, BD drug use, and outcomes. To assess the association between CP and adherence we used logistic regression models with patient random effects,

to account for clustering within patients across repeated measures. These models predict patient reports of missing at least 30% or more BD medication doses in the last 30 days at each visit, using a measure of CP vs non-CP recorded at the prior visit (to correspond with the time period of adherence measurement), adjusting for other patient demographic and clinical traits.

To assess the association between CP and side effect burden, we used multivariate linear regression models with patient random effects and similarly lagged measure of CP to predict current side effect burden. We assessed overall side effect burden (total FIBSER score) and each sub-category: frequency, intensity, and functioning. We also used logistic regression models to assess the likelihood of having a total FIBSER score ≥9 or category scores ≥3 to assess the likelihood of reporting a higher category of FIBSER score overall and for each sub-item. In sensitivity analyses, we assessed the association between side effect burden and non-adherence, as well as included side effect burden in the adherence model to assess whether it mediated the relationship between CP and adherence.

We used logistic regression models to examine the patient traits associated with clinical response among those with CP use for the majority of the study period. To address potential confounding by indication, all models adjusted for a wide range of sociodemographic and clinical characteristics to account for potential patient-level differences, such as disease severity and social determinants of health, that are likely associated with medication management and use of CP. Sociodemographic characteristics, measured at baseline, include age category (<30, 31–45, or 46+), sex, race (white, black, other), education (having a high school diploma vs. General Equivalency Diploma (GED) or less schooling), and employment status (employed or student vs. retired, on disability, or other). We also adjusted for baseline measures of clinical severity, including having a diagnosis of Bipolar I vs. II, a history of psychiatric hospitalization, a history of suicide attempt, and having a comorbid diagnosis of generalized anxiety disorder or social phobia/social anxiety, as well as a time-changing measures of symptom severity (the Bipolar Inventory of Symptoms Scale (BISS) depression and mania score). Lastly, we adjusted for the patient's randomization arm (lithium+APT vs. quetiapine+APT). We conducted a parallel analysis to examine traits associated with clinical response among those without CP to assess whether there were differences between those with and without CP.

RESULTS

The mean age of the study population was 38.9 years old, 68% had bipolar I, the mean baseline CGI-BP-S was 4.5, and the mean number of bipolar medications was 2.0. Overall, 43% had any CP over the study period (N=209/482, data not shown in table); 25% had CP for more than half of study visits (N=122/482, Table 1). Those with a majority of visits with vs. without CP used an average of 3.4 BD medications over the study compared with 1.5; they were also less likely to be employed or a student (34% vs. 49%), more likely to have comorbid anxiety (48% vs. 37%), were older (mean age 41.3 vs. 38.1 years old), and had higher baseline BISS depression scores (39.8 vs. 36.7, all p-values<0.05). BD severity as reflected by CGI-BP-S scores improved for most trial participants over the course of the

study: 16% of those with a majority of visits with CP vs. 24% of those without CP experienced remission ($p<0.05$).

CP, side effect burden, and adherence

We examined side effect burden and adherence at each patient-visit for those with vs. without documented CP at the prior visit. In unadjusted analyses, CP was associated with worse side effect burden, on average, with higher mean total FIBSER scores of 6.3 vs. 5.3, and higher mean scores for each of the subscales: frequency (2.3 vs. 2.0), intensity (2.2 vs. 1.9), and burden (1.8 vs. 1.5, $p<0.05$ for all comparisons, Table 2). Similarly, a higher proportion of patient-visits with vs. without CP reported higher scores: i.e., total score of nine or higher (39% vs. 28%) or subscores of three or higher: frequency (45% vs. 35% experiencing side effects for 50% or more of the last week); intensity (48% vs. 38% reported experiencing moderate intensity side effects); and burden (34% vs. 25% reported experiencing moderate impairment from side effects, p-value<0.05 for all comparisons, Table 2). In multivariate analyses, differences in mean scores and the likelihood of reporting higher scores were not significantly different for those with vs. without CP (e.g., adjusted difference in total FIBSER score= 0.05, 95% CI [−0.41,0.52]; OR=1.32, 95% CI [0.96, 1.82], respectively).

Overall, participants reported missing at least 30% of BD medication doses in the last 30 days at 12% of study visits. Non-adherence was more common among those with vs. without CP recorded at the prior visit (16% vs. 10%), including in multivariate analyses (OR=2.5, 95% CI [1.8, 3.5], Table 2). Findings were similar in sensitivity analyses examining the association between CP and reports of missing any doses of BD drugs in the last 30 days (Supplementary Table 1).

