A 6-Month, Prospective, Randomized Controlled Trial of Customized Adherence Enhancement Versus Bipolar-Specific Educational Control in Poorly Adherent Individuals With Bipolar Disorder

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ABSTRACT

Objective: Nonadherence in bipolar disorder (BD) ranges from 20% to 60%. Customized adherence enhancement (CAE) is a brief, BD-specific approach that targets individual adherence barriers. This prospective, 6-month, randomized controlled trial conducted from October 2012 to July 2017 compared CAE versus a rigorous BD-specific educational program (EDU) on adherence, symptoms, and functional outcomes in poorly adherent individuals.

Methods: One hundred eighty-four 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. Other outcomes were scores on the Global Assessment of Functioning, Montgomery-Asberg Depression Rating Scale, Young Mania Rating Scale, and Clinical Global Impressions Scale. Assessments were conducted at screening, baseline, 10 weeks, 14 weeks, and 6 months.

Results: The sample mean (SD) age was 47.40 (10.46) years; 68.5% were female, and 63.0% were African American. At screening, individuals missed a mean (SD) of 55.15% (28.22%) of prescribed BD drugs within the past week and 48.01% (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 scores versus those in EDU. Past-week TRQ score improvement remained significant after adjustment for multiple comparisons. There were no treatment arm differences in BPRS scores or other symptoms, possibly related to low symptom baseline values. Baseline-to–6-month comparison showed significantly higher GAF scores ($P = .036$) for CAE versus EDU. Although both groups used more mental health services at 6 months compared to baseline, increase for CAE was significantly less than that for EDU ($P = .046$).

Conclusions: Whereas 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.

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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 nonadherence ranges from 20% to 60%.[2–5]

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

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 who are at high risk for future nonadherence and may not have access to (or interest in) high-intensity, specialized care. Treatment approaches should be patient-focused and take into account individual reasons for nonadherence.

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 versus a rigorous control, BD-specific education (EDU), evaluated effects of CAE versus EDU on

Clinical Points

- As with other chronic conditions, sustaining medication adherence is a problem for many individuals with bipolar disorder (BD), and nonadherence ranges from 20% to 60%.
- Compared to a rigorous and BD-focused educational control, customized adherence enhancement (CAE) improves adherence and functional status.
- Although this randomized controlled trial suggests that curriculum-driven CAE can be implemented by social workers, it is likely that adherence promotion is most effective when prioritized by all members of the treatment team, including prescribers.

medication adherence, BD symptoms, and functional status in poorly adherent patients. We hypothesized that CAE would improve adherence, symptoms, and functioning more than EDU.

METHODS

Overall Study Description

This US National Institute of Mental Health (NIMH)–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 1 phone call with the study interventionist over an 8-week time period. Primary study outcome was change in adherence 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 BD, either type I or type II, as confirmed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID)[14]; presence of BD for at least 2 years; being prescribed at least 1 evidence-based BD medication (ie, lithium, anticonvulsant, or antipsychotic) for at least 6 months; and being ≥ 20% nonadherent 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) and was registered at ClinicalTrials.gov (identifier: NCT00183495) and completed from October 2012 to July 2017. Study participants were recruited from clinician referrals, via 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 randomized controlled trial (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.

Customized adherence enhancement. 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 4 treatment modules whose inclusion is determined based upon an individual's reasons for nonadherence (adherence barriers) identified at baseline. Adherence barriers are evaluated with items from the Attitudes toward Mood Stabilizers Questionnaire (AMSQ) and Rating of Medication Influences (ROMI).[17–21] The modules are as follows: psychoeducation focused on the role of medication in BD management, modified motivational enhancement therapy (MET) to address nonadherence 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 1).

