Running Head: CBT-AD in type 2 diabetes and depression

A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in patients with uncontrolled type 2 diabetes

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ABSTRACT

Objective: To test cognitive behavioral therapy for adherence and depression (CBT-AD) in type-2 diabetes. We hypothesized that CBT-AD would improve adherence, depression, and, secondarily, hemoglobin A\textsubscript{1c} (A1C).

Research Design and Methods: 87 adults with unipolar depression and uncontrolled type-2 diabetes received Enhanced Treatment As Usual (ETAU) including medication adherence-, self-monitoring of blood glucose (SMBG)-, and lifestyle-counseling; a provider letter documented psychiatric diagnoses. Those randomized to the intervention arm additionally received 9-11 sessions of CBT-AD.

Results: Immediately after acute treatment (4-months), adjusting for baseline, CBT-AD had 20.7 percentage points greater oral medication adherence on electronic pill cap (95% CI: -31.14, -10.22, =.000); 30.2 percentage points greater SMBG adherence via glucometer downloads (95% CI: -42.95, -17.37, p=.000); 6.44 points lower depression scores on the Montgomery-Asberg Depression Rating Scale (95% CI: 2.33, 10.56, p=.002); .74 points lower on the Clinical Global Impression (95% CI: .16, 1.32, p=.01); and .72 units lower A1C (95% CI: .29, 1.15, p=.001) relative to ETAU. Analyses of 4-, 8- and 12-month follow-up time-points indicated that CBT-AD maintained 24.3 percentage points higher medication adherence (95% CI: -38.2, -10.3, p=.001); 16.9 percentage points greater SMBG adherence (95% CI: -33.3, -5, p=.043); and .63 units lower A1C (95% CI: .06, 1.2, p=.03) after acute treatment ended. For depression, there was some evidence of continued improvement post-treatment, but no between-groups difference.

Conclusions: CBT-AD is an effective intervention for adherence, depression, and glycemic control, with enduring and clinically meaningful benefits for diabetes self-management and glycemic control, in adults with type-2 diabetes and depression.
Trial Registration: http://clinicaltrials.gov/show/NCT00564070

Key words: Cognitive behavioral therapy (CBT), diabetes, depression, adherence
Despite clear evidence linking glycemic control and risk for complications (1) approximately 50% of adults with diabetes achieve glycemic control targets (A1C <7%)(2). Patient nonadherence to medications prescribed to treat diabetes is common (3) and clearly related to poor glycemic control, risk for hospitalization, and mortality (4). Clinical depression is highly prevalent in diabetes, being up to two times more common among patients with diabetes than those without (5). Depression in diabetes is not only distressing in and of itself, but it is also consistently associated with poor adherence to self-care behaviors (6), worse glycemic control (7), complications (8–10), and mortality (11).

Although a few trials exist that have tested the efficacy of treatments for depression in adults with diabetes with generally positive effects on depression, effects on health outcomes such as glycemic control and adherence are, at best, mixed (12). An early small trial of cognitive behavioral therapy (CBT) demonstrated an improvement in glycemic control (13) but subsequent larger trials of collaborative care have failed to impact glycemic control (14,15) or self-care and medication adherence (16). Accordingly, treating depression alone may not result in changes in health behaviors or outcomes, and hence an integrative approach may be necessary.

Adapting an approach used successfully in adults with HIV/AIDS (17,18), we integrated the treatment of depression and nonadherence (19–22) using cognitive behavioral therapy intervention strategies. The objective of the current study was to test, in a 2-arm randomized controlled trial, Cognitive Behavioral Therapy for Adherence and Depression (CBT-AD) combined with a series of diabetes self management and adherence interventions which we call enhanced treatment as usual (ETAU), versus ETAU alone, in patients with uncontrolled type 2 diabetes and depression. We had two major hypotheses. First, we hypothesized that those assigned CBT-AD would have better adherence, decreased depression, and improved glucose
control than those assigned ETAU at immediately post-treatment (4 months). Second, we hypothesized that observed post-treatment between-group differences in these outcomes would be sustained over 8- and 12-month follow-up.

RESEARCH DESIGN AND METHODS

Design and procedures.

This was a 12-month single-blinded randomized trial. All participants had enhanced treatment as usual (ETAU). Accordingly, they met once with a nurse educator to set goals for self-monitoring blood glucose (SMBG), twice with a dietitian to set individualized diet and physical activity goals, and once with an adherence counselor to help with these self-management goals. There were two arms: 1) CBT-AD plus ETAU or 2) ETAU alone. Assessments were at baseline, 4 (immediately post-treatment), 8, and 12 months and took place at Massachusetts General Hospital (Diabetes Center, Behavioral Medicine Service and/or Clinical Research Program in Boston, MA). The period of recruitment was June 2007 to March 2011, with one-year follow up lasting until March 2012.

All procedures were reviewed and approved by the Institutional Review Board at Massachusetts General Hospital. All participants completed an informed consent process with a study clinician, including signing an informed consent form.

Participants.

