Program ACTIVE II: Outcomes From a Randomized, Multistate Community-Based Depression Treatment for Rural and Urban Adults With Type 2 Diabetes

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OBJECTIVE

Depression (major depressive disorder [MDD]) in adults with type 2 diabetes mellitus (T2DM) is associated with worsened diabetes complications, increased health care costs, and early mortality. Program ACTIVE II was a randomized, controlled, multicenter treatment trial designed to test the comparative effectiveness of cognitive behavioral therapy (CBT) and/or community-based exercise (EXER) on diabetes and depression outcomes compared with usual care (UC).

RESEARCH DESIGN AND METHODS

Using a 2 × 2 factorial randomized controlled trial design, adults with T2DM for ≥1 year who met DSM-IV-TR criteria for MDD were randomized to CBT (10 sessions occurring over 12 weeks; *N* = 36), EXER (12 weeks of community-based exercise including six sessions with a personal trainer; *N* = 34), CBT+EXER (concurrent over a 12-week period; *N* = 34), and UC (*N* = 36). Primary outcomes were depression remission rate (assessed by psychiatric interviewers blind to assignment) and change in glycemic control (HbA_{1c}).

RESULTS

The mean age was 56.0 years (SD 10.7). Participants were female (77%), white (71%), and married (52%). After controlling for education and antidepressant use, odds of achieving full MDD remission in the intervention groups were 5.0–6.8 times greater than UC ($P < 0.0167$). The CBT+EXER group demonstrated improved HbA_{1c} compared with UC. For participants with a baseline HbA_{1c} ≥7.0%, exploratory post hoc subgroup analysis showed that the CBT+EXER group had a 1.1% improvement in HbA_{1c} ($P < 0.0001$) after controlling for covariates.

CONCLUSIONS

The Program ACTIVE behavioral treatment interventions demonstrated clinically meaningful improvements in depression outcomes in adults with T2DM and MDD. These community-based interventions are complementary to medical care and extend access to those in rural and urban areas.

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The personal and economic burden of type 2 diabetes mellitus (T2DM) is considerable and growing worldwide. More than 30.2 million adults in the U.S. have diabetes (1), resulting in annual T2DM-related costs of >$327 billion (2). Low-income urban and rural areas, such as the Appalachian region, bear a disproportionate burden of the U.S. T2DM epidemic (1). Similar to urban underresourced areas, the Appalachian region bears a disproportionate burden of major depressive disorder (MDD) (10.6%) compared with non-Appalachian areas in the U.S. (7.6%) (3).

Patients with T2DM are two times more likely to experience depressive symptoms than their peers without diabetes, with one in four patients reporting elevated depressive symptoms and 11.4% meeting the criteria for MDD (4). Depressive symptoms are associated with worsened diabetes outcomes including higher blood glucose levels, greater rates and severity of diabetes complications, decreased adherence to diabetes care regimens, increased functional disability, increased health care costs (4), decreased quality of life (QOL), and earlier all-cause mortality (5).

In the general population, cognitive behavioral therapy (CBT) (6) and exercise (7) have been widely demonstrated to be effective treatments for depression (8). However, few randomized, controlled, behavioral treatment trials tailored for the treatment of depression and T2DM have been studied (9,10). Lustman et al. (9) conducted a randomized controlled trial (N = 51 participants with T2DM) of a 10-week individualized CBT compared with diabetes education. The remission rate of MDD was 85% in those receiving CBT at the end of the intervention period (9). Although no group differences in baseline-adjusted HbA_{1c} levels were found at posttreatment assessment, the CBT arm showed a 0.7% improvement in HbA_{1c} at the 6-month follow-up assessment compared with control subjects (9).

In the Pathways Study, problem-solving therapy was integrated within primary care settings to treat depression in adults with T2DM (11). Participants randomized to a stepped-care problem-solving therapy intervention reported higher levels of treatment exposure, satisfaction with care, and improved depression outcomes compared with patients in the usual care (UC) group. No improvements in glycemic control were observed (11). Subsequent trials of the collaborative care model that have targeted multiple intervention targets (depression, HbA_{1c}, dyslipidemia, and blood pressure) have demonstrated consistent improvements in depression outcomes and mixed results on improvements in HbA_{1c} (12).

Piette et al. (13) tested a combination of telephone-based manualized CBT (12 weeks) with a prescribed walking program compared with enhanced UC in a sample of 291 veterans with T2DM and depressive symptoms. At the 12-month follow-up, 58% of participants in the intervention group reported mild depressive symptoms. Step counts were higher and systolic blood pressure was lower in the intervention group. No changes were observed in HbA_{1c} at the 12-month follow-up assessment (13). In this study, telephone-based CBT and walking interventions were combined and could not be evaluated for depression and HbA_{1c} outcomes separately.