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

Bipolar-specific patient education. Participants randomized to EDU also had 5 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-BD study.[22] As with CAE, there were 4 core sessions followed by 1 "booster" session and 1 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, 2 part-time social workers delivered CAE and 2 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's fidelity assessment included use of a modified Motivational Interviewing Treatment Integrity (MITI) code.[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 range from perfect adherence (0% missed) to missing all medication (100% missed). A mean TRQ was calculated for individuals receiving more than 1 BD medication.[25] The Medication Event Monitoring System (MEMS; Aprex Corp, Fremont, California) supplemented the TRQ. Participants were given the MEMS cap at screening, and MEMS data were 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). Although 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 Impressions Scale (CGI).[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 was evaluated using a standardized form 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 psychological constructs 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 score was believed to represent the self-reported adherence behavior least likely to be impacted by recall bias, past-month TRQ and MEMS data were collected as a validation of recent adherence behaviors. We noted a priori that we would consider representing scores as binary outcomes, indicating whether or not an adherence threshold had been met (eg, 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 during 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 score, past-month TRQ, MEMS data), we set the significance threshold to .0167 so that simultaneous Type I error is at most .05. Secondarily, GAF, YMRS, MADRS, and CGI scores 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, sex, 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 toward 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 months were specifically considered as well. Type I error level for secondary and post hoc analyses was set at .05.

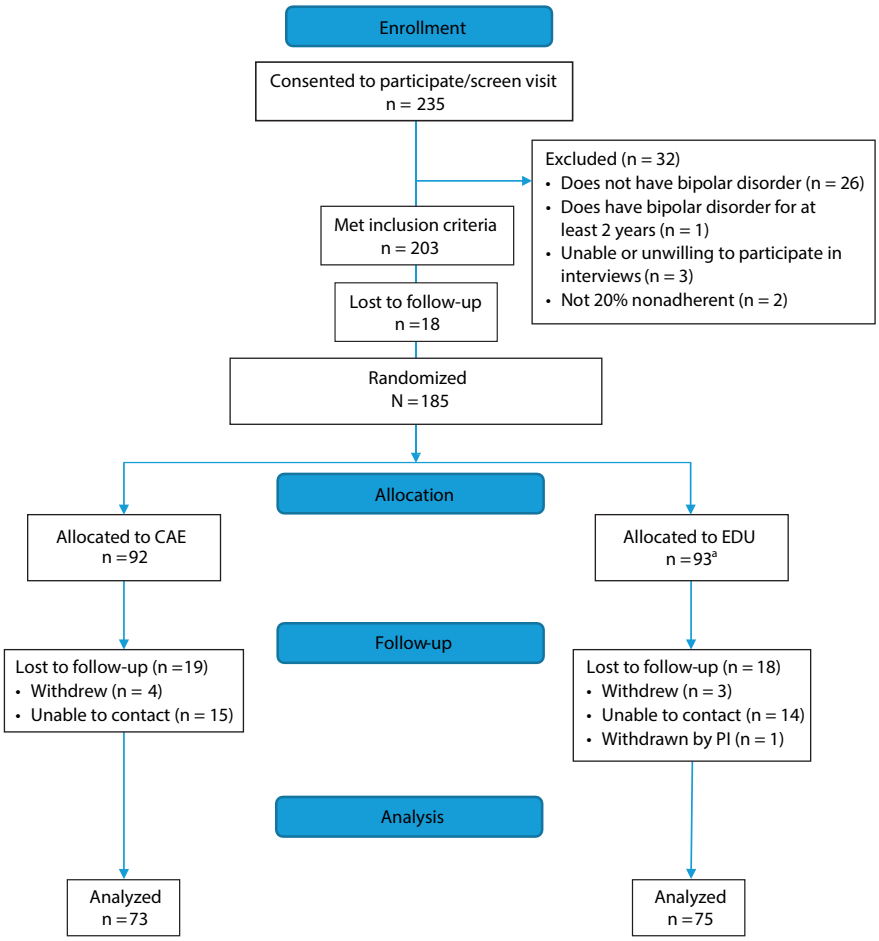
RESULTS

Figure 1 illustrates the study flow. Very shortly after randomization, it was identified that 1 individual in EDU did not fit study inclusion criteria. This individual was terminated from the study without participating in any intervention. Altogether, 147 (79.9%) of 184 individuals had 6-month data; the overall attrition rate was thus <20% and similar between arms.