87 adults between the ages of 18-70 with sub-optimally controlled type 2 DM (physician-defined, A1C ≥ 7% (53 mmol/mol)) despite treatment with an oral hypoglycemic, who also met DSM-IV (23) criteria for a diagnosis of depression (66 current major depressive episode, 11 current dysthymic disorder, 10 major depression in partial remission and prescribed antidepressant treatment) were enrolled. Antidepressants for depression, oral hypoglycemic
medications, and insulin all needed to be stable for 2 months. The Mini International Neuropsychiatric Inventory (24) was used to establish baseline psychiatric diagnoses. The assessment of depression during baseline was conducted by a study clinician (Masters or Doctoral level psychologist trained via audio-tape supervision in the treatment and assessment protocols). Other treatments for depression, such as medications, were allowed to be continued or started by usual care providers, if deemed to be indicated. If at any visit, treatment for depression beyond what the study provided was judged to be clinically indicated, or if self-report depression scores increased by 25% compared to the average of their past two scores, participants were given appropriate referrals (e.g., additional therapy, medication evaluation) and continued to be followed per the assessment schedule. Participants who experienced severe depression (i.e. requiring intensive treatment such as hospitalization) were dropped from the study.

Participants who had active untreated major mental illness (e.g., untreated psychosis), bipolar disorder, eating disorder, mental retardation, dementia, or active suicidality, were unable or unwilling to provide informed consent, or had a history of or were undergoing current CBT for depression were excluded.

Interventions

Enhanced Treatment As Usual (all participants).

Provider letter and monitoring of depression. After the baseline assessment, a letter was sent to each patient’s health care provider regarding any psychiatric diagnoses for which the patient met criteria. The letter stated that participation in the study should not alter the provider’s normal course of assessment or treatment for these conditions. At follow-up assessments, if clinically indicated, referrals for depression treatment were also provided. This
was if their self-report depression scores increased by 25% compared to the average of the prior two, and also determined via a case-by-case basis, including but not limited to situations such as suicidal ideation

*Nurse and Dietitian Visits.* Before randomization, the nurse diabetes educator met with each patient for diabetes self-management education and counseling. The goal of these visits was to establish tailored goals for diabetes self-care, including medication adherence (for both oral medications and/or insulin), glucose monitoring, exercise, and foot care. The dietitian conducted a nutritional assessment and then set two individualized nutrition goals and one activity goal that were selected based on likelihood of impacting glucose control and each participant’s self-confidence in his or her ability to achieve them. These were evaluated and revised as necessary at the second visit after randomization.

*Adherence Counseling.* All participants had one session of “Life-Steps” (25,26), a stand-alone CBT intervention designed to improve adherence to medical recommendations and individualized diabetes self-management goals set by the dietitian and nurse. In this intervention, after brief discussion about patient-generated reasons for engaging in treatment, 11 cognitive and behavioral steps to adherence are discussed (e.g. setting a daily schedule, having reminder cues for medications, managing getting to appointments), and the interventionist and patient generate a plan and back-up plan for each (see on line Appendix for further details).

**CBT-AD.** The intervention group then participated in CBT-AD delivered across 9-12 sessions, with the Life-Steps intervention delivered as session one. For additional details please see on line Appendix and/or the published treatment manuals (19,20). The subsequent modules include 1) introducing the patient to the nature of cognitive behavioral therapy and motivational interviewing for behavior change (≈ one session); 2) increasing pleasurable activities and mood
monitoring (≈ one session); 3) thought monitoring and cognitive restructuring (adaptive thinking) (≈ five sessions); 4) problem-solving as a skill to aid in decision-making processes, particularly those related to diabetes self-care (≈ two sessions); 5) relaxation training (≈ two sessions). The therapist and participant were able to structure the number of sessions spent on each module to meet the participants’ individual needs. For all modules participants were encouraged to apply these skills generally, but they were linked to diabetes self-care whenever possible. Participants were offered up to two booster sessions, which usually happened the time of the 8 and 12-month follow-up assessments. For additional details please see on line Appendix and/or the published treatment manuals (19,20).

Outcomes

Medication adherence. Each patient was given a Medication Event Monitoring System (MEMS; AARDEX Inc.) electronic pill cap, which fits on a medication bottle and registers each time the patient’s medication bottle is opened. This allowed for calculation of a percentage of doses taken. A “corrected” score was used if participants could recall times when they took pills but did not use the bottle (17,18,27–29). Participants informed study staff of changes to medications during the course of the study, and this was accounted for in the calculation of these adherence scores.

Adherence to Glucose Monitoring. One Touch Ultra meters (LifeScan, Inc) for daily glucose control also provided frequency of self-monitoring, which, compared to the individualized goals from the nurse visits, also yielded a percentage (30,31) adherence score.

The Montgomery-Asberger Depression Rating Scale (MADRS) (32) is a structured, validated, ten-item interview, completed by blinded assessor.
Clinical Global Impression (CGI; 1 = not ill to 7 = extremely ill) (33), also rated by a blinded assessor, is single-item, valid and reliable measure of the severity of global impairment and distress related to depression.

Assessment of diabetes control was determined by measurement of A1C, at the MGH laboratory one of the reference labs for the National Glycohemoglobin Standardization Program (34,35), using a Biorad Variant 2 Turbo, normal range 3.8 to 6.4% (18 to 46 mmol/mol). No point-of care A1C tests were used.

Sample size.