No studies have evaluated the comparative effectiveness of CBT and exercise alone and in combination implemented within community settings by partnering with community-based fitness and mental health providers. Program ACTIVE II was designed to test the comparative effectiveness of CBT and/or community-based exercise (EXER) to UC. We hypothesized that participants assigned to the CBT+EXER treatment would show the greatest improvement in depression and HbA_{1c} followed by those in the EXER group in comparison with the CBT group.

RESEARCH DESIGN AND METHODS

Program ACTIVE II was a multicenter, repeated-measures, randomized controlled trial conducted in three U.S. states (Ohio, West Virginia, and Indiana). The study used a community-engaged research approach in which community organizations participated in recruitment, intervention implementation, and dissemination of findings. The study protocol was approved by the institutional review boards of Indiana University, Ohio University, and West Virginia University. A Data Safety Monitoring Board provided ethical and safety oversight with expert consultation in the primary disciplines involved in the content of the study: endocrinology, medicine, and exercise physiology.

The study design is described in detail elsewhere (14). Participants were screened by telephone and invited to attend a baseline assessment visit during which inclusion and exclusion criteria were further evaluated (see MEASURES below). At the beginning of the baseline assessment visit, the informed consent process was performed by the study staff, and participants provided written consent to participate in the study. Following a case consensus conference by the principal investigators and randomization, participants attended follow-up assessment visits at postintervention (week 13 following group assignment) and 6 and 12 months postintervention.

Inclusion and exclusion criteria are shown in Supplementary Table 1. Respondents who met eligibility criteria were invited to participate in the baseline screening assessment and referred to their local study site (14).

Advertising was conducted in physician offices, newspapers, radio stations, community centers, partnering community organizations, and community events. Patients of partner medical practices were contacted by phone for recruitment to the study by research staff (14). Participants were recruited from May 2012 to May 2016. Follow-up assessment visits were conducted from August 2012 to July 2017.

Randomization Plan

Study participants were randomly assigned to one of the four groups: 10 sessions of standardized CBT delivered by trained master's and doctoral-level community mental health professionals (CBT alone), 12 weeks of community-based exercise (EXER alone) using standardized materials and delivered by trained community exercise professionals, concurrent CBT and EXER interventions (CBT+EXER), or UC. All participants were offered Dining with Diabetes, a U.S. Centers for Disease Control and Prevention–certified nutrition education program offered through county extension programs in their state as an incentive for study participation.

Randomization used a 1:1:1:1 ratio. A block size of four was used, and separate randomization lists were prepared for each study site. The study statistician provided computer-generated randomization lists using SAS software. Randomization lists were loaded in a password-protected study database, and the study coordinators pressed a button to electronically randomize the participants using the lists in the order that the lists were prepared.

Sample Size

We used a 2 × 2 factorial study design. To assess the main effect of EXER, we used the change in HbA_{1c} at posttreatment from baseline, and to assess the main effect of CBT, we used the MDD remission rate at postintervention. The study had 80% power to detect an effect size of 0.50 for the change in HbA_{1c} with a sample size of 32 in each of the four groups. Based on literature review, we assumed 60% and 30% remission rates for the CBT and non-CBT groups, respectively (14). The proposed sample size provided 93% power to detect an absolute difference of 30% improvement in remission rate while relative improvement was 100%; that is, the absolute difference of improvement in remission rate to the remission rate in the non-CBT group.

Measures

Psychological, behavioral, and physiologic measures were administered at baseline and postintervention assessment periods to assess primary and secondary outcomes (14). In addition, measures pertinent to the clinical care of individuals assigned to specific interventions (e.g., Beck Depression Inventory-II [BDI-II] for those assigned to the CBT groups; physical activity diaries for those assigned to the EXER groups) were administered throughout the intervention period for the purposes of clinical monitoring. Data collected at the baseline (time 1) and postintervention assessment (time 2) time points are reported in this study.

The Structured Clinical Interview for the DSM-IV-TR was used to establish MDD diagnostic eligibility during the baseline assessment visit and to determine diagnosis status at the postintervention assessment visit. The Structured Clinical Interview for the DSM-IV-TR has been shown to have validity and adequate inter-rater (κ = 0.61–0.68) and test-retest reliabilities (r = 0.64–0.69) for the diagnosis of major depression (15). Interviewer inter-rater agreement against a gold standard for Program ACTIVE interviewers was Cohen $\kappa > 0.90$ level. A case conference diagnosis assignment process was used to achieve consensus on psychiatric diagnosis and to prevent rater drift. The BDI-II was used to assess severity of depressive symptoms (16). The BDI-II has been shown to have excellent test-retest reliability and validity when used in populations with T2DM (17). The Automatic Thoughts Questionnaire was collected to assess severity of depressogenic cognitions (18).