Overall Sample Description

Demographic and clinical variables are noted in Table 1. Treatment adherence at screening was poor with a mean (SD) of 55.15% (28.22%) of days with missing BD drug doses within the past week and 48.01% (28.46%) within the past month. As demonstrated in previous work[25] and very likely due to the effect of adherence monitoring, there was a slight improvement in baseline TRQ scores, with a mean (SD) past-week TRQ score of 44.2 (31.2) and past-month TRQ score of 38.3 (28.8). Mean (SD) sample age was 47.4 (10.46) years; the sample included 126 women (68.5%), 116 African Americans (63.0%), and 6 Hispanic individuals (3.3%). The mean (SD) duration of education was 12.7 (2.37) years. The majority had type I BD (n = 136, 73.9%), and participants had a mean (SD) age at onset of 24 (12.3) years. 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 (28.8%) living in a private home and 27 (14.7%) being married. Psychiatric comorbidity was common, with current alcohol disorder in 10.5% (n = 18), posttraumatic stress disorder in 40.5% (n = 64), and generalized anxiety disorder in 23.9% (n = 42). The BPRS scores were relatively low at baseline with a mean (SD) of 34.60 (7.88), although

Figure 1. CONSORT Diagram of Study Flow



[a]One subject was withdrawn from the study by the Principal Investigator immediately after randomization, prior to EDU intervention.
Abbreviations: CAE = customized adherence enhancement, EDU = rigorous bipolar disorder–specific educational program, PI = Principal Investigator.

functional scores were also relatively low with a mean (SD) of 59.48 (8.57).

As illustrated in Table 1, there were few differences in baseline variables between CAE and EDU. There was a significant but low-magnitude difference in number of psychiatric medications prescribed in the CAE group (mean [SD] = 1.39 [0.61]) versus the EDU group (1.72 [0.92]). TRQ scores were similar between arms. Most individuals had multiple adherence barriers, including 173 (94%) in medication routines, 170 (92.4%) in BD knowledge, 157 (85.3%) in clinician communications, and 142 (77.2%) in substance use as an impediment to adherence. There were 116 individuals (63.0%) 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 individuals (47.8%) 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 no sessions. In EDU, there were 51 individuals (55.4%) 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 no 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 past-week ($P = .001$) and past-month ($P = .048$) TRQ scores compared to EDU. Past-week TRQ scores remained significantly improved after adjustment for multiple comparisons. There were no differences between arms in BD symptoms as measured by the BPRS, MADRS, YMRS, or CGI. There were no differences in adherence outcomes comparing type I versus II BD or in relation to number of medications prescribed.

Table 1. Baseline Demographics and Clinical Characteristics of 184 Poorly Adherent Individuals With Bipolar Disorder[a]

