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Emotional Distress Predicts Reduced Type 2 Diabetes Treatment Adherence in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

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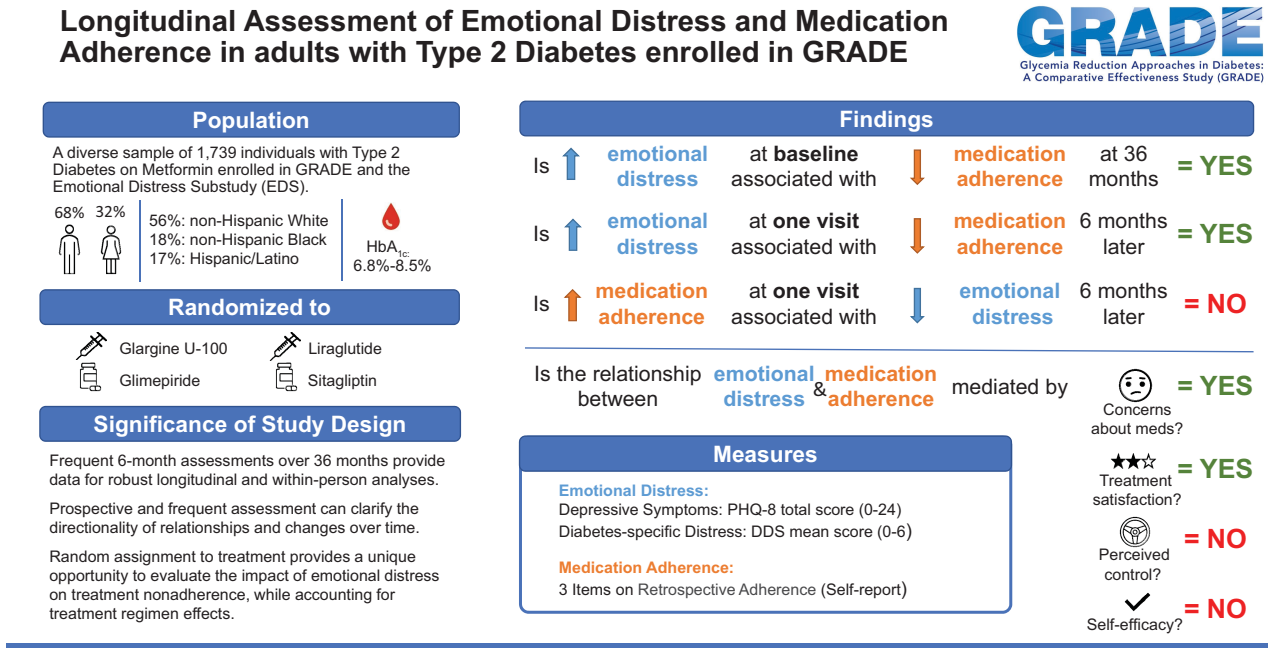

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Prior studies have mostly relied on cross-sectional data, limiting our understanding of the directionality of the relationship between emotional distress constructs and medication nonadherence.
- **What is the specific question(s) we wanted to answer?**
  We wanted to examine whether baseline depressive symptoms and diabetes distress predict medication adherence over time, and vice versa, and to examine mediators and moderators.
- **What did we find?**
  Findings provide strong evidence that depressive symptoms and diabetes distress each predict subsequent medication nonadherence in type 2 diabetes mellitus (T2DM). These effects were mediated by medication concerns and treatment satisfaction. No moderation by treatment assignment was observed.
- **What are the implications of our findings?**
  If causal, findings suggest that interventions targeting emotional distress among adults with T2DM would likely generate positive effects on diabetes treatment adherence.

Emotional Distress Predicts Reduced Type 2 Diabetes Treatment Adherence in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

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OBJECTIVE

We examined longitudinal associations between emotional distress (specifically, depressive symptoms and diabetes distress) and medication adherence in Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE), a large randomized controlled trial comparing four glucose-lowering medications added to metformin in adults with relatively recent-onset type 2 diabetes mellitus (T2DM).

RESEARCH DESIGN AND METHODS

The Emotional Distress Substudy assessed medication adherence, depressive symptoms, and diabetes distress in 1,739 GRADE participants via self-completed questionnaires administered biannually up to 3 years. We examined baseline depressive symptoms and diabetes distress as predictors of medication adherence over 36 months. Bidirectional visit-to-visit relationships were also examined. Treatment satisfaction, beliefs about medication, diabetes care self-efficacy, and perceived control over diabetes were evaluated as mediators of longitudinal associations.