The study was powered for adherence and depression outcomes, based on our initial work in HIV (17) which had effect sizes in excess of 1.0 for these outcomes. The recruitment goal was 100 completers, which would have allowed for excess of 95% power to detect an effect size of 1.0 for adherence and depression using a GLM ANOVA approach for the post-treatment effect. We experienced slower than anticipated recruitment but still had sufficient power to conduct the analyses with 87 participants.

Randomization.

We stratified randomization based on prescription of medication (oral medication, insulin, both), sex, and CGI score (≥ 3 cutoff) in blocks of four. The randomization sequence was generated by the data manager; participants were assigned to study arm by the research assistant. Study interventionists conducted the enrollment visits.

Blinding.

Participants, study assessors, interventionists, and dietitians were blinded to study assignment during the baseline visit, three nurse/dietitian visits, and the adherence counseling visit.
Statistical methods.

The two sets of analyses corresponded to the two study hypotheses: 1) CBT-AD will result in superior adherence, depression, and glucose control; and 2) the benefits will be maintained over 8 months. All analyses used SPSS v19 or 20, and followed intent-to-treat principles. For significant differences, parameter estimates (B) are in the units of the measure to best describe the clinical implication of the results.

The first set of analyses corresponds to the first hypothesis, that the CBT-AD condition would have superior outcomes at the end of acute treatment. Accordingly, we evaluated between-group differences at the 4-month assessment (i.e. immediately post-treatment), controlling for baseline scores. To allow for intent to treat principles, we used general linear models with multiple imputation to provide conservative estimates for missing data (completer analyses revealed a similar pattern of results, though with stronger p values and larger parameter estimates). For the first set of analyses, we hypothesized that the CBT-AD condition would have lower depression, higher adherence, and lower A1C than the ETAU condition.

The second set of analyses corresponds to the second hypothesis: that those who participated in the treatment would maintain their benefit. According, we evaluated the follow-up data using mixed effects modeling with the 4, 8, and 12 month data. These models did not include baseline values. They contained a term for treatment condition, which measured the difference between the two conditions over the entire follow-up period, a term for time, which measured the extent to which the values decreased or increased over time averaged over both conditions, and an interaction term, which measured whether the change with time, after acute treatment was discontinued, was different in the two treatments over the follow up period. The purpose of these analyses was to examine if there was an effect for the treatment condition term.
Accordingly, we hypothesized that there would be significant main effect for treatment condition such that after acute treatment discontinuation, the CBT-AD condition would maintain lower depression, higher adherence, and lower A1C than the comparison condition. Additionally, we hypothesized that there would not be an effect for time after acute treatment discontinuation, improvements in the CBT condition would not wane, and the comparison condition would also not make changes after the 4-month assessment. Finally, we hypothesized that the there would not be a significant effect for the interaction of time by condition during this follow-up period, such that both groups would maintain scores similar to those at the 4-month assessment.

RESULTS

Participant Characteristics and Flow

A CONSORT diagram of participant flow is depicted in Figure 1. Table 1 depicts baseline characteristics for those randomized. None of the demographic or outcome data differed by treatment arm. For the post-treatment outcome, retention was 90%, and 83% of participants returned for either the 8- or 12-month follow-up. Three participants (all in ETAU) were dropped due to severe depression requiring more intensive treatment (2 at 4-month and 1 at 8-month). There were no study related adverse events.

Post-treatment (acute/4-month) outcomes (Table 2).

Adherence. At post-treatment, controlling for baseline, the CBT-AD arm had 20.7 percentage points higher adherence to medications as assessed by electronic pill cap (95% CI: -31.14, -10.22, p=.000) and 30.2 percentage points higher electronically-assessed two-week SMBG (95% CI: -42.95, -17.37, p=.000) compared to the ETAU arm.

Depression. Controlling for baseline, the CBT-AD arm had 6.22 lower depression scores on the MADRS than the control arm (95% CI: 2.33, 10.56, p=.002) and .74 lower ratings on the
Clinical Global Impression (95% CI: .16, 1.32, p=.01), where lower scores indicate less depression on both scales.

*Diabetes Control (see Figure 2).* Controlling for baseline, the CBT-AD group had superior glycemic control as indicated by a .72 difference in A1C compared to the ETAU group (95% CI: .29, 1.15, p=.001).

**Follow-up / Maintenance of Gains (Table 3)**

*Adherence.* For medication adherence, a significant main effect for study arm indicated that the CBT-AD arm maintained 24.3 percentage points higher medication adherence than ETAU during the follow-up period (95% CI: -38.2, -10.3, p=.001). The main effect for time was not significant (p=.14), indicating that adherence gains did not significantly decline or improve from the time of treatment discontinuation to the follow-ups. The interaction of time by study arm was not significant (p=.09), indicating that the non-significant main effect for time over the follow-up period was not different by study arm: that after acute treatment ended, both groups did not differ at month 8 or month 12 from the scores they had right after the acute treatment ended (at month 4).

For adherence to glucose monitoring goals, a significant main effect for study arm indicated that the CBT-AD arm maintained 16.9 percentage points better glucose monitoring adherence than ETAU during the follow-up period (95% CI: -33.3, -5.5, p=.043). A significant effect for time (p=.001), however, indicated some decline over follow-up: scores at month 8 were 12.5 percentage points lower than at month 4 (95% CI: 5.9, 19.1, p=.001) and 9.1 percentage points lower at month 12 months than at month 4 (95% CI: 2.7, 15.5, p=.006), without significant differences between 8 and 12 months (B = -3.4, 95% CI: -9.5, 2.7, p=.27). The interaction effect between time by study arm was not significant (p=.24) indicating that
these declines over time after acute treatment ended (at month 4) did not differ by study arm (i.e. both groups had decreased adherence to SMBG goals over time; but the CBT-AD arm remained superior).