In sensitivity analyses, we also examined the relationship between side effect burden and adherence and found mean FIBSER scores were higher among those who missed >30% of BD medication doses in the last 30 days vs. those who did not (6.1 vs. 5.4, $p<0.05$). In multivariate analyses, those who reported side effect burden in the highest category (i.e., scores>12) had greater odds of non-adherence (OR=1.8, 95% CI: 1.3–2.7) compared with those in the lowest category (scores≤6); however, the relationship between CP and non-adherence did not change in analyses that included side effect burden in the model.

Traits associated with clinical remission

Among those with a majority of visits with CP, those with bipolar disorder II (OR=4.03, 95% CI [1.01, 16.14] vs. bipolar I), were more likely to experience clinical remission (Table 3). Those with comorbid social or generalized anxiety disorder (OR=0.23, 95% CI [0.06, 0.93]) and those who were non-adherent to their CP regimen (OR=0.18, 95% CI [0.05, 0.69]) were less likely to respond. Sensitivity analyses examining the traits associated with clinical improvement were similar to analyses examining remission (Supplementary Table 2).

In parallel analyses among patients without CP for a majority of visits, we found that comorbid anxiety disorder was also negatively associated with likelihood of clinical

remission, but did not find significant associations between bipolar disorder II or non-adherence with remission (for full model results, see Supplementary Table 3).

DISCUSSION

In this study of trial participants with bipolar I or II disorder, we found that CP was common, with one-quarter of patients having CP for the majority of the study, and nearly half having CP at any point during the study. Similar to other studies, we found that CP use was more common among BD patients with worse depression severity at baseline, comorbid anxiety, and who were not currently employed or students.[2,40,41] As expected, these associations likely reflect the more frequent use of CP for patients with greater clinical complexity or insufficient response to more simple drug regimens.

Patients reported that their BD medication regimens had side effects that resulted in at least moderate impairment with day-to-day functioning at over one-quarter of visits, and this was more frequent among those with vs. without CP. These trends were similar for the other domains of side effect burden measured, i.e., frequency and intensity. Contrary to our *a priori* hypotheses, however, CP was not a significant predictor of worse side effect burden after adjusting for other patient traits, including socio-demographic characteristics and measures of disease and symptom severity. Nevertheless, we found that those with CP had more than twice the odds of reporting that they missed 30% or more of any bipolar medication in the past 30 days compared to those without CP.

The lack of association between CP and overall side effect burden, but worse adherence could be related to our measure of side effect burden. This study did not systematically collect information on the types of side effects that patients experienced at each study visit, which could be more informative about patients' likelihood to adhere to their treatment regimen compared with a general summary score. For example, a separate study identified that among participants with bipolar disorder, weight gain and lethargy were the side effects most commonly cited as reasons for discontinuing medications.[42] Such side effects could be more common among those with vs. without CP. Moreover, the reasons for non-adherence are multifaceted and are not likely to be related to side effect burden alone. For example, other studies have found that BD patients are also more likely to discontinue medications if they do not perceive them to be effective or clinically necessary, if they have trouble paying for medications, or if they have greater difficulties with their medication routines.[27,28,37] These factors are likely to be linked with CP.

We found that 16% of BD patients who used CP for the majority of study visits achieved remission compared with 24% of those without CP. The lower rates of remission among those with CP is not surprising given CP is more common among more complex and refractory cases. However, there is limited information on the clinical correlates of patients who receive CP who are more likely to respond, which could help better target CP to patients who are most likely to benefit. After adjusting for adherence, patients with BD I vs. II or with comorbid anxiety were significantly less likely to achieve remission on CP. Further research is needed to assess the effectiveness of CP and specific drug combinations across subgroups of BD patients.

As expected, those who were non-adherent to their complex BD regimens were also less likely to achieve remission. Although this study did not examine this directly, non-adherent patients could be more likely to receive CP if clinicians add medications to address clinical non-response. In either case, it is important to evaluate adherence in relation to changes in BD drug regimens, especially as they become more complex.

Our study has limitations to note. First, this trial was not designed to assess the causal effects of CP on the outcomes of interest, and there could be unmeasured confounding. However, this study collected detailed and time-changing measures of symptom severity, which we adjusted for in our models, as well as other clinical indicators, such as history of psychiatric hospitalization and suicide attempt, to address potential confounding by indication. Further, we had detailed information on individuals' sociodemographic characteristics and our models adjusted for random-effects at the patient level to address clustering within-patient and identify off both cross-sectional and longitudinal (within-person) variation in CP use.

