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A 6-month, prospective, randomized controlled trial of customized adherence enhancement vs. bipolar-specific educational control in poorly-adherent individuals with bipolar disorder

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Abstract

Objective: Non-adherence in bipolar disorder (BD) ranges from 20–60%. Customized adherence enhancement (CAE) is a brief, BD-specific approach that targets individual adherence barriers. This prospective, 6-month, randomized controlled trial compared CAE vs. a rigorous BD-specific educational program (EDU) in poorly-adherent individuals on adherence, symptoms, and functional outcomes.

Methods: 184 participants with DSM-IV BD were randomized to CAE (N=92) or EDU (N=92). Primary outcome was adherence change measured by the Tablets Routine Questionnaire (TRQ) and BD symptoms measured by the Brief Psychiatric Rating Scale (BPRS). Other outcomes were the Global Assessment of Functioning (GAF), Montgomery Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS) and Clinical Global Impression (CGI). Assessments were conducted at screening, baseline, 10 weeks, 14 weeks and 6 months.

Results: The sample mean age was 47.4 years (SD 10.46), 68.5% female, 67.9% African-American. At screening individuals missed an average of 55.2% (SD= 28.22) of prescribed BD drugs within the past week and 48.0% (SD= 28.46) in the past month. Study attrition was <20%. At 6 months, individuals in CAE had significantly improved past week ($p=.001$) and past month ($p=.048$) TRQ vs. EDU. Past week TRQ remained significant after adjustment for multiple comparisons. There were no treatment arm differences on BPRS or other symptoms, possibly related to low symptom baseline. Baseline to 6-month change showed significantly higher GAF ($p=.036$) for CAE vs. EDU. While both groups used more mental health services, increase for CAE was significantly less vs. EDU ($p=.046$)

Conclusion: While both CAE and EDU were associated with improved outcomes, CAE had additional positive effects on adherence, functioning and mental health resource use compared to EDU.

Clinical Trials Registration: ClinicalTrials.gov identifier: NCT00183495

Keywords

adherence; compliance; bipolar disorder; manic-depressive disorder; mood stabilizer

Introduction:

Bipolar disorder (BD) is typically treated with medications including mood stabilizing medications and/or antipsychotic compounds.¹ As with other chronic conditions, sustaining medication adherence is problematic for many with BD, and non-adherence ranges from 20–60%.^{2–5}

Poor adherence in BD imposes substantial burden and is a strong predictor of recurrence, performing better than gender, type of BD, medication type, or lack of family support.⁶ In a study of over 1,300 BD individuals followed over 21 months, non-adherence was associated with poor recovery and high relapse.⁷ Other reports found substantially increased costs for individuals with poor vs. good adherence.^{8,9}

To improve adherence in BD, it is critical to address adherence barriers, which stem from a variety of factors including incomplete understanding of the role of medications in recovery, medication side effects and use of substances that impede adherence with prescribed treatments.¹⁰ Additionally, there is a need to support patients that: 1.) are at high risk for future non-adherence, 2.) may not have access to (or interest in) high-intensity, specialized care, and 3) are patient-focused, taking into account individual reasons for non-adherence.

Customized Adherence Enhancement (CAE) is a brief, practical BD-specific approach that identifies individual adherence barriers and then targets these areas for intervention using a flexibly-administered modular format.^{11, 12} This prospective, 6-month, randomized controlled trial of CAE vs. a rigorous control, BD-specific education (EDU) in poorly-adherent patients evaluated effects of the CAE vs. EDU on medication adherence, BD symptoms and functional status. We hypothesized that CAE would improve adherence, symptoms and functioning more than EDU.

Methods:

Overall study description:

This U.S. National Institute of Mental Health funded study enrolled 184 participants randomized to CAE (N=92) or EDU (N=92). Randomization was based on a randomized block design with random block sizes. Individuals had 5 face-to-face meetings and one phone call with the study interventionist over an 8-week time period. Primary study outcome was change from baseline to 6-month follow-up as measured by the Tablets Routine Questionnaire (TRQ) and global BD symptoms assessed with the Brief Psychiatric Rating

Scale (BPRS)¹³. Other key outcomes were functional status, and other BD symptoms including mania, and depression.