*Depression.* For the MADRS, there were no significant effects for study arm (p=.16) during the follow-up period. There was a trend, however, toward continued improvement over follow-up for both study arms (p=.06). Depression scores were 2.4 points lower at month 12 compared to month 8 (95% CI: .23, 4.5, p=.03) and 2.5 points lower at month 12 compared to month 4 (95% CI: .10, 4.8, p=.04) without significant differences between 4 and 8 months (B = .10, 95% CI: -2.1, 2.3, p=.9). The interaction was not significant, indicating that these time point improvements did not differ by study arm (p=.22). Accordingly, although the trend for improvement occurred in both conditions, the better scores in the CBT-AD condition were not sustained after acute treatment discontinuation.

For the CGI there was an absence of main effects for study arm (p=.10) during the follow-up period. There also were not effects for time (p=.28), indicating that scores did not significantly decline or improve after the treatment ended. The interaction effect was also not significant (p = .40), indicating that the non-significant effects for time did not differ by study arm during follow-up. Accordingly, although the CBT-AD condition did not have significantly worsening of scores after acute treatment discontinuation, the superiority over the control condition was no longer significant in the follow-up period.

*Diabetes Control (see Figure 2).* The CBT-AD arm maintained superior glycemic control compared to the ETAU group, as indicated by .63 lower A1C values (95% CI: .06, 1.2, p = .03), over the follow up. The main effects for time were not significant (p=.53), indicating maintenance of gains from the time of treatment discontinuation to month 8 or month 12. The
interaction effect was not significant (p=.49), indicating that the non-significant effects for time did not differ by study arm during follow-up. Accordingly, the CBT-AD condition retained superior A1C scores during the follow-up period.

**DISCUSSION**

After completing 4 months of CBT-AD patients with uncontrolled type 2 diabetes and depression had lower A1C (0.72 unit reduction), 21 percentage points better medication adherence, and 30 percentage points better adherence to self-monitoring of blood glucose than patients assigned to ETAU. For glycemic control, the effect of the intervention was comparable to the addition of a weak hypoglycemic medication (36). These gains were maintained over the 8 months of follow-up (after the acute provision of intervention) with between-group differences evident for glycemia and the two adherence outcomes.

For depression, right after acute treatment ended, at the 4-month assessment, those who received CBT-AD had scores that were 6.44 points better on the MADRS, and .74 points better on the CGI for depression, as compared to ETAU participants, indicating significantly lower levels of depression in the CBT-AD group. Although mean scores over time revealed continued improvement for both conditions, there was a lack of between-group difference in the post-intervention follow-up period. There are at least two possible conclusions from these data. The first is that the effects of CBT-AD on depression were not robust enough to be maintained over time, relative to alerting providers of depression diagnoses. However, depression scores in the intervention condition did not worsen during the follow-up, and data showed a trend for continued improvement in scores on the MADRS. Further, scores did not change differently across the two conditions during the follow-up. Therefore, another possible conclusion is this pattern of results could be related to the study design. Whenever clinically indicated,
participants were referred for further care for depression. At baseline, referring primary care providers were informed that depression had been detected in ETAU participants. Despite this, there were significant group differences on both depression outcomes. At follow-up, study staff (not primary care providers) directly referred ETAU participants with clinically significant depression for treatment outside of the study. Additionally, participants who were severely depressed (n=3, all in the ETAU group) were dropped from the study at month 4 (or any other time point, but it only happened at month 4) for ethical reasons, and referred to more intensive care. This ethical consideration may have affected the distribution of scores in the ETAU group, with the most severe scores for depression no longer being present. If it were not for this needed design, we may have seen stronger effects for depression. The maintenance of clinically significant effects on diabetes self-management and glycemic control over the follow-up, despite the lack of maintenance of our depression effects, suggests some degree of independence between these outcomes. This may also explain why previous trials that have been successful in treating depression in diabetes have failed to demonstrate corresponding benefits for self-management or glycemic control (14,15,16).

One difference between this study and earlier investigations of treatments for depression in diabetes (12–16) is that the current study integrated adherence counseling into the psychosocial treatment of depression versus treating depression without also specifically targeting adherence. The rationale for our integrative approach was based on the documented association of depression and poor diabetes treatment adherence (6) and the failure of previous trials to consistently impact glycemic control or diabetes self-management (12). Since the initiation of our trial, we are aware of two others that have taken a similarly integrative approach. One was successful in improving depression, medication adherence, and glycemic control for
patients already prescribed antidepressants (37). A second failed to impact self-management or medication adherence but did impact glycemic control and depression (38). However, this second trial differentially provided medications for depression, glycemic control, blood pressure, and lipids to experimental participants, relative to controls, which may have accounted for glycemic benefits observed in the absence of improvements in self-management (39). Our results therefore add to the evidence base for the conclusion that treating depression may be necessary but not sufficient to improve diabetes outcomes in depressed adults living with type 2 diabetes. Treating depression may allow patients to maximally benefit from adherence/self-care interventions such as those provided to both the experimental intervention and the comparison arms in the present study. The magnitude of our effects suggests the benefits on glycemic control of such an approach would be clinically meaningful.