Psychosocial functioning was measured using the Medical Outcomes Study SF-12 (19). Internal consistency (test-retest reliability) in adult samples has been found to be r = 0.81–0.88 with acceptable validity in T2DM samples (20). The Physical Component Score and Mental Component Score subscales were calculated. Diabetes Quality of Life Measure was used to assess diabetes-specific QOL (21). It has demonstrated acceptable levels of reliability, internal consistency, and external validity in T2DM samples (22). Diabetes-related distress was assessed using the Diabetes Distress Scale 17 for T2DM samples. The measure has been found to have acceptable levels of reliability, internal consistency, and external validity of T2DM samples (23).

Medical variables included current and past medical history data, T2DM duration, prescribed diabetes treatment regimen, medication history, number, and severity of diabetes complications. Glycated hemoglobin (HbA_{1c}) samples were drawn via nonfasting venipuncture and analyzed at Clinical Laboratory Improvement Amendments–licensed testing facilities with locations throughout the study recruitment areas.

The Six-Minute Walk Test (6MWT) as originally described by Guyatt et al. (24) was used to evaluate aerobic capacity before and after exercise intervention with minor safety modifications at one site (Indiana University) to reduce cardiovascular risk associated with maximal exertion. Total distance covered was measured in meters with a distance-measuring wheel (25). Resting, exercise, and recovery blood pressures were measured via auscultation with a calibrated sphygmomanometer at rest and peak performance by fitness directors during the exercise intervention, in conjunction with collection of Borg exertion ratings for clinical monitoring purposes (26). Anthropometric measurements were taken to estimate body composition and regional adipose distribution. BMI was calculated. Height and weight were measured on a Detecto physician's scale with stadiometer, measuring height to the nearest half inch and weight to the pound. Waist circumference (girth) was assessed with a constant tension tape measure (Gulick tape) at the narrowest portion of the torso, while a hip measurement was made at the maximum posterior extension of the buttocks. The waist-to-hip ratio was calculated (27).

Baseline assessment data were reviewed by the study team to determine eligibility for enrollment. Participants were randomized to one of the four intervention groups (CBT, EXER, CBT+EXER, or UC), and all were offered the Dining with Diabetes nutrition education program within 1 week of randomization.

Interventions

CBT Intervention. Participants received 10 sessions of individual CBT using a manualized approach based on Beck's model of cognitive therapy (16) delivered by trained master's and doctoral-level licensed community mental health providers. Manualized interventions that use a standardized set of materials were used to increase the fidelity of the intervention delivery. Psychotherapy practices ranged from individual private practices to community mental health centers. Ten sessions were scheduled weekly over the course of the 12-week period. Therapists attended telephone-based peer supervision sessions facilitated by the principal investigator (M.d.G.) and coinvestigator (Y.P.) during treatment with participants. Treatment involved the identification and restructuring of "automatic thoughts" (i.e., cognitive biases) that work in the service of depressogenic core cognitive beliefs (16). The use of cognitive and behavioral tools modeled in therapy and practiced by participants outside sessions provided participants with an opportunity to generalize skills to situations beyond the therapeutic relationship.

Exercise Intervention. Trained instructors from community fitness centers provided six classes of monitored instruction on exercise to participants to meet heart rate and activity-level goals. Fitness centers included community centers, Young Men's Christian Association (YMCA) franchises, and physical therapy practices. The exercise intervention was adapted from the Diabetes Prevention Program (28). Membership to the fitness centers was provided to participants by the study throughout the 12-week intervention period.

Participants were assigned exercise goals of performing 150 min/week of moderate activity at 40 to <60% of heart rate reserve, comparable to a Rating of Perceived Exertion of 11–13. Goals could

be modified based on the results of the 6MWT. Due to the high prevalence of sedentary behaviors in this population, physical activity goals were initially set low and increased in a graduated fashion (100 min in week 1 to 150 min by week 4) over the 12-week intervention period. Targets for intensity of activity began at 40% of heart rate reserve in week 1 and progressed as tolerated, but remained below 60% of heart rate reserve. Participants were trained to exercise in a manner consistent with American College of Sports Medicine recommendations including 10 min of preactivity (warm-up and stretching), 30 min of active exercise (endurance), and 10 min of postactivity (cool down and recovery) (17,26). Heart rate and blood pressure were measured at rest, at peak activity level, and following recovery. Participants were trained to use the Borg Scale (29) during their activity to monitor exercise intensity. Participants were provided with a supplemental workbook designed to address psychological barriers associated with physical activity (e.g., social support, motivation, and behavioral goals). Participants in these arms were contacted biweekly by the study team to evaluate any exercise-related adverse events.