Participants and recruitment:

Study inclusion criteria were either type I or type II BD as confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID),¹⁴ BD for at least two years, prescribed at least one evidence-based BD medication (i.e. lithium, anticonvulsant, or antipsychotic) for at least six months and 20% non-adherent as assessed by the TRQ. Only individuals unable to participate in study procedures, unable to provide informed consent, and at high risk of harm to self or others were excluded. The study was approved by the local Institutional Review Board (IRB), was registered at ClinicalTrials.gov (identifier: NCT00183495) and completed from October, 2012 to July, 2017. Study participants were recruited from clinician referrals, IRB-approved advertisement, and via health system electronic health record search.

Interventions:

Both CAE and EDU are brief adjuncts to standard mental health treatment and RCT participants continued to receive treatment as usual with their regular mental health clinicians. The CAE and EDU interventionists were licensed social workers trained and supervised by a PhD-level psychologist.

CAE:

Drawn from the extant literature,^{15, 16} and iterative pilot work, CAE is a curriculum-driven intervention flexibly delivered as a series of up to four treatment modules whose inclusion is determined based upon an individual's reasons for non-adherence (adherence barriers) identified at baseline. Adherence barriers are evaluated with items from the Attitudes towards Mood Stabilizers Questionnaire (AMSQ) and Rating of Medication Influences (ROMI).^{17–21} The modules are Psychoeducation focused on the role of medication in BD management, Modified Motivational Enhancement Therapy (MET) to address non-adherence related to substance use, Communication with Providers to facilitate appropriate treatment expectations and optimize side effect management, and Medication Routines intended to incorporate medication-taking into lifestyle (see Appendix).

CAE participants had a core series of up to four in-person one-to-one sessions spaced about 1 week apart over a 4–6 week period, and one “booster” session four weeks after the core sessions. There was one follow-up phone call between core session completion and the booster session.

Bipolar-specific patient education (EDU):

Participants randomized to EDU also had five in-person sessions using the patient workbook from the NIMH-funded Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study and following the general educational format of the Collaborative Care “control” intervention in the STEP study.²² Like CAE, there were four core sessions followed by one “booster” session and one phone call between the core and

booster sessions. EDU addresses BD treatment broadly including diagnosis and management, and allows time for questions and therapist interaction as needed.

Intervention Fidelity:

To minimize potential contamination, two part-time social workers delivered CAE and two part-time social workers delivered EDU. Interventionists delivered only CAE or only EDU with no cross-coverage. All sessions were video-recorded and 25% of all sessions were randomly assessed on CAE module-specific tasks and EDU-specific tasks using a standardized 0–10 scale. The CAE MET module fidelity assessment included use of a modified Motivational Interviewing Treatment Integrity code (MITI).²³

Measures:

Medical burden was evaluated with the self-reported Charlson Comorbidity Index.²⁴ Assessments were conducted at screening, baseline, 10 weeks (after completion of CAE or EDU), 14 weeks and 6 month (24 week) follow-up. Adherence and global symptom measurement (BPRS) was conducted by a single blinded rater.

Treatment Adherence:

Adherence was assessed for each BD maintenance medication using the TRQ, which derives a proportion (%) of days with missed medication doses in the last week and last month. TRQ scores ranges from perfect adherence (0% missed) to missing all medication (100% missed). An average TRQ was calculated for individuals on more than one BD medication.²⁵ The Medication Event Monitoring System [(MEMS®) Aprex Corp., Fremont, Calif., USA] supplemented the TRQ. Participants were given the MEMS cap at screening and MEMS was assessed at baseline (screening and baseline approximately 1–2 weeks apart). MEMS data capture was very problematic in this sample, particularly beyond baseline, with high rates of failing to use or bring in MEMS caps (64% missing MEMS caps at 6-months). While TRQ scores were consistently correlated with symptom scores (worse adherence = worse symptoms), there was no consistent correlation between symptoms and available MEMS data.

BD Symptoms:

BD symptoms were measured with the BPRS,¹³ Montgomery Asberg Depression Rating Scale (MADRS),²⁶ Young Mania Rating Scale (YMRS)²⁷ and Clinical Global Impression – Bipolar Version (CGI-BD).²⁸

Functional Status:

Functional assessment was conducted with the Global Assessment of Functioning (GAF).²⁹

Additional evaluations:

Past 3-month self-reported health resource use using a standardized form was evaluated for mental health outpatient visits (psychiatrist, psychologist, other mental health providers), medical outpatient visits and hospitalizations. Medication attitudes were evaluated with the 10-item Drug Attitude Inventory (DAI).^{30, 31} Other attitudinal effects were assessed with the