We used a self-reported measure of adherence, which could be subject to reporting error. Indeed, the levels of adherence in this trial population were higher than other published reports, such as those examining medication possession ratios using claims data in insured samples of patients with BP.[43] This could reflect potential over-reporting of adherence in our study or differences in the study populations. If the levels of mis-reporting are similar across those with and without CP, this would not bias our estimates. Moreover, studies that rely on drug refill data to determine adherence could also be subject to error because it is not possible to determine when patients have been prescribed medications but never fill them using dispensing data (which would undercount primary non-adherence) or to differentiate non-adherence from physicians' decisions to reduce the number of drugs in the regimen (which could overstate non-adherence). In contrast, the CHOICE study used a novel medication tracking form to capture physician prescribing behavior and clinical decision making with respect to prescription drug choices, which we used to determine the size of patients' drug regimens at each time point. The focus on a clinical trial population could also be less generalizable to the general population of patients with bipolar disorder, although CHOICE strove to maximize generalizability by using the broadest inclusion criteria possible and allowing clinicians to prescribe additional drugs in the regimen, consistent with real-world clinical practice.[33] Given the sample size and study setting, we also did not attempt to differentiate between different types of CP based on clinical appropriateness. Lastly, the trial included six-months of follow-up, which could limit our ability to detect changes in longer-term outcomes.

In conclusion, we found CP was significantly associated with nonadherence to bipolar medications, and among those with CP, those who were non-adherent were less likely to achieve remission. Among those using CP, we found that after adjusting for non-adherence, those with comorbid anxiety and BD I were less likely to achieve remission. Better targeting CP to patients most likely to benefit could improve clinical outcomes in BP, while minimizing the potential adverse effects of CP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Use of 3+ drugs in BD associated with poorer adherence to medications
- Among patients with CP, non-adherent patients less likely to achieve remission
- Clinicians should address adherence before adding medication to a treatment regimen

Table 1.

Characteristics of study population for those with vs. without complex polypharmacy (CP) for the majority of study

	All (N=482) Col %	Non-CP (N=360) Col %	CP[a] (N=122) Col %	P-value
Age: <25	14%	16%	8%	0.055
25–35	27%	28%	23%	
35–45	23%	20%	30%	
45–55	26%	26%	27%	
55+	10%	10%	12%	
Sex: Female	59%	58%	62%	0.353
Race: White	72%	70%	80%	0.073
Black	21%	24%	14%	
Other	7%	7%	7%	
Education: High School/GED or less	25%	27%	20%	0.157
Employment: Employed or student[b]	45%	49%	34%	0.005*
Current diagnosis: BD I (vs. BD II)	68%	66%	74%	0.131
Social or generalized anxiety disorder	39%	37%	48%	0.034*
Lifetime history of substance use disorder	45%	44%	45%	0.903
Lifetime history of psychiatric hospitalization	47%	45%	53%	0.120
Lifetime history of suicide attempt	39%	38%	41%	0.561
Randomized to lithium + APT	50%	48%	56%	0.129
Quetiapine + APT	50%	52%	44%	
Improvement in CGI-BP-S score ≥1	77%	79%	70%	0.055
Remission (CGI-BP-S score ≤2 for 8+ weeks)	22%	24%	16%	0.042
	Mean (SD)	Mean (SD)	Mean (SD)	
Age	38.9 (12.1)	38.1 (12.3)	41.3 (11.4)	0.010*
Baseline CGI-BP-S (overall, out of 7)	4.5 (0.9)	4.5 (0.9)	4.6 (0.8)	0.125
Baseline BISS depression score (0/88)	37.5 (14.0)	36.7 (14.2)	39.8 (13.5)	0.035*
Baseline BISS mania score (0/92)	19.1 (12.2)	19.6 (12.6)	17.7 (10.7)	0.137
Mean number of BD medications	2.0 (1.0)	1.5 (0.5)	3.4 (0.7)	<.001*

*p<0.05 for unadjusted difference between CP and non-CP in two-sided test statistic.

[a]Complex polypharmacy was defined as being prescribed ≥3 bipolar drugs for greater than 50% of study visits.

[b]Employment is defined as employed or student status, while unemployed includes those who are retired, on disability, and other.

Abbreviations: CP = Complex Polypharmacy, BD = Bipolar Disorder, APT = Adjunctive Personalized Therapy, CGI-BP-S = Clinical Global Impressions – Bipolar Scale

Table 2.