There are several limitations to the study results to note. First, the study was meant to examine whether treating depression with an evidenced-based and comprehensive approach would be superior to enhanced treatment as usual which included nurse and dietician counseling and adherence counseling. We chose this approach because CBT is a widely studied treatment of depression, and well-designed depression treatment trials in diabetes had already demonstrated that depression treatment did not consistently result in improved glycemic control or diabetes self-management (14,15,39). We therefore sought to test an integrative approach in a design that could evaluate whether a more time-intensive intervention would have greater efficacy on a comprehensive set of depression and diabetes outcomes, relative to less intensive, but still significant enhancements to usual care. This design allows for greater translation of our findings to clinical practice in that there were no artificial restrictions on additional treatment in either arm, and the comparison group we evaluated more closely represents models of care that
could be implemented in practice. However, our design cannot address questions about the role of increased attention and non-specific support provided as part of our intervention. Second, the MEMs cap for the medication adherence outcome may be an underestimate of true adherence in that participants could take pills and not use the cap. To correct for this, we asked participants at study visits whether they recalled taking the pills without using the cap, and used a corrected adherence score (27–29). Third, the sample was 86% white, and hence additional study is needed to extend this to racial or ethnic minorities. Fourth, although brief for psychotherapy, the treatment was intensive, and the study design required patients to meet criteria for a depressive disorder. Subsequent work suggests that the relationship between depression and worse outcomes in diabetes is incremental and that patients with subclinical depression could also benefit from treatment (40). Finally, regarding antidepressants, due to variability in dose, type of medicine, and timing of any changes, and lack of measuring adherence, we were not able to include this as a variable in the analyses. Including this systematically may have increased the precision of the estimate of the effect of the intervention over and above ETAU, which can include use of antidepressants.

**Conclusion.** Given the high prevalence of depression in patients with diabetes, and the association of depression with poor adherence and outcomes, interventions to treat depression and improve adherence could improve diabetes care. Overall, these results suggest that a behavioral intervention for depression and diabetes treatment nonadherence (CBT-AD) (19,20), is effective for managing depression and treatment nonadherence and improving glycemic control in depressed adults with type 2 diabetes.
Author Notes

1. Of the 87 participants randomized, 84 had A1C levels of 7.0 (53 mmol/mol) or greater. Three participants had A1C approaching 7 (53 mmol/mol) on study blood draw but a self-reported A1C of above 7 (53 mmol/mol; levels were 6.8 (51 mmol/mol), 6.9 (52 mmol/mol), and 6.9 (52 mmol/mol)). These participants were entered into the study with a protocol exception as the study blood draw A1C values were considered essentially equivalent to 7 (53 mmol/mol).

2. Although we originally planned to also use average blood glucose downloaded from participants' glucometers as an additional indicator of glycemic control, experience with the initial participants and in our pilot demonstrated that this was not feasible as values would depend on timing of monitoring and whether the participant was fasting. In light of the burden to patients and the potential for error of reporting of fasting/not fasting, we dropped this outcome in favor of A1C, which is a superior indicator of glycemic control over time.

3. We monitored progress on depression at study visits using the Center for Epidemiologic Studies Depression Scale (CESD).

4. The full protocol may be accessed by request to the corresponding author.
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Author Contributions: Steven Safren, with Jeffrey Gonzalez, together led efforts to conceive of the study with input from the team. Safren was PI of the project, he performed the acute outcome analyses, lead the writing efforts for the first draft of the manuscript and
integrated co-author comments and edits. Gonzalez helped shape the CBT-AD intervention, provided clinical supervision to the study therapists and edited the manuscript, particularly the introduction and discussion. Deborah Wexler conducted background research, assisted with study operations and edited the manuscript. Christina Psaros played a strong role in study operations and implementation, and edited the manuscript, and drafted the methods section. Linda Delahanty contributed to the design, particularly of the nutritionist and nurse-delivered interventions and edited the manuscript. Aaron Blashill performed the follow-up analyses and wrote that part of the results section of the manuscript. Aleksandra Margolina edited the manuscript for submission and provided support throughout the submission process. Enrico Caglierio contributed to the biomedical conceptualization of the study, and oversaw study design operations and interface with the Diabetes Clinic, and edited the manuscript.

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MGH/Harvard Medical School.

Dr. Steven A. Safren had full access to all the data in the study and takes responsibility
for the integrity of the data and accuracy of data analysis. Dr. Safren conducted the pre-post
analyses, and Dr. Blashill (with input from Dr. Safren) the follow-up analyses.