Variable	Total (N = 184)	EDU (n = 92)	CAE (n = 92)	Statistic[b]
Age, mean (SD), y	47.40 (10.46)	45.91 (10.94)	48.88 (9.81)	$t_{182} = 1.94$, $P = .054$
Sex				
Male	58 (31.5)	33 (35.9)	25 (27.2)	Fisher exact: $P = .267$
Female	126 (68.5)	59 (64.1)	67 (72.8)	
Ethnicity				
African American	116 (63.0)	53 (57.6)	63 (68.5)	
White	49 (26.6)	28 (30.4)	21 (22.8)	$\chi^2_3 = 5.04$, $P = .17$
Other	9 (4.9)	7 (7.6)	2 (2.2)	
Mixed	10 (5.4)	4 (4.3)	6 (6.5)	
Hispanic	6 (3.3)	4 (4.3)	2 (2.2)	Fisher exact: $P = .341$
Education, mean (SD), y	12.67 (2.37)	12.69 (2.51)	12.65 (2.24)	$t_{180} = -0.11$, $P = .913$
Marital status (total n = 183)[c]				
Single, never married	98 (53.6)	47 (51.1)	51 (55.4)	
Married/cohabiting	27 (14.8)	15 (16.3)	12 (13.0)	
Separated/divorced/widowed	58 (31.7)	29 (31.5)	29 (31.5)	$\chi^2_3 = 1.50$, $P = .683$
Employment (total n = 182)[d]				
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 (total n = 175)[e]				
BD-I	136 (77.3)	68 (76.4)	68 (79.1)	Fisher exact: $P = .719$
BD-II	39 (22.2)	21 (23.6)	18 (20.9)	
Age at BD onset, mean (SD), y	24.02 (12.34)	23.74 (12.40)	24.29 (12.23)	$t_{180} = 0.29$, $P = .769$
Current comorbid disorders				
Alcohol (total n = 171)	18 (10.5)	11 (12.6)	7 (8.3)	Fisher exact: $P = .457$
PTSD (total n = 158)	64 (40.5)	32 (40.0)	32 (41.0)	$\chi^2_3 = 1.10$, $P = .777$
OCD (total n = 176)	25 (14.2)	9 (10.2)	16 (18.2)	$\chi^2_2 = 2.29$, $P = .319$
Generalized anxiety disorder (total n = 176)	42 (23.9)	21 (23.9)	21 (23.9)	$\chi^2_2 = .000$, $P = 1.00$
No. of psychiatric medications, mean (SD)	1.55 (0.79)	1.72 (0.92)	1.39 (0.61)	**$t_{158.34} = -2.84$, $P = .005$**
No. of nonpsychiatric medications (total n = 163), mean (SD)	2.18 (1.97)	2.21 (1.96)	2.15 (1.99)	$t_{161} = -0.19$, $P = .849$
Charlson Comorbidity Index total score, mean (SD)	0.34 (0.97)	0.24 (0.75)	0.43 (1.15)	$t_{156.05} = 1.37$, $P = .173$
Breakdown of modules[f]				
Psychoeducation	170 (92.4)	82 (89.1)	88 (95.7)	Fisher exact: $P = .163$
Substance abuse	142 (77.2)	74 (80.4)	68 (73.9)	Fisher exact: $P = .380$
Improved communication	157 (85.3)	77 (83.7)	80 (87.0)	Fisher exact: $P = .678$
Medication routines	173 (94.0)	87 (94.6)	86 (93.5)	Fisher exact: $P = 1.00$
TRQ score for BD medications, 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 score, mean (SD)	34.60 (7.88)	34.82 (7.82)	34.38 (7.67)	$t_{181} = 0.84$, $P = .707$
MADRS score, mean (SD)	18.01 (8.73)	18.16 (8.60)	17.86 (8.90)	$t_{182} = -0.24$, $P = .814$
YMRS score, mean (SD)	8.04 (5.06)	8.01 (5.36)	8.07 (4.76)	$t_{182} = 0.07$, $P = .942$
GAF score, mean (SD)	59.48 (8.57)	59.53 (8.52)	59.43 (8.67)	$t_{182} = -0.08$, $P = .939$

[a]Values shown as n (%) unless otherwise noted. Boldface indicates statistical significance.
[b]Statistical comparison is between CAE and EDU groups.
[c]For EDU, total n = 91.
[d]For EDU, total n = 91. For CAE, total n = 91.
[e]For EDU, total n = 89. For CAE, total n = 86.
[f]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, and problems with medication routines).
Abbreviations: BD = bipolar disorder, BPRS = Brief Psychiatric Rating Scale, CAE = customized adherence enhancement, EDU = rigorous bipolar disorder–specific educational program, GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, TRQ = Tablets Routine Questionnaire, YMRS = Young Mania Rating Scale.