RESULTS

At baseline, mean ± SD age of participants (56% of whom were White, 17% Hispanic/Latino, 18% Black, and 66% male) was 58.0 ± 10.2 years, diabetes duration 4.2 ± 2.8 years, HbA_{1c} 7.5% ± 0.5%, and medication adherence 89.9% ± 11.1%. Higher baseline depressive symptoms and diabetes distress were independently associated with lower adherence over 36 months ($P < 0.001$). Higher depressive symptoms and diabetes distress at one visit predicted lower adherence at the subsequent 6-month visit ($P < 0.0001$) but not vice versa. Treatment assignment did not moderate relationships. Patient-reported concerns about diabetes medications mediated the largest percentage (11.9%–15.5%) of the longitudinal link between emotional distress and adherence.

CONCLUSIONS

Depressive symptoms and diabetes distress both predict lower adherence to glucose-lowering medications over time among adults with T2DM. Addressing emotional distress and concerns about anticipated negative effects of taking these treatments may be important to support diabetes treatment adherence.

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Emotional distress, including depression and diabetes-related distress, is a prevalent problem for patients with type 2 diabetes mellitus (T2DM) (1–4). Diabetes distress, which reflects the specific burdens of living with diabetes and its treatment (5,6), has been distinguished from depression (3) and is associated with negative health outcomes including poor glycemic control, complications, mortality, and reduced quality of life (7–10). Depression is up to twice as common among individuals with diabetes compared with those without diabetes (1,2) and has been consistently associated with poor health outcomes (11–13). Reduced medication adherence is believed to be one factor linking depressive symptoms and diabetes distress to negative health outcomes in diabetes, with evidence supporting that both constructs are linked to lower diabetes treatment adherence (10,14–17).

Yet, evidence is unclear with respect to the independent relationships of depressive symptoms and diabetes distress with diabetes treatment adherence. Only a handful of studies have included examination of these constructs together, with conflicting results on whether depressive symptoms (14) or diabetes distress (17,18) is more closely related to nonadherence. One issue is measurement overlap between the two emotional distress constructs. Additionally, depressive symptoms include cognitive-affective as well as somatic symptoms that overlap with glucose dysregulation and treatment side effects (e.g., fatigue, appetite changes), making it difficult to distinguish whether symptoms are due to depression or diabetes among individuals diagnosed with T2DM (19). Prior work has shown differing relationships with medication adherence. Findings of two studies show that only somatic depressive symptoms, and not cognitive-affective symptoms, were significantly associated with lower medication adherence (14,17), while those of another study showed similar relationships between cognitive-affective and somatic symptoms and medication adherence among individuals with suboptimally controlled T2DM, with neither symptom dimension showing an independent effect when entered in the same model (20).

Prior studies have mostly relied on cross-sectional data, limiting our understanding of the directionality of the relationship between emotional distress constructs and reduced medication adherence. The literature largely conceptualizes depressive symptoms or diabetes distress as the predictor and reduced medication adherence as the consequence, though limited evidence supports reduced medication adherence as a contributor to emotional distress (21). The available longitudinal studies often include only two time points, limiting the ability to model changes over time (18). Most importantly, prior studies are limited by overlap between measures of emotional distress and the effects of treatment regimen differences and diabetes progression, among other overlapping factors.

Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) was a randomized controlled trial comparing the metabolic effects of four common glucose-lowering medications when combined with metformin in relatively recent onset T2DM (<10 years diagnosed) (22–24). Random assignment to treatment provided a unique opportunity to evaluate the impact of emotional distress on reduced treatment adherence, while accounting for treatment regimen effects. In the GRADE Emotional Distress Substudy (EDS), longitudinal assessments of depressive symptoms and diabetes distress were conducted every 6 months for participants over 3 years. GRADE-EDS included assessment of potential mediators that may explain associations between emotional distress and medication nonadherence based on prior literature. Specifically, treatment satisfaction, beliefs about medication, diabetes care self-efficacy, and perceived control over diabetes are associated with emotional distress (depressive symptoms, diabetes distress) and medication adherence, suggesting potential mediation (25–28). The aims of this analysis are to *1*) determine whether baseline depressive symptoms and diabetes distress predict medication adherence over the 36-month follow-up; *2*) assess short-term (6-month) bidirectional visit-to-visit relationships among emotional distress variables (depressive symptoms and diabetes distress) and medication adherence over the 36-month period; *3*) test for mediation of associations between emotional distress and medication adherence by participant-reported treatment satisfaction, beliefs about medication, self-efficacy for self-care, and perceived control over diabetes; and *4*) explore whether the association between emotional distress and medication nonadherence over time differs among the randomly assigned treatment groups.