General Self-Efficacy Scale (GSES)^{32, 33} and the Stigma for Mental Illness Scale (SMIS).³⁴ A supplemental qualitative evaluation of adherence barriers is described elsewhere.^{35, 36}

Data Analysis:

Our primary intent-to-treat analyses evaluated mixed effects using longitudinal analysis of TRQ for the primary adherence outcome and sample size was calculated based on preliminary data. While past week TRQ was felt to be the self-reported adherence behavior least likely to be impacted by recall bias, past month TRQ and MEMS were collected as a validation of recent adherence behaviors. We *a priori* noted that we would consider representing scores as binary outcomes, indicating whether or not an adherence threshold had been met (e.g. 80% adherent using established thresholds). We also noted that we would consider generalized linear mixed models for binary outcomes.

For TRQ and BD symptoms, mixed effects longitudinal analyses of TRQ and BPRS scores over the 4 time periods were conducted. Inferential focus was on treatment-by-time interactions, which indicate whether response trajectories differ by treatment. To adjust for multiple comparisons of the 3 adherence outcomes (past week TRQ, past month TRQ, MEMS), we set the significance threshold to .0167, so that simultaneous Type I error is at most 0.05. Secondly, GAF, YMRS, MADRS, and CGI were also modeled. A treatment variable was included indicating randomization to either CAE or EDU. We fit models with time period as a categorical variable, subject-level random intercepts, and an autoregressive correlation of order 1. To account for possible imbalances across groups and other sources of variation, gender, age, marital status and race were included in the mixed models. As for missing data, using mixed model methods, statistical parameter estimation is unbiased under the missing at random (MAR) assumption.

For TRQ outcomes, due to non-normality and values skewed towards either 0% or 100%, we considered longitudinal mixed models with binary outcomes using an established threshold (missing > 20% vs. 20%).¹⁰ Given the interest in longer-term outcomes, post-hoc mixed model analyses of differences from baseline to 6-month were specifically considered as well. Type I error level for secondary and post-hoc analyses was set at 0.05.

Results:

Overall sample description:

Figure 1 illustrates the study flow. Very shortly after randomization, it was identified that one individual in EDU did not fit study inclusion criteria. This individual was terminated from the study without participating in any intervention. Altogether, there were 74/184 (80.4%) individuals who had 6-month data; the overall attrition rate was thus < 20% and similar between arms.

Screening/baseline same:

Demographic and clinical variables are noted in Table 1. Treatment adherence at screening was poor with an average of 55.15% (SD= 28.22) of days with missing BD drug doses within the past week and 48.01% (SD= 28.46) within the past month. As demonstrated in

previous work²⁵ and likely due to the effect of adherence monitoring, there was a slight improvement in baseline TRQ, with past week TRQ of 44.2 (SD 31.2) and past month TRQ of 38.3 (SD 28.8). Mean sample age was 47.4 years (SD 10.46), 126 women (68.5%), 125 African-Americans (67.9%), 6 Hispanics (3.3%). Mean years of education was 12.7 (SD 2.37). The majority had Type 1 BD (N=136, 73.9%) with an average age of onset of 24 years (SD 12.3). Consistent with the negative effects of BD on occupational and personal role achievement, only a small minority were employed full time (N=7, 3.8%), with 53 (29.1%) living in a private home and 27 (14.7%) being married. Psychiatric comorbidity was common, with current alcohol disorder in 10.5 % (N=18), post-traumatic stress disorder in 40.5% (N=64) and generalized anxiety in 23.9% (N=42). The BPRS scores were relatively low at baseline with a mean of 34.60 (SD 7.88) although functional scores were also relatively low with a mean of 59.48 (SD 8.57).

As illustrated by Table 1, there were few baseline CAE vs. EDU variable differences. There was a significant but low magnitude difference in psychiatric medications prescribed in the CAE group (1.39, SD 0.61) vs. the EDU group (1.72, SD 0.92). TRQ scores were similar between arms. Most individuals had multiple adherence barriers including 173 (94%) in medication routines, 170 (92.4%) in the BD knowledge, 157 (85.3%) in clinician communications and 142 (77.2%) in the substance use as an impediment to adherence. There were 116 (63.0 %) individuals with all 4 barriers identified, 48 (26.1%) with 3 barriers identified, and 20 (10.9%) with 1 or 2 barriers identified.