Statistical Analyses

Descriptive statistics (mean and SD) were used to summarize all baseline continuous variables. Baseline clinical and demographic data were compared among the four treatment groups. Dichotomous and ordinal variables were examined using either χ^2 test or Fisher exact test. Continuous measures were examined using ANOVA.

The primary outcomes were depression remission and change in HbA_{1c} at the posttreatment assessment visit (time 2). Secondary outcomes included changes in psychological and medical outcomes. The changes in all outcomes were analyzed using an ANCOVA model. Treatment group–specific least square means were estimated from the ANCOVA model and each of the three treatment groups, CBT, EXER, and CBT+EXER, were compared with the UC group. Group comparisons were adjusted for the baseline value of the outcome variable and education status. Analyses of change in HbA_{1c} were adjusted for changes to diabetes medications. A logistic regression model was used to model attainment of partial or full remission, adjusting for education status and change in antidepressant or neuropathic pain medication. The main effects of EXER and CBT on the remission rates and the changes in HbA_{1c} were estimated from the ANCOVA and the logistic regression models when there was no interaction effect between EXER and CBT. Bonferroni correction method for multiple comparisons was used for three pairwise comparisons; that is, familywise type I error rate of 0.0167 was used instead of 0.05 for all primary outcomes. Because secondary outcomes analyses were considered to be exploratory, we did not apply this adjustment for multiple comparisons on all secondary outcomes. We did not assess the main effect of EXER and CBT on secondary outcomes because we were primarily interested in comparing three active treatment groups with UC. A negative binomial distribution was used to model the number of adverse events because of overdispersion. Sensitivity analyses were performed to account for missing data at posttreatment and included the multiple imputation method with the assumption that missing data at postintervention assessment was a function of treatment group and baseline value of the response variable.

RESULTS

Sample Characteristics

The CONSORT enrollment flow chart is shown in Fig. 1. One hundred eighty participants completed in-person screening assessments for eligibility from which *N* = 140 participants were enrolled (78% response rate). Demographic characteristics of the enrolled sample (*N* = 140) are shown in Table 1. The mean age was 56 years (SD 10.7), and the sample was 77% female, 71% white, and 52% married. Participants represented a broad range of educational attainment and income levels drawn from underresourced rural and