**Previous Presentations:** Acute outcomes have been presented at the Annual Meeting of
the Association for the Advancement of Cognitive and Behavioral Therapies (November 2012).
Follow-up outcomes have presented at The Annual Meeting of the Society of Behavioral
Medicine (March 2013).
REFERENCES


Table 1: Baseline Demographics and Outcomes by Study Condition

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<td>Other</td>
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<td>2 (4.8%)</td>
</tr>
<tr>
<td>Native American</td>
<td>2 (4.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Ethnicity n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>45 (100.0%)</td>
<td>39 (92.9%)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0 (0.0%)</td>
<td>3 (7.1%)</td>
</tr>
<tr>
<td><strong>Insulin Status n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Medications only</td>
<td>21 (46.7%)</td>
<td>18 (42.9%)</td>
</tr>
<tr>
<td>Insulin Only</td>
<td>8 (17.8%)</td>
<td>7 (16.7%)</td>
</tr>
<tr>
<td>Both Oral Medications and</td>
<td>16 (35.6%)</td>
<td>17 (40.5%)</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical and adherence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>characteristics (unadjusted)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication Adherence (SD)</td>
<td>76.64% (25.99)</td>
<td>85.66% (24.62)</td>
</tr>
<tr>
<td>Glucose Monitoring</td>
<td>54.27% (35.63)</td>
<td>67.07% (32.20)</td>
</tr>
<tr>
<td>Depression – MADRS*</td>
<td>25.60 (8.99)</td>
<td>23.31 (7.20)</td>
</tr>
<tr>
<td>Depression – CGI †</td>
<td>4.42 (1.29)</td>
<td>3.98 (1.09)</td>
</tr>
<tr>
<td>A1C ‡</td>
<td>8.81% (73 mmol/mol)</td>
<td>8.74% (72 mmol/mol)</td>
</tr>
</tbody>
</table>

* MADRS = Montgomery Asberg Depression Rating Scale
† CGI = Clinical Global Impression
‡ A1C = Glycated hemoglobin
Table 2: Adjusted Post-Treatment (4-month) Outcome Scores* by Treatment Arm

<table>
<thead>
<tr>
<th></th>
<th>CBT-AD</th>
<th>ETAU</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard Error</td>
</tr>
<tr>
<td>MEMS</td>
<td>90.37</td>
<td>3.48</td>
</tr>
<tr>
<td>Glucose Monitoring</td>
<td>79.79</td>
<td>4.03</td>
</tr>
<tr>
<td>MADRS†</td>
<td>14.22</td>
<td>1.45</td>
</tr>
<tr>
<td>CGI‡</td>
<td>2.44</td>
<td>0.21</td>
</tr>
<tr>
<td>A1C§</td>
<td>7.86% (62 mmol/mol)</td>
<td>8.58% (70 mmol/mol)</td>
</tr>
</tbody>
</table>

* Scores are adjusted for baseline scores in the GLM analyses; all mean score differences were statistically significantly superior for the CBT-AD condition compared to ETAU. See online appendix for graphical depiction of these scores.
† MADRS = Montgomery Asberg Depression Rating Scale
‡ CGI = Clinical Global Impression
§ A1C = Glycated hemoglobin
Table 3: Adjusted Follow-up Outcome Scores* by Study Condition (Mean and Standard Error).

<table>
<thead>
<tr>
<th></th>
<th>Month 4</th>
<th></th>
<th>Month 8</th>
<th></th>
<th>Month 12</th>
<th></th>
<th>Condition</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CBT-AD</td>
<td>ETAU</td>
<td>CBT-AD</td>
<td>ETAU</td>
<td>CBT-AD</td>
<td>ETAU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEMS</td>
<td>91.37 (1.51)</td>
<td>73.99 (5.20)</td>
<td>80.81 (4.37)</td>
<td>73.40 (5.68)</td>
<td>88.63 (2.10)</td>
<td>64.38 (6.75)</td>
<td>.001</td>
<td>.14</td>
<td>.09</td>
</tr>
<tr>
<td>Glucose Monitoring</td>
<td>79.03 (4.07)</td>
<td>51.08 (5.19)</td>
<td>63.61 (5.63)</td>
<td>41.46 (6.57)</td>
<td>64.40 (5.61)</td>
<td>47.51 (6.11)</td>
<td>.043</td>
<td>.001</td>
<td>.24</td>
</tr>
<tr>
<td>MADRS†</td>
<td>14.83 (1.79)</td>
<td>20.03 (1.60)</td>
<td>16.62 (1.66)</td>
<td>18.02 (1.98)</td>
<td>13.72 (1.70)</td>
<td>16.21 (1.83)</td>
<td>.16</td>
<td>.06</td>
<td>.22</td>
</tr>
<tr>
<td>CGI‡</td>
<td>2.53 (0.24)</td>
<td>3.08 (0.23)</td>
<td>2.63 (0.25)</td>
<td>2.87 (0.29)</td>
<td>2.22 (0.23)</td>
<td>2.86 (0.26)</td>
<td>.10</td>
<td>.28</td>
<td>.40</td>
</tr>
<tr>
<td>A1C§</td>
<td>7.75 (61 mmol/mol)</td>
<td>8.57 (70 mmol/mol)</td>
<td>8.01 (64 mmol/mol)</td>
<td>8.57 (70 mmol/mol)</td>
<td>7.93 (63 mmol/mol)</td>
<td>8.44 (69 mmol/mol)</td>
<td>.03</td>
<td>.53</td>
<td>.49</td>
</tr>
</tbody>
</table>

*Scores are adjusted through the use of mixed effects analyses.
†MADRS = Montgomery Asberg Depression Rating Scale
‡CGI = Clinical Global Impression
§A1C = Glycated hemoglobin
See on line appendix for graphical depiction of these scores.
FIGURE LEGENDS