Attendance and safety:

Overall, both CAE and EDU were well-attended. In CAE there were 44 (47.8%) individuals who attended all 5 sessions, 7 (7.6%) who attended 4 sessions, 9 (9.8%) who attended 3 sessions, 6 (6.5%) who attended 2 sessions, 16 (17.4%) who attended 1 session, and 10 (10.9%) who attended 0 sessions. In EDU there were 51 (55.4%) individuals who attended all 5 sessions, 2 (2.2%) who attended 4 sessions, 9 (9.8%) who attended 3 sessions, 12 (13.0%) who attended 2 sessions, 9 (9.8%) who attended 1 session and 9 (9.8%) who attended 0 sessions. There were no study-related adverse events as confirmed by an external data safety monitoring board.

Longitudinal Outcomes:

Table 2 notes changes in the outcomes of adherence, BD symptoms and functioning. At 6 months, individuals in CAE had significantly improved mean scores in past week ($p=.001$) and past month ($p=.048$) TRQ compared to EDU. Past week TRQ remained significant after adjustment for multiple comparisons. There were no differences between arms in BD symptoms as measured by BPRS, MADRS, YMRS or CGI. There were no differences in adherence outcomes comparing Type I vs. II BD or in relation to number of medications prescribed.

Because adherence improvement might result in eventual downstream changes in functioning or symptoms that lag behind adherence change, we also evaluated change from baseline compared to six-month adherence and functional outcomes. Baseline to 6-month differences for GAF and TRQ past month (dichotomized as adherent vs. non-adherent using

the 20% established cut-point), adjusted for by gender, age, marital status and race, were statistically significant ($p=.036$ and $p=.045$, respectively).

With respect to secondary outcomes, both treatment groups used more outpatient services compared to baseline. Possibly this was due to better recall during study participation. However, the increase in resource use was significantly less for CAE (mean change -0.12) vs. EDU (mean change 0.20) ($p=.046$). There was no difference in use of medical services ($p=.129$) or hospitalizations ($p=.984$), although use of these services was low at all time-points in both groups. There were no treatment group differences in drug attitudes, self-efficacy or stigma as measured with the DAI, GSES and SMIS respectively.

Adherence barrier burden:

Table 3 shows clinical characteristics that were different in groups with different numbers of adherence barriers. Individuals with more adherence barriers were more likely to have worse past adherence, be African-American, be less well-educated, have worse manic (YMRS) or global BD symptoms (BPRS). Gender was inconsistently associated with adherence barriers while functioning and depressive symptoms did not appear to be associated with number of adherence barriers.

Discussion:

In this sample of poorly-adherent patients with BD, both CAE and EDU were associated with improved outcomes; however, CAE had additional positive effects on adherence, functioning and mental health resource use compared to EDU. These findings are important given the high rates of poor adherence in BD, and established negative health outcomes associated with poor adherence. A literature review¹⁰ on BD adherence interventions suggested that psychoeducation, motivational interviewing, financial incentives, and cognitive behavioral treatment are all potentially promising; however, existing reports are generally small, uncontrolled and/or enrolled mostly adherent individuals. To the best of our knowledge, this trial is the first to both target poorly-adherent BD patients and use a randomized controlled design. Findings suggest that this brief, person-centered adherence promotion approach provides additional benefit compared to off-the-shelf BD interventions.

A unique study feature is the large proportion of African-Americans (approximately 2/3 of the sample), a group that is often under-represented in standard clinical trials. More adherence barriers and worse adherence were found in minorities and those with social disadvantages (i.e. less education). This sample had BD for an average of over 2 decades, with extensive comorbidity, high rates of unemployment and limited functional status.

In contrast to our original expectation, we did not find a difference in BD symptoms as measured with the BPRS across intervention arms. However, it is notable that baseline BD symptom severity was low with a mean BPRS score of 34.6, and overall improvement was very modest with an endpoint BPRS of just over 31 in both study arms. Leucht and colleagues³⁷ noted that the BPRS cut-off for “mildly ill” in patients with serious mental illness corresponds to a BPRS total score of at least 31, “moderately ill” to a BPRS score of at least 41, and “markedly ill” to a BPRS score of at least 53. In our previous CAE pilot, the

BPRS baseline mean was 43.6 (SD 12.0) vs. an endpoint mean of 36.1 (SD 12.4).¹¹ Perhaps floor effects with the BPRS made it difficult to observe changes. Other BD symptoms also did not separate by treatment arm, although as with BPRS, overall change in symptom severity was modest, and perhaps hard to evaluate due to floor effects.