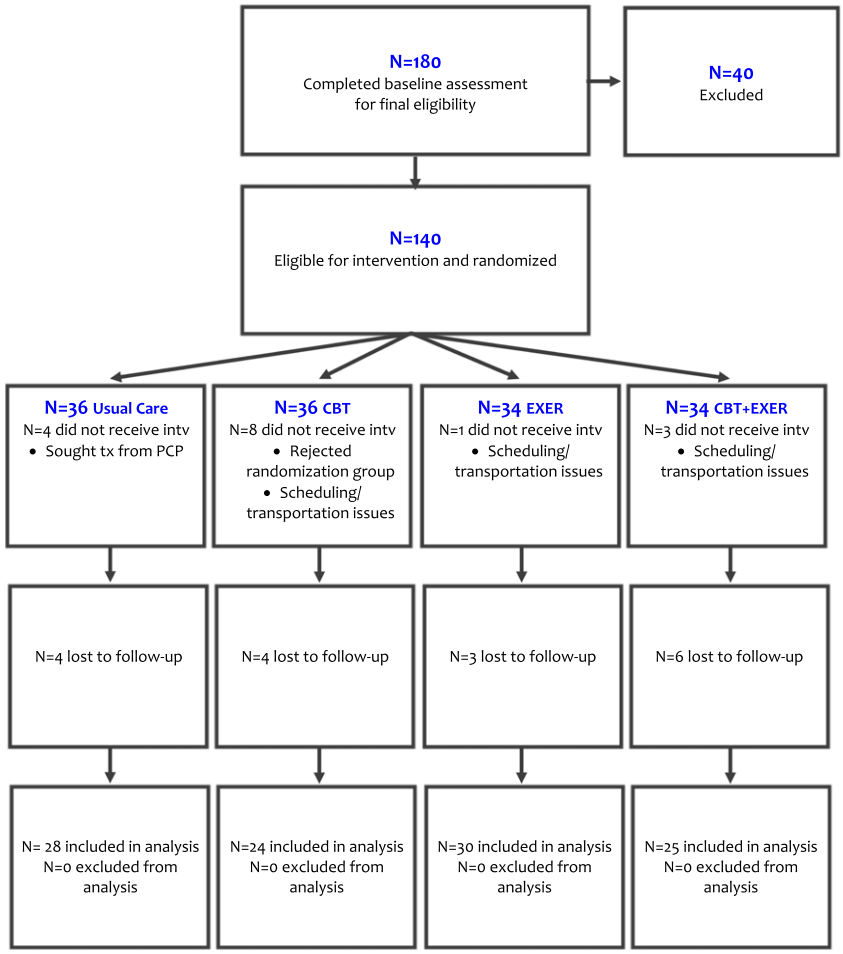

Figure 1—Program ACTIVE II CONSORT flow chart. Intv, intervention; PCP, primary care provider; Tx, treatment.

Table 1—Baseline demographic characteristics for Program ACTIVE II

Outcome	CBT (*N* = 36)	CBT+EXER (*N* = 34)	EXER (*N* = 34)	UC (*N* = 36)	*P* value
Age, years, mean (SD)	57.9 (10.9)	57.1 (10.7)	54.6 (10.7)	54.2 (10.4)	0.367
Sex					0.788
Male	10 (27.8)	6 (17.7)	8 (23.5)	9 (25.0)	
Female	26 (72.2)	28 (82.4)	26 (76.5)	27 (75.0)	
Race					0.376
White	27 (79.4)	25 (78.1)	25 (75.8)	22 (62.9)	
Not white	7 (20.6)	7 (21.9)	8 (24.2)	13 (37.1)	
Marital status					0.935
Now married	19 (52.8)	14 (41.2)	20 (58.8)	20 (55.6)	
Never married	5 (13.9)	7 (20.6)	4 (11.8)	5 (13.9)	
Divorced	8 (22.2)	9 (26.5)	5 (14.7)	7 (19.4)	
Separated/widowed/other	4 (11.1)	4 (11.8)	5 (14.7)	4 (11.1)	
Education					0.066
Less than or equal to high school	13 (36.1)	7 (20.6)	5 (14.7)	3 (8.3)	
Trade school/part college	8 (22.2)	14 (41.2)	15 (44.1)	13 (36.1)	
4-Year college or higher	15 (41.7)	13 (38.2)	14 (41.2)	20 (55.6)	
Income					0.823
≤$20,000	7 (20.6)	8 (25.0)	9 (27.3)	9 (26.5)	
$21,000–40,000	14 (41.2)	13 (40.6)	10 (30.3)	9 (26.5)	
$41,000–60,000	6 (17.7)	4 (12.5)	8 (24.2)	5 (14.7)	
≥$61,000	7 (20.6)	7 (21.9)	6 (18.2)	11 (32.4)	
Home ownership (yes)	23 (67.7)	21 (65.6)	21 (67.7)	29 (82.9)	0.363
Work outside home (yes)	16 (47.1)	17 (53.1)	21 (63.6)	21 (60.0)	0.528
Household size, mean (SD)	2.49 (1.3)	1.88 (0.9)	2.33 (1.3)	2.32 (1.2)	0.177
Difficulty making ends meet					0.637
Hard or very hard	17 (50.0)	13 (40.6)	15 (45.5)	22 (62.9)	
50/50	13 (38.2)	14 (43.8)	15 (45.5)	10 (28.6)	
Easy or very easy	4 (11.8)	5 (15.6)	3 (9.1)	3 (8.6)	
Medications, *N* (%)					NS
Diet and exercise only	2 (5.9)	2 (5.6)	2 (6.1)	3 (9.1)	
Single noninsulin medication (e.g., metformin)	8 (23.5)	1 (27.8)	9 (27.3)	13 (39.4)	
Two or more noninsulin medications (e.g., metformin plus sulfonylureas)	7 (20.6)	10 (27.8)	8 (24.2)	9 (27.3)	
Basal insulin only	9 (26.5)	7 (19.4)	6 (18.2)	2 (6.1)	
Intensive bolus insulin (e.g., basal bolus insulin or premixed insulin)	8 (23.5)	7 (19.4)	8 (24.2)	6 (18.2)	
Health insurance (yes)	30 (88.2)	29 (90.6)	30 (90.9)	29 (82.9)	0.716
Current PCP (yes)	34 (100.0)	30 (93.8)	31 (93.9)	33 (94.3)	0.542
Current endocrinologist (yes)	11 (32.4)	7 (21.9)	8 (24.2)	8 (22.9)	0.748

