Customized Adherence Enhancement for Individuals With Bipolar Disorder Receiving Antipsychotic Therapy

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Objective: **A three-month prospective trial of a psychosocial intervention—customized adherence enhancement (CAE)—was conducted with 43 medication-nonadherent individuals with bipolar disorder.** ***Methods:*** **CAE modules were administered as indicated by a screen that identifies reasons for nonadherence. The primary outcome was change in adherence to mood-stabilizing medications as measured by the Tablet Routines Questionnaire and pill counts. Secondary outcomes included change in symptoms, measured by the Hamilton Rating Scale for Depression (HAM-D), Young Mania Rating Scale (YMRS), and Brief Psychiatric Rating Scale (BPRS).** ***Results:*** **Participants completed 76% of sessions. Dropout at three months was 13 (30%). Adherence improved from a baseline mean± SD of 34%±27% of tablets missed in the past month to only 10%± 15% ($p<.001$). BPRS, HAM-D, and YMRS scores all indicated significant improvement at three-month follow-up ($p<.05$).** ***Conclusions:*** **Although conclusions must be tempered by the uncontrolled design, CAE appeared to be well accepted and was associated with improvements in adherence, symptoms, and functioning. (*Psychiatric Services* 63:176–178, 2012; DOI: 10.1176/appi.ps.201100133)**

Medication nonadherence among persons with bipolar disorder is associated with illness relapse and with suicide (1). A limited but growing literature suggests that it is possible to enhance treatment adherence among patients with bipolar disorder, although approaches that address the broad spectrum of problems that are experienced by persons with bipolar disorder do not always specifically improve their adherence (2–5).

Here we report findings from a prospective trial of a psychosocial intervention—customized adherence enhancement (CAE)—in a sample of 43 patients with bipolar disorder who were medication nonadherent. We hypothesized that CAE would improve medication adherence in this vulnerable group.

Methods

The study was approved by the local institutional review board (IRB), and all participants provided written informed consent. The study was conducted between April 2009 and August 2010.

Prospective study participants were referred by treating clinicians or were self-referred in response to IRB-approved study advertisements that were posted at a large academic medical center and affiliated hospital sites, an adjacent university campus, local libraries, and other community sites. Study participants were age 18 or older with type I or type II bipolar disorder confirmed by diagnostic interview (6). Participants were poorly adherent, which was defined as missing 20% or more of prescribed medication in the past week or the past 30 days as measured by self-report on the Tablet Routines Questionnaire (TRQ) or by pill counts. All participants had a diagnosis of bipolar disorder for at least two years, were taking second-generation antipsychotics, and were receiving care at our academic center or its affiliated sites. Individuals who were unable to participate in interviews and those at high risk of suicide were excluded.

CAE was implemented over six weeks, and outcomes were evaluated at six-week and three-month follow-ups. The primary study outcome was change from baseline in adherence to

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prescribed mood-stabilizing medications. Secondary outcomes were change in symptoms, functioning, and attitudes.

CAE, a brief adjunct to standard mental health treatments, is a manualized modular intervention. Participants are assigned to receive up to four CAE modules on the basis of an initial screening that identifies reasons for nonadherence. The screen uses preset cut-off scores on the Attitudes Towards Mood Stabilizer Questionnaire (7,8) and the Rating of Medication Influences scale (9). Modules include psychoeducation, modified motivational enhancement therapy, communication with providers, and medication routines. [The four modules are described in more detail in an online appendix to this report at ps.psychiatryonline.org.] CAE was delivered by a doctoral-level psychologist and two nondoctoral interventionists, all trained to preset qualification criteria.

Treatment adherence was evaluated with the Morisky Scale (10), with the TRQ (7,8), and by pill counts. An average adherence rating was calculated for patients who were taking more than one maintenance medication for bipolar disorder. Symptoms were measured with the Hamilton Rating Scale for Depression (HAM-D) (11), the Young Mania Rating Scale (YMRS) (12), and the Brief Psychiatric Rating Scale (BPRS) (13). Possible scores on the HAM-D range from 0 to 52, with higher scores indicating a worse condition. Possible scores on the YMRS range from 0 to 60, with higher scores indicating a worse condition. Possible scores on the BPRS range from 18 to 126, with higher scores indicating a worse condition. Functioning was measured with the Global Assessment of Functioning (GAF) (14). Possible scores range from 1 to 100, with higher scores indicating better functioning. Attitudes toward medication were measured with the ten-item version of the Drug Attitude Inventory (DAI) (15).

Paired t tests and Wilcoxon signed-rank tests were used to test adherence change from baseline. Longitudinal mixed models were used to analyze repeated measurements of adherence using the TRQ for both the past month and past week. This pre-post, intent-to-treat analysis included all enrolled individuals; maximum likelihood methods were employed for missing data. Subject-level random effects were modeled, and time was viewed as a fixed categorical variable. Data analysis was conducted using IBM SPSS Statistics, version 19.

Results

Among 91 individuals screened, 65 (71%) met inclusion criteria, and 43 (47%) were enrolled in the study. The most common reasons for not meeting inclusion criteria were not being a patient at the facility (N=13) and not being on a second-generation antipsychotic (N=5). The mean±SD age of participants was 43.1±11.3 years; 28 of the 43 participants (65%) were women, and 28 (65%) were African Americans.