Our baseline to 6-month follow-up evaluation suggests that CAE is associated with higher functional status compared to EDU. It seems reasonable to conclude that functioning improves in individuals who are able to achieve adherence, although being able to realize functional gains may lag behind adherence improvement and can take time to occur.³⁸ Because individuals were followed for only 6 months, it is not clear if functional improvement would continue or be sustained. Additionally, individuals who have lived with BD for many years may end up with few social supports to help in recovery. Perhaps CAE would have more robust effects if it were to be implemented in individuals early in the course of their illness who may have more social and occupational opportunities. While both CAE and EDU groups had increased mental health resource use during the course of the study, the increase was significantly less in CAE vs. EDU. Possibly resource use differences were related to relatively greater functional status in the CAE group vs. EDU.

This study had a number of limitations including the single-site setting, short duration, subjective adherence evaluation, inadequate use of MEMS to monitor adherence,^{10, 39} and the fact that clinical trial volunteers may not represent the full range of BD patients. Low baseline BD symptom levels may limit generalizability. In spite of these limitations, the brevity of CAE and the fact that it can be implemented by social workers make it a practical consideration for routine care and in practices where resources are limited.

In conclusion, CAE appears acceptable to individuals who are often not included in typical research studies (minorities, individuals with poor adherence). Compared to a rigorous and BD-focused educational control, CAE improves adherence and functional status. Individuals in CAE may have less use of additional supportive mental health services compared to those in EDU. While this RCT suggests that CAE can be implemented by social workers, it is likely that adherence promotion is ideally prioritized by all members of the treatment team, including prescribers. Studies that investigate how the CAE approach might be readily scaled-up and incorporated into typical clinic workflows are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Points:

- As with other chronic conditions, sustaining medication adherence is a problem for many individuals with BD, and non-adherence ranges from 20–60%
- Compared to a rigorous and BD-focused educational control, CAE improves adherence and functional status.
- While this RCT suggests that curriculum-driven CAE can be implemented by social workers, it is likely that adherence promotion is ideally prioritized by all members of the treatment team, including prescribers.

Figure 1:
CONSORT diagram of study flow

^aOne was withdrawn from the study by the PI immediately after randomization, prior to EDU intervention

Table 1:

Baseline demographics and clinical characteristics of 184 poorly-adherent individuals with bipolar disorder

	Total N= 184	EDU N= 92	CAE N= 92	Statistic[*]
Age Mean (SD)	47.40 (10.46)	45.91 (10.94)	48.88 (9.81)	t(182)= 1.94, p= .054
Gender N (%)				
Male	58 (31.5)	33 (35.9)	25 (27.2)	Fisher's exact: p=.267
Female	126 (68.5)	59 (64.1)	67 (72.8)	
Ethnicity N (%)				
African-American	116 (63.0)	53 (57.6)	63 (68.5)	
White	49 (26.6)	28 (30.4)	21 (22.8)	$\chi^2(3)= 5.04$, p= 0.17
Other	9 (4.9)	7 (7.6)	2 (2.2)	
Mixed	10 (5.4)	4 (4.3)	6 (6.5)	
Hispanic N (%)	6 (3.3)	4 (4.3)	2 (2.2)	Fisher's exact: p= .341
Education (years) Mean (SD)	12.67 (2.37)	12.69 (2.51)	12.65 (2.24)	t(180)= -0.11, p= .913
Marital Status (N= 183)		n= 91	n= 92	
Single, never married	98 (53.6)	47 (51.6)	51 (55.4)	
Married/co-habiting	27 (14.8)	15 (16.5)	12 (13.0)	
Separated/Divorced/Widowed	58 (31.7)	29 (31.9)	29 (31.5)	$\chi^2(3)= 1.50$, p= .683
Employment N (%), (N=182)		n= 91	n= 91	
Full time, homemaker, or full-time student	7 (3.8)	5 (5.5)	2 (2.2)	
Part time	12 (6.6)	5 (5.5)	7 (7.7)	$\chi^2(3)= 3.12$, p= .374
Unemployed or disabled	151 (83.0)	73 (80.2)	78 (85.7)	
Other	12 (6.6)	8 (8.8)	4 (4.4)	
BD diagnostic type		n= 89	n= 86	
N (%) (total N= 175)				
BD-I	136 (77.7)	68 (76.4)	68 (79.1)	Fisher's exact: p= .719
BD-II	39 (22.3)	21 (23.6)	18 (20.9)	
Age of BD onset (years)				
Mean (SD)	24.02 (12.34)	23.74 (12.40)	24.29 (12.23)	t(180)= 0.29, p= .769
Current Comorbid disorders N (%)				
Alcohol (N=171)	18 (10.5)	11 (12.6)	7 (8.3)	Fisher's exact: p= .457
PTSD ^a (N= 158)	64 (40.5)	32 (40.0)	32 (41.0)	$\chi^2(3)=1.10$, p= .777
OCD ^b (N=176)	25 (14.2)	9 (10.2)	16 (18.2)	$\chi^2(2)= 2.29$, p=.319
Generalized Anxiety (N= 176)	42 (23.9)	21 (23.9)	21 (23.9)	$\chi^2(2)= .000$, p= 1.00
No. of psychiatric meds				
Mean (SD)	1.55 (0.79)	1.72 (0.92)	1.39 (0.61)	t(158.34)= -2.84, p= .005
No. of non-psychiatric meds				
(Total N= 163) Mean (SD)	2.18 (1.97)	2.21 (1.96)	2.15 (1.99)	t(161)= -0.19, p= .849