Association between CP use and side effect burden and adherence

Side effect burden (FIBSER)[a]	All Unadj mean	Non-CP Unadj mean	CP Unadj mean	Adjusted diff (95% CI):[c] CP vs. non-CP
Total Score (0/18)	5.6 (4.9)	5.3 (4.8)	6.3 (5.2)*	0.05 [−0.41, 0.52]
Frequency (0/6)	2.0 (1.9)	2.0 (1.9)	2.3 (2.0)*	0.06 [−0.12, 0.25]
Intensity (0/6)	2.0 (1.7)	1.9 (1.7)	2.2 (1.8)*	−0.03 [−0.19, 0.14]
Burden (0/6)	1.5 (1.6)	1.5 (1.5)	1.8 (1.7)*	0.05 [−0.11, 0.20]
Side effect burden (FIBSER)[a]	**All %**	**Non-CP %**	**CP %**	**Adjusted OR (95% CI):[c] CP vs. non-CP**
Total Score>=9	31%	28%	39%*	1.32 [0.96, 1.82]
Frequency≥3 (≥50% of the time)	38%	35%	45%*	1.17 [0.86, 1.60]
Intensity≥3 (≥moderate)	41%	38%	48%*	1.08 [0.79, 1.46]
Burden≥3 (≥moderate)	28%	25%	34%*	1.21 [0.89, 1.63]
Non-adherence (TRQ)[b]	**All Unadj %**	**Non-CP Unadj %**	**CP Unadj %**	**Adjusted OR (95% CI):[c] CP vs. non-CP**
Missed ≥30% of BD medication doses in last 30 days	12%	10%	16%*	2.51 [1.81, 3.50]*

*p<0.05 for unadjusted difference between CP and non-CP in two-sided test statistic.

[a]FIBSER=Frequency, Intensity, and Burden Side Effects Rating Scale. We used linear regression models to estimate adjusted differences in side effect burden scores (total FIBSER score and subscores) and logistic regression models to estimate differences in the odds of having moderate-severe side effect burden by CP.

[b]Non-adherence assessed using revised Tablets Routine Questionnaire (TRQ). We used a logistic regression model to estimate differences in the odds of being non-adherent to bipolar medications by CP.

[c]All models included patient-level random effects, adjusted for age group, sex, education (HS/GED or less v. more), race, employment, Bipolar I v II diagnosis, history of psychiatric hospitalization, past suicide attempt, BISS depression score, BISS mania score, and randomization group.

Table 3.

Characteristics associated with remission among those with majority use of CP[a]

	Unadj % with remission	OR	[95% CI]
Age group: <30 years	22%	1.27	[0.22, 7.25]
31–45 years old	15%	1.0	Reference
46+ years	15%	0.76	[0.17, 3.32]
Sex: Female	14%	1.15	[0.31, 4.32]
Male	20%	1.0	Reference
Race: Black	6%	0.24	[0.02, 2.87]
Other	13%	1.41	[0.10, 19.19]
White	19%	1.0	Reference
Education: <High School	8%	0.79	[0.12, 4.98]
High School or more	19%	1.0	Reference
Unemployed[b]	10%	0.31	[0.09, 1.13]
Employed	29%	1.0	Reference
Subtype: Bipolar II	31%	**4.03**	**[1.01, 16.14]**
Bipolar I	11%	1.0	Reference
Lifetime history of psych hospitalization	16%	1.12	[0.25, 5.09]
No history of hospitalization	18%	1.0	Reference
Lifetime history of suicide attempt	16%	2.04	[0.50, 8.41]
No history of suicide attempt	17%	1.0	Reference
Comorbid anxiety	7%	**0.23**	**[0.06, 0.93]**
No comorbid anxiety	25%	1.0	Reference
BISS depression score	NA[c]	0.65	[0.25, 1.67]
BISS mania score	NA[c]	0.32	[0.09, 1.10]
Randomized to: Lithium + APT	18%	1.40	[0.37, 5.32]
Quetiapine + APT	15%	1.0	Reference
Non-adherence: Missed >30% BD med doses anytime on CP	8%	**0.18**	**[0.05, 0.69]**
Did not miss >30% doses	27%	1.0	Reference

[a]Logistic regression model among study participants with CP use for majority of visits (N=122)

[b]Employment is defined as employed or student status, while unemployed includes those who are retired, on disability, and other.

[c]Mean baseline BISS depression scores were 32/92 for those achieving remission v. 41/92 for those not achieving remission. Mean baseline BISS mania scores were 11/92 for those achieving remission v. 19/92 for those not achieving remission.