Figures are counts (%) until mentioned otherwise. PCP, primary care physician.

urban geographic areas. Demographic characteristics did not differ by randomization group. A majority of the enrolled participants (107 out of 140) completed both baseline and postintervention assessments. Participants who did not complete the interventions reported difficulty with scheduling and/or transportation barriers to attendance. A small proportion in each sample was unable to be reached by study staff after enrollment (i.e., lost to follow-up) attributable to transiency of work, telephone access, or changes in living location/circumstances. There were no significant differences by study site in rates or characteristics of noncompleters.

Evaluation of adverse events for the interventions indicated that the nature and number of adverse events across all three active treatment groups did not differ from the UC group ($P > 0.19$).

Primary Outcomes

At postintervention (Table 2), full remission from MDD was 66% in the CBT arm, 72% in the EXER arm, and 71% in the CBT+EXER arm compared with 32% in UC. There was an interaction effect between CBT and EXER on full remission rate ($P = 0.05$); that is, the odds ratio (OR) of CBT group when compared with UC was substantially different from the OR of CBT+EXER when compared with the EXER group. Pairwise comparisons showed that the odds of achieving full remission from MDD for all intervention groups (CBT: 5.0; EXER: 6.8; and CBT+EXER: 5.9; all $P < 0.0167$) were greater than the UC group after controlling for education level at baseline and changes to antidepressant medications during the intervention period.

At baseline, no differences were observed in mean HbA_{1c} values (EXER: 8.1%, SD 1.7%; CBT: 8.0%, SD 1.6%; CBT+EXER: 7.5%, SD 1.6%; and UC: 8.0%, SD 1.9%). Analysis of whole sample changes in HbA_{1c} showed no interaction effect between EXER and CBT on the change in HbA_{1c}.

Table 2—OR for depression remission compared with UC at postintervention assessment

	OR (95% CI)			*P* value		
	CBT	CBT+EXER	EXER	CBT	CBT+EXER	EXER
Model 1: full/partial remission MDD	12.44 (1.33, 116.66)	2.28 (0.61, 8.50)	5.80 (1.30, 25.81)	**0.028**	0.218	**0.021**
Model 2: full remission MDD	5.00 (1.39, 17.98)	5.90 (1.69, 20.58)	6.78 (2.03, 22.64)	**0.014**	**0.006**	**0.002**

Logistic regression analysis. Treatment group comparisons were adjusted for baseline education status and change in antidepressant or neuropathic pain medications (0 if no change and 1 if an increase) at postassessment. *P* values reaching statistical significance appear in boldface type.

Therefore, the response to the CBT+EXER interventions was considered additive. The main effect of EXER and CBT on the change in HbA_{1c} was not significant. Among all three pairwise comparisons, only the CBT+EXER group showed significant improvement compared with UC. Analysis of mean changes in weight and BMI showed no differences in the treatment groups compared with UC.

We also performed an exploratory subgroup analysis for the majority of the sample with a baseline $HbA_{1c} \geq 7.0\%$. A minority of the sample (N = 49) that completed baseline and postintervention data had baseline HbA_{1c} values $<7.0\%$. For these individuals who were already reaching their glycemic management goals, there was limited variability to be able to make an improvement in HbA_{1c} attributable to the intervention. There was no interaction effect between CBT and EXER. The main effect of EXER (mean $\pm$ SE) was -0.71 ± 0.35 (P = 0.048), but CBT did not show any significant effect. The CBT+EXER arm showed a 1.1% improvement in HbA_{1c} ($P < 0.0001$) compared with UC after controlling for baseline education and changes in diabetes medications (Table 3).

Secondary Outcomes

Mean values at baseline and postintervention for secondary outcome variables are shown in Supplementary Table 2, and change in mean values are shown in Table 4.

Depression Outcomes

At the postintervention time point, participants assigned to CBT, EXER, or CBT+EXER reported greater improvement in depressive symptoms ($P < 0.05$) and greater improvement in negative automatic thoughts ($P < 0.05$) compared with UC (Table 4).

Psychosocial Outcomes

As shown in Table 4, participants in the EXER and CBT+EXER groups showed improvements in physical QOL ($P < 0.05$) and diabetes-specific QOL ($P < 0.01$) compared with UC at postintervention. Participants in all three active intervention groups (CBT, EXER, and CBT+EXER) showed improvements in diabetes-related distress compared with UC at postintervention.