RESEARCH DESIGN AND METHODS

Description of GRADE and EDS

GRADE was a parallel treatment group, unmasked randomized clinical trial comparing four commonly used glucose-lowering medications in metformin-treated participants who were followed for 3 to 7.5 years. The four medications included basal insulin glargine U-100, sulfonylurea glimepiride, glucagon-like peptide 1 agonist liraglutide, and dipeptidyl peptidase 4 inhibitor sitagliptin. A total of 5,047 individuals were recruited at 1 of 36 clinical centers and 9 additional subsites throughout the U.S. Eligibility criteria included age ≥30 years, except for American Indian and Alaska Natives (eligible if age ≥20 years), diagnosis of T2DM within 10 years, HbA_{1c} 6.8%–8.5% (51–69 mmol/mol), treatment with a minimum dose of 1,000 mg/day metformin alone, and willingness to take a second diabetes medication including injectable medication. Additional details of the GRADE protocol have previously been published (22).

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**A complete list of members of the GRADE Research Group can be found in the supplementary material online.*

This article is part of a special article collection available at https://diabetesjournals.org/collection/2066/Reports-from-the-GRADE-Study.

This article is featured in podcasts available at diabetesjournals.org/care/pages/diabetes_care_on_air.

EDS was embedded in GRADE more than halfway through GRADE recruitment; 1,739 participants were enrolled from 2015 to 2017. Once EDS began, the GRADE consent form was amended to include information on EDS and all individuals who enrolled in GRADE at a site participating in EDS were automatically enrolled in EDS. As enrollment was ongoing over the 5-year period of GRADE, a participant's baseline visit in GRADE was also the baseline visit in EDS. Further, baseline measures were collected prior to initiation of the assigned additional glucose-lowering medication. All GRADE sites were invited to participate in EDS. A total of 26 centers and 8 subsites representing academic hospitals, HMOs, and Veterans Affairs medical centers across the U.S. obtained institutional review board approval and participated. Participants were given additional compensation for EDS procedures. Those who screened positive for depression were offered information on treatment options and were given the option of having their health care provider notified. Additional details of the EDS protocol have previously been published (23).

Participants were assessed quarterly and continued their assigned medication regimen until they reached a confirmed HbA_{1c} level >7.5% (>58.5 mmol/mol) (the secondary metabolic outcome). Once this point was reached, additional medications were added (22,29). Participants initially randomized to noninsulin medications had glargine added to their regimen, followed by prandial rapid-acting insulin aspart if after the addition of glargine the participants' HbA_{1c} levels remained above a confirmed value of 7.5%. Metformin was then continued, and the initially assigned noninsulin medication was discontinued. Participants assigned to the insulin glargine arm who reached a confirmed value of HbA_{1c} >7.5% had prandial rapid-acting insulin aspart added to their regimen. Any additional glucose-lowering medications were prescribed by the participants' health care providers. The primary metabolic results have previously been reported (29). Analyses for the current report were limited to participants enrolled in GRADE-EDS and included baseline as well as longitudinal assessments collected every 6 months over a maximum of 36 months.

Measures

Demographic and Health Information

Participant characteristics collected at baseline include age, sex, race/ethnicity, educational attainment, and income. Participants also self-reported their medical history including diabetes onset. All physical and metabolic measurements, including height and weight (measured in duplicate and averaged, used to calculate BMI), were performed by certified staff who were centrally trained. HbA_{1c} was measured with a high-performance liquid chromatography method (22,29).

Medication Adherence

Adherence to glucose-lowering medications was assessed with the validated three-item instrument for retrospective adherence (30,31). The three self-report items include the following questions, in reference to the prior 30 days: *1*) "On how many days did you miss at least one dose of any of your diabetes medicines?" (answer ranging from 1 to 30 days), *2*) "How good a job did you do at taking your diabetes medicines in the way you were supposed to?" (1, very poor, to 6, excellent), and *3*) "How often did you take your diabetes medicines in the way you were supposed to?" (1, never, to 6, always) (30,31). A total score for the three items was calculated on a scale of 0 to 100, with higher scores representing better adherence. The continuous total score was used for all analyses. We use the commonly used cutoff score of 80% (31) to categorize individuals as adherent (≥80%) and nonadherent (<80%) in presenting baseline characteristics of the sample (Table 1).