A total of 13 (30%) individuals were assigned to receive four treatment modules, 23 (54%) were assigned to receive three modules, five (12%) were assigned to receive two modules, and two (5%) were assigned to receive one module. Module assignment was 39 participants (91%) for psychoeducation, 40 (93%) for medication routines, 33 (77%) for communication with providers, and 21 (49%) for modified motivational enhancement therapy.

Participation was generally good. Participants completed 76% of sessions. Only six enrolled participants (14%) did not participate in any sessions. Dropout at three months was 13 (30%).

Baseline mean±SD nonadherence rates (missed prescribed tablets as reported on the TRQ) were 32%±30% (median=29%) in the past week and 34%±27% (median=29%) in the past month. At three months mean TRQ improved among the 30 remaining participants to missing only 13%±25% (median=0%) of prescribed tablets in the past week and 10%±15% (median=0%) in the past month. When Wilcoxon signed-rank tests were used, tests of median differences being zero were rejected at p=.002 (z=–3.06) and p<.001 (z=–4.06), respectively, for past week and past month. The time variable was statistically significant in a longitudinal mixed model with heterogeneous first-order autoregressive covariance; estimated effects indicated that adherence levels improved significantly (F test, p<.01).

Morisky scores improved significantly from baseline to three months (t=–4.32, df=29, p<.001). Mean proportion of missed tablets improved from a baseline of 63%±27% of prescribed tablets to 46%±34%; however, this decrease was not statistically significant, possibly because nearly half of the participants did not bring in pill bottles for counts. Pill counts, which were available for 22 participants, did not correlate with baseline TRQ scores for the past week or for the past month. Further analyses were conducted to determine whether a sampling bias of the pill counts was present at baseline—that is, whether less adherent individuals were less likely to bring in pill bottles. Two separate logistic regressions indicated that neither TRQ scores for the past week nor TRQ scores for the past month were a significant predictor of failure to bring in pill bottles at the baseline visit.

Scores on the BPRS improved from baseline to three months from 30.9±7.3 (median=30.5) to 27.6±8.6 (median=24.0) (t=–2.18, df=28, p=.038). Over this period HAM-D scores improved from 11.8±5.1 (median=11.5) to 8.7±5.9 (median=8.0) (t=–2.73, df=28, p=.011), and YMRS scores improved from 9.8±4.9 (median=9.5) to 6.4±4.6 (median=6.0) (z=–3.10, p=.002). GAF scores improved from 59.9±5.5 (median=60.0) to 68.2±11.5 (median=70.0) (z=3.26, p=.001). Scores on the DAI also improved significantly (t=3.66, df=29, p=.001).

Among participants who completed their assigned CAE modules, most (90%, 27 of 30 participants) felt that the benefit of the intervention exceeded the burden, most (90%, N=27) felt that CAE was "about right" in the number of sessions and timing, and all strongly agreed or agreed that CAE addressed all important issues specific to their situation. There was no difference in dropout between the doctoral-level interventionist and the two others.

Discussion

The literature on adherence in bipolar disorder suggests that people who are nonadherent to prescribed medications have a poor prognosis (1,2). This prospective trial of CAE, a manualized psychosocial intervention designed to improve adherence among nonadherent patients with bipolar disorder, was associated with improved adherence, symptoms, and functioning at a three-month follow-up. Self-reported adherence improved among CAE participants; on average, they missed taking about 34% of prescribed medications at baseline and only about 10% at the three-month follow-up. This improvement in adherence may explain why these patients had improved symptoms and functional status. Experiencing these medication-related benefits may have led, in turn, to the observed improvements in attitudes toward treatment.

Although interpretation of study findings must be tempered by the methodological limitations of an uncontrolled design, reliance on indirect and imperfect methods of measuring adherence (self-report and pill counts), a short follow-up period, and lack of correction for multiple comparisons, the positive findings are still encouraging. Lack of correlation between TRQ scores and pill counts may reflect a mismatch between the adherence time frame for pill counts (one to 90 days) and for the TRQ (past week or past 30 days). For example, if an individual obtained a new bottle of pills a day or two before the pill count assessment and took his or her tablets each day since obtaining the bottle, he or she could appear to be fully adherent even though he or she may have been largely nonadherent for the past week or past month. Alternatively, adherence measurement based on a 90-day pill supply in cases where most of the missed doses had been missed soon after obtaining the 90 pills could have led to a lack of correlation between pill count and TRQ score, which would be based on more recent behavior.

The brevity of the CAE intervention contrasts with current evidence-based psychosocial interventions, which require more time and intensity. In addition, other psychosocial interventions are not targeted toward patients with poor adherence and may be best suited for implementation in resource-heavy settings. The brief duration and narrow focus of CAE may make the intervention acceptable to individuals who may not have access to (or interest in) long-term, high-intensity, and specialized care. However, given that nearly one-third of individuals dropped out, CAE appears insufficient to engage all individuals with bipolar disorder. Our findings also suggest that interventionists without doctoral-level degrees can be adequately trained to deliver CAE.

Conclusions

Patients with bipolar disorder who are medication nonadherent often have a poor prognosis. The CAE intervention may be helpful for patients with this disorder who are known to be suboptimally adherent; however, findings need to be confirmed in controlled trials.

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