Figure 1: Participant Flow
Figure 1

Assessed for Eligibility (N = 209)

Reasons for exclusion
- Did not meet inclusion criteria (n = 99)
  - CGI too low and not on antidepressant (n = 21)
  - HbA1c <7% (53 mmol/mol) (n = 31)
  - Untreated mental illness that would have interfered with study participation (n = 11)
  - Not stable on diabetes medication (n = 5)
  - Received CBT within past 3 years (n = 1)
- Met inclusion/exclusion criteria at baseline, but dropped out prior to randomization (n = 23)

Randomized (n = 87)

Randomized to CBT (n = 45)
- Completed Treatment and 4-month assessment (n = 40)
  - Did not complete Treatment or 4 month assessment (n = 5)
    - 2 lost interest
    - 2 sickness
    - 1 job interference

Randomized to ETAU (n = 42)
- Completed 4-Month (Post Treatment) Assessment (n = 38)
  - Dropped out (n = 4)
    - 3 Lost interest
    - 1 Lost contact

Allocation

4 Month Follow Up
- Completed Assessment (n = 36)
  - Did not Complete Assessment (n = 9)
    - 4 unable to schedule (1 HbA1c obtained from medical record)
  - Dropped Out (n = 0 new drop outs, 5 total)

8 Month Follow Up
- Completed 12-Month Assessment (n = 38)
  - Dropped Out (n = 2; 7 total)
    - 2 lost contact
    - note – 4 who did not complete 8-month assessment returned for this visit

12 Month Follow Up
- Used in pre-post (acute outcome) analyses (n=45; all outcome)
- Used in follow-up analyses (n=40 depression and HbA1c outcomes; n=40glucose monitoring; n = 37 for MEMs)

Used in pre-post (acute outcome) analyses (n=42; all outcomes)
- Used in follow-up analyses (n=38 depression and HbA1c outcomes; n=36 glucose monitoring; n = 29 for MEMs)

Removed from Study by PI due to worsening of depression; referred for more intensive treatment (n = 2)
### Appendix 1: Further details off the Cognitive Behavioral Interventions

#### I. Life-Steps Adherence Counseling Intervention

All participants had one session of “Life-Steps”, a stand-alone cognitive behavioral therapy (CBT) intervention designed to improve adherence to medical recommendations and self-care goals, in this case, set by the dietitian and nurse. The counseling begins with a discussion of their illness, including cognitions related to illness and self-care behaviors. The discussion also involves a review of general struggles with adherence, how participants have coped with their illness, and general goal setting for self-care. It then consists of eleven informational, problem-solving, and cognitive-behavioral steps that target a range of self-care behaviors. In each step, patients and the clinician define the problem, generate alternative solutions, make decisions about the alternatives, and make a plan about how to implement solutions. The steps are

1. Provide education, interactively, about adherence
2. Plan for transportation to medical appointments
3. Plan for obtaining medications or other self-care items
4. Plan for optimizing communication with medical and mental health care providers
5. Plan for coping with side-effects of medications and medical regimens
6. Formulate a daily schedule for medications and other self-care behaviors (i.e. glucose monitoring for diabetes, exercise etc).
7. Plan for storing medications
8. Develop cues for taking medications or implementing other self-care procedures (i.e. glucose monitoring)
9. Prepare for adaptively coping with slips in adherence and preventing relapse
10. Review all new plans
11. Follow-up phone call (optional)

One important aspect of the intervention is to try to help patients change their cognitions about self-care behaviors in that we elicit positive reasons for being adherent (e.g. “I want to be healthy for my children”) and actively think such thoughts when engaging in adherence behaviors instead of focusing on potential cognitive barriers (e.g. “This illness limits me”, “Taking these medicines remind me that I am sick”). By the end of the session the therapist and participant collaboratively establish ways to implement the goals set by the nutritionist and the nurse for diet and self-care behaviors, including glucose monitoring.

#### II. Cognitive Behavioral Therapy for Adherence and Depression (CBT-AD)

The core modules in CBT-AD are summarized briefly below, and a more detailed description of CBT-AD can be found elsewhere. Although the modules are presented in a specific sequence, the treatment is designed to provide the clinician with the flexibility to adapt the treatment to the patient’s needs. The number of sessions spent on each module is designed to be flexible as well, in order to address areas that are particularly salient to the patient or difficult for the patient to implement.

As reviewed above, the overall intervention is organized into a one-session intervention focused on adherence, followed by four modules focused on adherence and depression (CBT-
AD). After Life-Steps, nine to eleven sessions of CBT-AD focus on addressing deficits in self-care and teaching specific cognitive behavioral skills to treat symptoms of depression. Each therapist determined whether the tenth and eleventh sessions were necessary on a case-by-case basis, depending on patient needs and the therapist’s assessment of patient progress. At the beginning of each treatment session, the patient completed the CES-D and several adherence questionnaires, and the patient’s glucometer and pill cap were read electronically. The therapist then addressed remaining ongoing deficits in self-care and established new goals as necessary.