Because adherence improvement might result in eventual downstream changes in functioning or symptoms that lag behind adherence change, we also evaluated changes in adherence and functional outcomes from baseline to 6 months. Baseline-to–6-month differences for GAF score and past-month TRQ score (dichotomized as adherent versus nonadherent using the 20% established cut-point), adjusted for by sex, 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 at 6 months compared to baseline, possibly due to better recall during study participation. However, the increase in resource use was significantly less for CAE (mean change = −0.12) versus 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

Table 2. Change in Medication Treatment Adherence, Bipolar Symptoms, and Functioning[a]

Variable	Screening[b]	Baseline	10 Weeks	14 Weeks	26 Weeks	Statistic[c]
Adherence						
TRQ score past week						
CAE	55.4 (28.2)	43.0 (31.3)	25.7 (29.4)	33.7 (34.5)	20.7 (29.0)	**P=.001**
EDU	55.0 (28.4)	45.4 (31.1)	35.0 (31.3)	31.7 (32.1)	30.3 (31.5)	
TRQ score past month						
CAE	46.9 (28.8)	43.8 (27.4)	24.5 (28.2)	30.1 (32.0)	21.0 (28.2)	**P=.048**
EDU	49.1 (28.3)	43.1 (30.3)	33.5 (28.7)	27.3 (27.3)	5.3 (25.8)	
Symptoms						
BPRS score						
CAE	36.1 (6.9)	34.4 (7.7)	31.3 (6.3)	31.2 (6.9)	31.6 (7.1)	P=.491
EDU	37.4 (8.3)	34.8 (7.8)	32.8 (7.3)	32.0 (7.4)	31.2 (7.7)	
YMRS score						
CAE	9.5 (5.1)	8.1 (4.8)	8.1 (5.5)	7.2 (5.1)	7.7 (6.2)	P=.443
EDU	9.2 (5.2)	8.0 (5.4)	8.2 (5.1)	7.9 (5.2)	8.7 (5.9)	
MADRS score						
CAE	19.3 (8.2)	17.9 (8.9)	14.0 (7.8)	14.3 (9.3)	13.0 (8.4)	P=.522
EDU	19.9 (9.3)	18.2 (8.6)	14.3 (9.6)	14.3 (10.0)	15.0 (10.9)	
CGI score						
CAE	NA	3.4 (1.0)	3.2 (1.1)	2.9 (1.1)	3.0 (1.2)	P=.910
EDU	NA	3.4 (1.0)	3.1 (1.2)	3.1 (1.2)	3.0 (1.5)	
GAF Score						
CAE	NA	59.4 (8.7)	63.6 (9.6)	63.9 (9.8)	65.8 (11.5)	P=.107[d]
EDU	NA	59.5 (8.5)	61.3 (10.8)	61.3 (9.9)	62.1 (12.1)	

[a]Values are unadjusted means (SD). Boldface indicates statistical significance.
[b]Screening visit did not include assessment with the CGI or GAF.
[c]*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% nonadherent or not). Models were adjusted for sex, age, race, and marital status.
[d]Comparison between baseline and 6-month GAF score: *P* = .036.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CAE = customized adherence enhancement, CGI = Clinical Global Impressions Scale, EDU = rigorous bipolar disorder–specific educational program, GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable, TRQ = Tablets Routine Questionnaire, YMRS = Young Mania Rating Scale.