Lipid Outcomes

Medical outcomes are presented in Table 3. Modest improvements in total cholesterol were observed in the CBT ($P < 0.05$) and EXER ($P < 0.05$) arms compared with UC at postintervention. No differences between the active intervention groups and UC were observed at postintervention on the 6MWT.

Sensitivity Analyses

Sensitivity analyses were performed on the primary and secondary outcomes, including change in HbA_{1c} for the subgroup with baseline values $\geq 7\%$. These analyses showed that baseline values were similar between subjects with missing values versus subjects without missing values. In addition, pairwise comparisons also showed very similar findings to what we observed for the subject without any missing values.

Table 3—Change in medical outcomes at posttreatment from baseline

	Treatment, least square mean (SE)[1]				*P* value compared with UC		
Outcome	CBT (N = 24)	CBT+EXER (N = 25)	EXER (N = 30)	UC (N = 28)	CBT	CBT+EXER	EXER
HbA_{1c}[2]							
All subjects	0.06 (0.13)	−0.17 (0.13)	−0.03 (0.13)	0.20 (0.13)	0.379	**0.016**	0.132
Baseline value ≥7% N = 60	0.06 (0.18) (N = 16)	−0.74 (0.21) (N = 10)	−0.07 (0.17) (N = 18)	0.31 (0.18) (N = 16)	0.254	**<0.0001**	0.074
Fasting glucose	10.61 (10.91)	−23.18 (10.46)	−4.70 (10.85)	1.65 (10.65)	0.562	0.091	0.653
Total cholesterol	−6.40 (6.26)	−4.15 (5.92)	−4.95 (6.21)	12.15 (6.11)	**0.039**	0.052	**0.037**
HDL	−0.47 (1.40)	1.19 (1.35)	−0.97 (1.41)	0.35 (1.37)	0.677	0.654	0.471
LDL	−6.24 (4.85)	−2.09 (4.59)	0.07 (4.82)	1.83 (4.73)	0.241	0.541	0.780
Triglycerides[3]	−1.58 (13.61)	−20.09 (12.88)	−8.57 (13.46)	10.43 (13.76)	0.538	0.099	0.293
BMI	0.60 (0.48)	0.04 (0.47)	0.14 (0.48)	0.91 (0.47)	0.646	0.183	0.218
6MWT distance (feet)	−6.16 (33.03)	0.74 (31.48)	65.60 (32.60)	23.68 (33.26)	0.529	0.605	0.329

P values reaching statistical significance appear in boldface type. [1]Treatment group comparisons for non-HbA_{1c} outcomes were adjusted for baseline education status and baseline outcome values. [2]Treatment group comparisons for HbA_{1c} were adjusted for baseline education status, baseline outcome values, and change in antidiabetic medication (0 if no change, 1 if an increase, and −1 if a decrease) at postassessment. [3]Outliers for N = 2 observations were removed for this value.

Table 4—Change in psychological outcomes at posttreatment from baseline

	Treatment, least square mean (SE)				*P* value compared with UC		
Outcome	CBT (*N* = 24)	CBT+EXER (*N* = 25)	EXER (*N* = 30)	UC (*N* = 28)	CBT	CBT+EXER	EXER
Depression*							
BDI-II	−15.24 (1.95)	−18.12 (1.81)	−14.11 (1.91)	−8.21 (1.88)	**0.011**	**<0.001**	**0.021**
Automatic Thoughts Questionnaire	−11.62 (2.57)	−11.96 (2.53)	−12.58 (2.69)	−2.85 (2.55)	**0.018**	**0.010**	**0.006**
Diabetes Distress**	−0.66 (0.17)	−0.57 (0.17)	−0.69 (0.17)	0.05 (0.16)	0.003	0.008	0.001
SF-12**							
Physical Component Score	−2.14 (1.66)	1.84 (1.59)	−1.06 (1.69)	−5.51 (1.62)	0.147	**0.001**	**0.047**
Mental Component Score	12.87 (2.50)	10.09 (2.45)	11.80 (2.61)	6.34 (2.49)	0.069	0.270	0.109
DQOL**	6.75 (2.09)	12.19 (2.09)	10.81 (2.23)	0.86 (2.29)	0.061	**<0.001**	**0.001**
Diabetes	7.72 (3.51)	6.44 (3.52)	9.44 (3.71)	−2.84 (3.84)	**0.045**	0.068	**0.014**
Impact of Diabetes	4.17 (1.87)	7.32 (1.84)	4.20 (1.96)	0.06 (1.85)	0.123	**0.005**	0.103
Satisfaction with Diabetes	12.71 (3.37)	21.61 (3.47)	19.12 (3.56)	7.22 (3.35)	0.254	**0.003**	**0.010**
Social Worry	8.28 (8.91)	5.98 (5.78)	12.93 (6.58)	0.68 (7.59)	0.479	0.579	0.130

Results are ANCOVA. Treatment group comparisons were adjusted for baseline education status and baseline outcome values. DQOL, Diabetes Quality of Life Measure. *P* values reaching statistical significance appear in boldface type. *Difference scores with negative values indicate improvement in constructs (e.g., depressive symptoms) from baseline to postintervention assessment. **Scored with positive difference scores indicating improvement in psychosocial outcomes.