	Total N= 184	EDU N= 92	CAE N= 92	Statistic[*]
Charlson Comorbidity Index Total Mean (SD)	0.34 (0.97)	0.24 (0.75)	0.43 (1.15)	t(156.05)= 1.37, p= .173
Breakdown of modules ^{**} , N (%)				
Psychoeducation	170 (92.4)	82 (89.1)	88 (95.7)	Fisher's exact: p= .163
Substance Abuse	142 (77.2)	74 (80.4)	68 (73.9)	Fisher's exact: p= .380
Improved Communication	157 (85.3)	77 (83.7)	80 (87.0)	Fisher's exact: p= .678
Medication Routines	173 (94.0)	87 (94.6)	86 (93.5)	Fisher's exact: p= 1.00
TRQ ^c for BD meds Mean (SD)				
Week	44.19 (31.16)	45.38 (31.14)	43.01 (31.30)	t(182)= -0.51, p= .608
Month	43.43 (28.82)	43.05 (30.28)	43.80 (27.43)	t(182)= 0.18, p= .861
BPRS ^d Mean (SD)	34.60 (7.88)	34.82 (7.82)	34.38 (7.67)	t(181)= 0.84, p= .707
MADRS ^e Mean (SD)	18.01 (8.73)	18.16 (8.60)	17.86 (8.90)	t(182)= -0.24, p= .814
YMRS ^f Mean (SD)	8.04 (5.06)	8.01 (5.36)	8.07 (4.76)	t(182)= 0.07, p= .942
GAF ^g Mean (SD)	59.48 (8.57)	59.53 (8.52)	59.43 (8.67)	t(182)= -.08, p= .939

^aPTSD: Post-Traumatic Stress Disorder;

^bOCD: Obsessive Compulsive Disorder;

^cTRQ: Tablets Routine Questionnaire;

^dBPRS: Brief Psychiatric Rating Scale;

^eMADRS: Montgomery-Asperg Depression Rating Scale;

^fYMRS: Young Mania Rating Scale;

^gGAF: Global Assessment of Functioning

^{*} Statistic is between CAE and EDU groups

^{**} Module assignment based upon the number of adherence barriers (maximum of 4, barriers included inadequate knowledge of BD as it relates to adherence, substance abuse as a barrier to adherence, poor communication with providers, problems with medication routines)

Table 2:

Change in medication treatment adherence, bipolar symptoms, and functioning

Variable*	Screening*	Baseline	10-weeks	14 weeks	26 weeks	Statistic**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Adherence						
TRQ Past week						p= 0.001
CAE	55.4 (28.2)	43.0 (31.3)	25.7 (29.4)	33.7 (34.5)	20.7 (29.0)	
EDU	55.0 (28.4)	45.4 (31.1)	35.0 (31.3)	31.7 (32.1)	30.3 (31.5)	
TRQ Past month						p= 0.048
CAE	46.9 (28.8)	43.8 (27.4)	24.5 (28.2)	30.1 (32.0)	21.0 (28.2)	
EDU	49.1 (28.3)	43.1 (30.3)	33.5 (28.7)	27.3 (27.3)	25.3 (25.8)	
Symptoms						
BPRS						p= 0.491
CAE	36.1 (6.9)	34.4 (7.7)	31.3 (6.3)	31.2 (6.9)	31.6 (7.1)	
EDU	37.4 (8.3)	34.8 (7.8)	32.8 (7.3)	32.0 (7.4)	31.2 (7.7)	
YMRS						p= 0.443
CAE	9.5 (5.1)	8.1 (4.8)	8.1 (5.5)	7.2 (5.1)	7.7 (6.2)	
EDU	9.2 (5.2)	8.0 (5.4)	8.2 (5.1)	7.9 (5.2)	8.7 (5.9)	
MADRS						p= 0.522
CAE	19.3 (8.2)	17.9 (8.9)	14.0 (7.8)	14.3 (9.3)	13.0 (8.4)	
EDU	19.9 (9.3)	18.2 (8.6)	14.3 (9.6)	14.3 (10.0)	15.0 (10.9)	
CGI						p= 0.910
CAE	N/A	3.4 (1.0)	3.2 (1.1)	2.9 (1.1)	3.0 (1.2)	
EDU		3.4 (1.0)	3.1 (1.2)	3.1 (1.2)	3.0 (1.5)	
GAF						
CAE		59.4 (8.7)	63.6 (9.6)	63.9 (9.8)	65.8 (11.5)	p= 0.107***
EDU	N/A	59.5 (8.5)	61.3 (10.8)	61.3 (9.9)	62.1 (12.1)	

Values are unadjusted means

* Screening visit did not assess CGI, GAF

** p-value refers to the group by time interaction using linear mixed effects analyses, except for TRQ past week and past month. These p-values are based on generalized linear mixed models with longitudinal binary outcomes (<= 20% non-adherent or not). Models were adjusted for gender, age, race, and marital status.

*** Comparison between baseline and 6-month GAF p =.03

Table 3:

Demographic & clinical variables at baseline among poorly-adherent individuals with BD who were assigned to 4, 3, 2 and 1 adherence modules

Variable	1 or 2 modules** (N= 20)	3 modules (N= 48)	4 modules (N= 116)	Statistic
Female N (%)	13 (65.0)	25 (52.1)	88 (75.9)	$\chi^2(2)= 9.02, p=.011$
Ethnicity N (%)				
African-American	9 (45.0)	24 (50.0)	90 (77.6)	
White	10 (50.0)	19 (39.6)	21 (18.1)	$\chi^2(4)= 17.69, p=.001$
Other	1 (5.0)	5 (10.4)	5 (4.3)	
Hispanic N (%)	0 (0.0)	3 (6.3)	3 (2.6)	$\chi^2(2)= 2.20, p=.333$
Education (yrs) Mean (SD)	13.90 (1.94)	13.14 (2.06)	12.25 (2.47)	F (2, 179) = 5.63, p= .004
BPRS Mean (SD)	31.60 (5.71)	32.38 (6.53)	36.05 (8.15)	F (2, 180)= 5.83, p= .004
YMRS Mean (SD)	5.90 (3.52)	9.46 (5.81)	7.82 (4.81)	F (2, 181) = 3.91, p= .022
MADRS Mean (SD)	16.50 (6.89)	17.06 (8.13)	18.66 (9.23)	F (2, 181) = .91, p= .406
GAF Mean (SD)	61.95 (10.54)	60.65 (7.71)	58.58 (8.47)	F (2, 181) = 1.94, p= .147
CGI -Overall Bipolar				
Illness Mean (SD)	3.05 (1.00)	3.35 (0.91)	3.46 (1.03)	F (2, 181)= 1.46, p= .234
TRQ				
Past Week Mean (SD)				
Screen	35.48 (18.67)	51.22 (28.16)	60.18 (28.03)	F (2, 181)= 7.69, p= .001
Baseline	31.19 (28.96)	36.11 (27.15)	49.78 (31.88)	F (2, 181)= 5.48, p= .005
TRQ				
Past Month Mean (SD)				
Screen	32.00 (20.50)	43.42 (26.82)	52.66 (29.15)	F (2, 181)= 5.61, p= .004
Baseline	26.28 (19.77)	35.27 (23.41)	49.76 (30.22)	F (2, 181)= 8.99, p= .000

*** Module assignment based upon baseline evaluation of adherence barriers/vulnerabilities.