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 weducated, and have worse manic symptoms (YMRS) or global BD symptoms (BPRS). Sex was inconsistently associated with adherence barriers, whereas 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 review[10] on BD adherence interventions suggested that psychoeducation, motivational interviewing, financial incentives, and cognitive-behavioral treatment are all potentially promising; however, existing studies are generally small and uncontrolled 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 two-thirds of the sample), a group that is often underrepresented in standard clinical trials. More adherence barriers and worse adherence were found in minorities and those with social disadvantages (ie, 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 psychiatric symptom severity was low with a mean BPRS score of 34.6, and overall improvement was very modest with an endpoint BPRS score of just over 31 in both study arms. Leucht and colleagues[37] noted that the BPRS cutoff for "mildly ill" in patients with serious mental illness

Table 3. Demographic and Clinical Variables at Baseline Among Poorly Adherent Individuals With Bipolar Disorder Who Were Assigned to 1, 2, 3, or 4 Adherence Modules[a]

Variable	1 or 2 Modules[b] (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, y	13.90 (1.94)	13.14 (2.06)	12.25 (2.47)	**$F_{2, 179} = 5.63$, $P = .004$**
BPRS score	31.60 (5.71)	32.38 (6.53)	36.05 (8.15)	**$F_{2, 180} = 5.83$, $P = .004$**
YMRS score	5.90 (3.52)	9.46 (5.81)	7.82 (4.81)	**$F_{2, 181} = 3.91$, $P = .022$**
MADRS score	16.50 (6.89)	17.06 (8.13)	18.66 (9.23)	$F_{2, 181} = 0.91$, $P = .406$
GAF score	61.95 (10.54)	60.65 (7.71)	58.58 (8.47)	$F_{2, 181} = 1.94$, $P = .147$
CGI overall bipolar illness score	3.05 (1.00)	3.35 (0.91)	3.46 (1.03)	$F_{2, 181} = 1.46$, $P = .234$
TRQ score past week				
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 score past month				
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)	**$F_{2, 181} = 8.99$, $P = .000$**

[a]Values shown as mean (SD) unless otherwise noted. Boldface indicates statistical significance.
[b]Module assignment based upon baseline evaluation of adherence barriers/vulnerabilities.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions Scale, GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, TRQ = Tablets Routine Questionnaire, YMRS = Young Mania Rating Scale.

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,[11] the BPRS baseline mean (SD) score was 43.6 (12.0) versus an endpoint mean (SD) of 36.1 (12.4). 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 the 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. Although both CAE and EDU groups had increased mental health resource use during the course of the study, the increase was significantly less in CAE than in EDU. Possibly resource use differences were related to relatively greater functional status in the CAE group versus 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 (eg, 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 most effective when 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.