CONCLUSIONS

T2DM with comorbid depression is in epidemic proportions, but access to treatment remains limited. This is the first study to examine the comparative effectiveness of two behavioral treatment approaches to depression and T2DM in which community fitness and mental health partners provided the depression treatment. We observed significant improvements in depression remission in all three active interventions compared with UC. We also observed statistically significant and clinically meaningful improvements in depressive symptoms (mean values moving from the moderate/severe range of BDI-II total scores to the mild/none range as characterized by Beck [16]) as well as improvements in diabetes distress scores (mean values moving from the clinically high to moderate range as determined by Polonsky et al. [23]). These findings are consistent with the primary study outcomes. Although prior trials tested individual interventions (9,12,13), this trial demonstrated that CBT alone, EXER alone, and combination therapy (CBT+EXER) were comparable in improving MDD diagnosis in an underserved T2DM population drawn from both rural and urban regions. These findings demonstrate that depression can be effectively treated in adults with T2DM using multiple behavioral strategies.

Analysis of glycemic control as a primary outcome did not show a significant effect of interventions on glycemic control in the whole sample. This finding is consistent with prior trials that have shown either delayed improvements in HbA_{1c} or improvement attributable to changes in diabetes medications (12,13). Further, in the current study, we observed that the EXER alone group showed improvement in depression remission outcomes but did not show a significant improvement in HbA_{1c}. This finding is consistent with Piette et al. (13), in which depression symptoms were observed to improve without a change in HbA_{1c}. This suggests that while exercise alone is sufficient to have a positive impact on depression, more intervention is required to observe a meaningful change in glycemic control.

Exploratory analyses of the subsample with clinically elevated baseline HbA_{1c} values (i.e., >7.0%) showed clinically meaningful improvement in the CBT+EXER group. While the mechanism of action for this finding cannot be precisely identified, the factorial analysis suggests that there is an additive effect on glycemic control when CBT and EXER are delivered concurrently. This suggests that there may be a synergistic effect when individuals receive support from individual therapists at the same time they are engaging in exercise at the level of American College of Sports Medicine and American Diabetes Association guidelines.

Findings from this study demonstrate the effectiveness of individual and combined behavioral approaches on depression outcomes to treat depression tailored for adults with T2DM. Moreover, the Program ACTIVE interventions are manualized treatment approaches that can be effectively delivered using existing community resources in both rural and urban environments. With modest training and support, the study demonstrated that resources that exist in rural and underserved urban communities could be leveraged to affect considerable improvement in depression outcomes for adults with T2DM and MDD. These findings suggest that these interventions can be adopted and used by a variety of behavioral health and exercise professionals to influence depression outcomes, including providers in regions with restricted access to specialist-level care resources.

The limitations to the study include a predominantly female sample and relatively small sample sizes in the subgroup analyses that may have precluded the observation of statistically significant changes in HbA_{1c} in the CBT and EXER arms. It is important to note that a sizeable reduction in HbA_{1c} was observed in the EXER arm (decrease of 0.65%; Cohen d = 0.44, a medium effect size) consistent with expectations for the physiologic impact of exercise on glucose. The magnitude of the effect size observed suggests that a larger sample size would reach statistical significance in large-scale replication. In addition, the wide CIs observed in the OR of depression remission in the CBT group may indicate limited reliability of this large effect size

estimate. Finally, the sample represented socioeconomic, ethnic, and geographic diversity, but did not include Latinos and Asian Americans, thereby limiting the generalizability of the findings to these populations. Consistent with many trials, participants in this study may not generalize to all adults with T2DM and MDD.

In summary, Program ACTIVE is a set of manualized interventions that has demonstrated clinically meaningful improvements in depression outcomes in adults with T2DM. These interventions enable behavioral health counselors and exercise professionals to extend the availability; of depression treatment options that are complementary to medical care for patients with T2DM to achieve improvements in outcomes for both disorders.

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