The first module of the intervention (approximately one session) introduces the patient to the nature of cognitive behavioral therapy and transitions into motivational interviewing for behavior change. The motivational interviewing component involves going over the pros and cons of changing to improve depression and diabetes self-care, as well as the pros and cons of not changing. It then involves providing a rating of motivation, and then the participant is asked to justify the rating. This is designed to reduce ambivalence about change, and maximize thoughts about the pros of changing and the cons of not changing.

The second module (approximately one session) focuses on behavioral activation and activity scheduling with mood monitoring. Monitoring of blood glucose levels and tracking dietary and physical activity behaviors that influence glucose levels is another key component of this module. Behavioral activation/activity scheduling involves identifying activities that the patient enjoys or used to enjoy doing, and helping them re-learn how to re-engage in these types of activities.

The third module (approximately five sessions) focuses on thought monitoring and cognitive restructuring. Elicitation of maladaptive cognitions, identification of distortions, and training in cognitive restructuring target both thoughts relevant to depression and those relevant to diabetes treatment adherence and self-care. A common cognitive strategy used with all patients was to challenge patients’ tendencies to engage in self-blame or avoidance in regard to glucose monitoring (e.g., ‘my glucose values are always bad so I’d rather not know’ or ‘I don’t want another reminder of how I’ve failed with my diabetes’) and to restructure these cognitions toward an approach to self-monitoring that was based in curiosity and hypothesis-testing rather than judgments of good versus bad numbers. For example, patients are encouraged to think about what factors (e.g., diet, exercise, adherence to medications) might explain personal variations in glucose values rather than exclusively focusing on the fact that values were too high.

The fourth module (approximately two sessions) focuses on problem-solving as a skill to aid in the decision-making process. Problem-solving can be used to address any remaining issues related to depression and self-care behaviors that have not been resolved at this point. There are two components to problem-solving as a skill: 1) selection of a solution/ action plan for a particular problem, and 2) breaking down that problem into manageable steps.

The fifth module (approximately two sessions) involves instruction in relaxation training, including diaphragmatic breathing and progressive muscle relaxation.

REFERENCES


Graphical Depiction of Adjusted Acute (4-month) Adherence Outcome Scores:

**MEMS Medication Adherence**

Significant effect for treatment condition (p=.000) showing superiority of CBT-AD

**Glucose Monitoring Adherence**

Significant effect for treatment condition (p<.0001) showing superiority of CBT-AD
Graphical Depiction of Adjusted Acute (4-month) Depression Outcome Scores:

Significant effect for treatment condition ($p=.002$) showing superiority of CBT-AD

Significant effect for treatment condition ($p=.01$)
Graphical Depiction of Adjusted Acute (4-month) HbA1c Outcomes:

Significant effect for treatment condition (p=.001) showing superiority of CBT-AD
**Graphical Depiction of Adjusted Follow-Up Adherence Outcome Scores:**

**Glucose Monitoring Adherence**

- Main effect for treatment condition (p=.001) showing superiority of CBT-AD.
- Main effect for time (p=.001) showing that month 8 (p=.001) and month 12 were lower than month 4.
- Interaction of time x condition not significant.

**MEMS Medication Adherence**

- Main effect for treatment condition showing superiority of CBT-AD (p<=.001)
- Main effect for time not significant showing that CBT-AD maintained their gains.
- Interaction of time x condition not significant.
Main effect for study condition not significant.
Main effect for time not significant (showing that CGI depression scores did not improve or decline during the follow-up period).
Interaction not significant.
Graphical Depiction of Follow-Up HbA1c Outcome Scores:

Main effect for treatment significant (p=.03) showing superiority of the CBT-AD condition.
Main effect for time not significant, showing that HbA1c values did not improve or worsen after the 4 month assessment.
Interaction not significant.
## Raw mean scores for all time points

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 4</th>
<th>Month 8</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CBT-AD</td>
<td>ETAU</td>
<td>CBT-AD</td>
<td>ETAU</td>
</tr>
<tr>
<td>MEMS</td>
<td>78.57</td>
<td>85.56</td>
<td>92.03</td>
<td>74.17</td>
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<td></td>
<td>(23.69)</td>
<td>(25.86)</td>
<td>(9.13)</td>
<td>(28.59)</td>
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<td>Glucose Monitoring</td>
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<td>67.07</td>
<td>79.03</td>
<td>52.05</td>
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<td></td>
<td>(35.62)</td>
<td>(32.20)</td>
<td>(26.04)</td>
<td>(31.63)</td>
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<tr>
<td>MADRS†</td>
<td>25.60</td>
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<td>14.82</td>
<td>20.03</td>
</tr>
<tr>
<td></td>
<td>(8.98)</td>
<td>(7.20)</td>
<td>(11.47)</td>
<td>(10.01)</td>
</tr>
<tr>
<td>CGI‡</td>
<td>4.42 (1.28)</td>
<td>3.98 (1.09)</td>
<td>2.53 (1.54)</td>
<td>3.08 (1.42)</td>
</tr>
<tr>
<td>HbA1C§</td>
<td>8.81 (73 mmol/mol)</td>
<td>8.73 (72 mmol/mol)</td>
<td>7.75 (61 mmol/mol)</td>
<td>8.57 (70 mmol/mol)</td>
</tr>
<tr>
<td></td>
<td>(1.77)</td>
<td>(1.40)</td>
<td>(1.25)</td>
<td>(1.58)</td>
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