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REFERENCES

1. Goodwin GM, Haddad PM, Ferrier IN, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2016;30(6):495–553.
2. Lingam R, Scott J. Treatment non-adherence in affective disorders. *Acta Psychiatr Scand*. 2002;105(3):164–172.
3. Colom F, Vieta E, Martínez-Arán A, et al. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. *J Clin Psychiatry*. 2000;61(8):549–555.
4. Sajatovic M, Valenstein M, Blow FC, et al. Treatment adherence with antipsychotic medications in bipolar disorder. *Bipolar Disord*. 2006;8(3):232–241.
5. Licht RW, Vestergaard P, Rasmussen NA, et al. A lithium clinic for bipolar patients: 2-year outcome of the first 148 patients. *Acta Psychiatr Scand*. 2001;104(5):387–390.
6. Li C, Chen C, Qiu B, et al. A 2-year follow-up study of discharged psychiatric patients with bipolar disorder. *Psychiatry Res*. 2014;218(1–2):75–78.
7. Hong J, Reed C, Novick D, et al. Clinical and economic consequences of medication non-adherence in the treatment of patients with a manic/mixed episode of bipolar disorder: results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study. *Psychiatry Res*. 2011;190(1):110–114.
8. Scott J, Pope M. Self-reported adherence to treatment with mood stabilizers, plasma levels, and psychiatric hospitalization. *Am J Psychiatry*. 2002;159(11):1927–1929.
9. Durrenberger S, Rogers T, Walker R, et al. Economic grand rounds: the high costs of care for four patients with mania who were not compliant with treatment. *Psychiatr Serv*. 1999;50(12):1539–1542.
10. Levin JB, Krivenko A, Howland M, et al. Medication adherence in patients with bipolar disorder: a comprehensive review. *CNS Drugs*. 2016;30(9):819–835.
11. Sajatovic M, Levin J, Tatsuoka C, et al. Six-month outcomes of customized adherence enhancement (CAE) therapy in bipolar disorder. *Bipolar Disord*. 2012;14(3):291–300.
12. Sajatovic M, Levin J, Tatsuoka C, et al. Customized adherence enhancement for individuals with bipolar disorder receiving antipsychotic therapy. *Psychiatr Serv*. 2012;63(2):176–178.
13. Overall JA, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10(3):799–812.
14. First MB, Spitzer RL, Gibbon M. *Structured Clinical Interview for Axis I DSM-VI Disorders-(SCID) Patient Edition, Version 2.0*. New York, NY: Biometrics Research Department: New York Pyschiatric Institute; 1996.
15. Bauer MS. Supporting collaborative practice management: The Life Goals Program. In: Johnson SL, Leahy RL, eds. *Psychological Treatment of Bipolar Disorder*. New York, NY: Guilford Press; 2005.
16. Bauer MS, McBride L. *Structured Group Psychotherapy for Bipolar Disorder: The Life Goals Program*. 2nd ed. New York, NY: Springer; 2003.
17. Peet M, Harvey NS. Lithium maintenance, 1: a standard education programme for patients. *Br J Psychiatry*. 1991;158(2):197–200.
18. Scott J. Predicting medication non-adherence in severe affective disorders. *Acta Neuropsychiatr*. 2000;12(3):128–130.
19. Devulapalli KK, Ignacio RV, Weiden P, et al. Why do persons with bipolar disorder stop their medication? *Psychopharmacol Bull*. 2010;43(3):5–14.
20. Sajatovic M, Levin J, Fuentes-Casiano E, et al. Illness experience and reasons for nonadherence among individuals with bipolar disorder who are poorly adherent with medication. *Compr Psychiatry*. 2011;52(3):280–287.
21. Sajatovic M, Ignacio RV, West JA, et al. Predictors of nonadherence among individuals with bipolar disorder receiving treatment in a community mental health clinic. *Compr Psychiatry*. 2009;50(2):100–107.
22. Miklowitz DJ, Otto MW, Frank E, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. *Arch Gen Psychiatry*. 2007;64(4):419–426.
23. Moyers TB, Martin T, Manuel JK, et al. The Motivational Interviewing Treatment Integrity (MITI) Code: Version 2.0. University of New Mexico Center on Alcoholism, Substance Abuse & Addictions website. https://casaa.unm.edu/download/miti.pdf.
24. Chaudhry S, Jin L, Meltzer D. Use of a self-report-generated Charlson Comorbidity Index for predicting mortality. *Med Care*. 2005;43(6):607–615.
25. Sajatovic M, Levin JB, Sams J, et al. Symptom severity, self-reported adherence, and electronic pill monitoring in poorly adherent patients with bipolar disorder. *Bipolar Disord*. 2015;17(6):653–661.
26. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
27. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
28. Guy W, ed. *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.
29. Spitzer RL, Gibbon M, Williams JBW, et al. Global Assessment of Functioning (GAF) Scale. In: Sederer LJ, Dickey B, eds. *Outcome Assessment in Clinical Practice*. 1st ed. Baltimore, MD: Williams and Wilkins; 1996.
30. Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. *Psychol Med*. 1983;13(1):177–183.
31. Awad AG. Subjective response to neuroleptics in schizophrenia. *Schizophr Bull*. 1993;19(3):609–618.
32. Ritsner MS, Blumenkrantz H. Predicting domain-specific insight of schizophrenia patients from symptomatology, multiple neurocognitive functions, and personality related traits. *Psychiatry Res*. 2007;149(1–3):59–69.
33. Vauth R, Kleim B, Wirtz M, et al. Self-efficacy and empowerment as outcomes of self-stigmatizing and coping in schizophrenia. *Psychiatry Res*. 2007;150(1):71–80.
34. Ritsher JB, Phelan JC. Internalized stigma predicts erosion of morale among psychiatric outpatients. *Psychiatry Res*. 2004;129(3):257–265.
35. Blixen C, Perzynski AT, Bukach A, et al. Patients' perceptions of barriers to self-managing bipolar disorder: a qualitative study. *Int J Soc Psychiatry*. 2016;62(7):635–644.
36. Blixen C, Levin JB, Cassidy KA, et al. Coping strategies used by poorly adherent patients for self-managing bipolar disorder. *Patient Prefer Adherence*. 2016;10:1327–1335.
37. Leucht S, Kane JM, Kissling W, et al. Clinical implications of Brief Psychiatric Rating Scale scores. *Br J Psychiatry*. 2005;187(4):366–371.
38. Bauer MS, McBride L, Williford WO, et al; Cooperative Studies Program 430 Study Team. Collaborative care for bipolar disorder, part II: impact on clinical outcome, function, and costs. *Psychiatr Serv*. 2006;57(7):937–945.
39. Levin JB, Sams J, Tatsuoka C, et al. Use of automated medication adherence monitoring in bipolar disorder research: pitfalls, pragmatics, and possibilities. *Ther Adv Psychopharmacol*. 2015;5(2):76–87.

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Supplementary Material

Article Title: A 6-Month, Prospective, Randomized Controlled Trial of Customized Adherence Enhancement Versus Bipolar-Specific Educational Control in Poorly Adherent Individuals With Bipolar Disorder

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List of Supplementary Material for the article

1. **Appendix 1** Description of CAE Modules

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix 1. Description of CAE Modules

1. **Psychoeducation on Medication Treatments:** Psychoeducation approaches bipolar disorder as a biological disorder that can be managed by appropriate medication treatments in conjunction with non-somatic coping strategies. Psychoeducation has been noted to improve medication adherence. This module uses a modified Life Goals Program. The module consists of 3 individual units including 1) basic information about bipolar disorder, its neurobiological underpinnings, and information on mania and depression, 2) a focus on medication management, identifying the purpose of medication, reviewing good and bad effects of medication, and 3) following discussion of functional impact of symptoms, the interventionist and individual with bipolar disorder collaboratively develop a personal symptom profile for the individual's own episodes of depression and mania as well as their early warning signs of impending relapse.

2. **Modified Motivational Enhancement Therapy (MET):** MET is an evidence-based psychosocial intervention for individuals with dual diagnosis. This 2-unit module helps individuals understand the effects of substance abuse on their bipolar disorder in general and on their adherence to medication specifically. Individuals are encouraged to access personal motivation to change their substance use, making it more likely that they will be adherent to their medication regimen. The module consists of a guided assessment of individual substance use/abuse followed by modified MET that addresses adherence specifically within the context of substance abuse.

3. **Communication with Providers:** Using principles from collaborative care, this module focuses on improving communication with providers from a patient-focused, patient-directed approach. Individuals with bipolar disorder are supported in examining and exploring key components of treatment planning with their provider, including expectations for medication response, and feared/experienced medication side effects. Key critical issues include understanding of differential burden of medication-related effects, and how these effects might be prioritized for discussion with a clinician. This 2-unit module also provides information on commonly utilized psychotropic agents.

4. **Medication Routines:** Complex medication regimens may interfere with daily activities and adherence. This 2-unit module focuses on assisting individuals to modify treatment regimens as appropriate, and facilitates discussion with providers. Using principles from interpersonal and social rhythm therapy for bipolar disorder, a key activity is to outline and review the individual's daily routine with respect to medication-taking and problem- solving regarding common barriers. This module emphasizes the use of prompts/reminders and self-monitoring/self-regulation to maximize and maintain adherence. A key activity in this module is a review of medication-taking patterns, including examination of when, where, and how medications are taken.