Depression Symptom Severity

The validated eight-item Patient Health Questionnaire (PHQ-8) was used to measure depressive symptoms (32). The PHQ-8 total score was treated as a continuous indicator of the severity of depressive symptoms, with total scores ranging from 0 to 24. A PHQ-8 score ≥10 indicated a positive screen signifying likely clinical levels of depressive symptoms (32). The validated PHQ-8 consists of four somatic (sleep, fatigue, appetite, and psychomotor changes) and four cognitive-affective (loss of interest, depressed mood, negative self-feelings, and difficulty concentrating) symptom items.

Diabetes Distress

The validated 17-item Diabetes Distress Scale (DDS) (6) was used to measure diabetes-related distress. The average DDS score ranges from 1 to 6 with higher scores indicating greater diabetes distress severity. An average score of ≥2 is typically used as the cutoff for the presence of significant diabetes distress (moderate or high [33]). The DDS has four subscales that focus on sources of diabetes distress: *1*) emotional burden related to diabetes and its management, *2*) regimen distress related to the burdens of adherence to medications and self-care, *3*) interpersonal distress related to one's perceived inadequacy of social support from family and friends, and *4*) physician distress related to perceived lack of support and clear direction from health providers.

Potential Mediators

Beliefs about medicines were captured with use of the validated Beliefs about Medicines Questionnaire (BMQ) (25), which includes two scales: Specific-Necessity (five items) and Specific-Concerns (five items). Both BMQ Specific-Necessity and Specific-Concerns scores were scaled to range from 1 to 5, with higher scores indicating stronger Specific-Necessity and Specific-Concerns beliefs. Diabetes care self-efficacy was assessed with the Perceived Diabetes Self-Management Scale (PDSMS) (27). Scores range from 8 to 40, with higher scores indicating higher self-efficacy. We also included a six-item Perceived Control subscale from the revised Illness Perception Questionnaire (IPQ-R) (34). With this subscale, participants are asked to rate their agreement on a 5-point scale with items assessing their perceived ability to influence the course of diabetes through their own actions. Total scores range from 6 to 30 with higher scores indicating higher perceived control. Satisfaction with diabetes treatment was assessed with the Diabetes Treatment Satisfaction Questionnaire (DTSQ) (28). The current status of treatment satisfaction (assessed with the original version of the DTSQ, now called the status version [DTSQs]) is captured at baseline and at each 6-month follow-up visit. Change in satisfaction is captured at the 12-month follow-up visit with use of the change-based version of the questionnaire (DTSQc) (35).

Table 1—Baseline characteristics of the EDS participants

	Total (n = 1,739)	Adherent (n = 1,499)†	Nonadherent (n = 236)†	P*
Age (years)	57.97 ± 10.21	58.39 ± 10.10	55.36 ± 10.60	0.0001
T2DM duration (years)	4.21 ± 2.81	4.27 ± 2.82	3.82 ± 2.72	0.0199
Sex				
Male	1,175 (68)	1,034 (69)	138 (58)	0.0018
Female	564 (32)	465 (31)	98 (42)	
Race/ethnicity				
Hispanic/Latino	292 (17)	235 (16)	56 (24)	<0.0001
Non-Hispanic Black or African American	317 (18)	253 (17)	63 (27)	
Non-Hispanic other	155 (9)	126 (8)	29 (12)	
Non-Hispanic White	975 (56)	885 (59)	88 (37)	
Education				
College/graduate school	711 (41)	628 (42)	81 (34)	0.0229
High school/GED or less	517 (30)	429 (29)	87 (37)	
Some college	511 (29)	442 (29)	68 (29)	
Income, USD				
10,000–20,000	163 (11)	137 (11)	25 (13)	<0.0001
20,000–50,000	477 (32)	393 (30)	83 (42)	
≥50,000	766 (51)	696 (54)	69 (35)	
<10,000	93 (6)	70 (5)	22 (11)	
Living arrangements				
Alone	295 (17)	251 (17)	42 (18)	0.0358
With another adult	1,376 (79)	1,197 (80)	178 (75)	
With children only	68 (4)	51 (3)	16 (7)	
Employment				
Currently employed full- or part-time	974 (56)	833 (56)	139 (59)	0.0013
Currently retired	459 (26)	417 (28)	42 (18)	
Other	306 (18)	249 (17)	55 (23)	
Smoking				
Never	900 (52)	771 (51)	125 (53)	0.0478
Past	617 (35)	546 (36)	71 (30)	
Current	222 (13)	182 (12)	40 (17)	
BMI (kg/m^2)	34.10 ± 6.48	33.99 ± 6.46	34.70 ± 6.60	0.1265
Hypertension	1,486 (85)	1,286 (86)	196 (83)	0.3129
Any diabetes complications	716 (41)	616 (41)	98 (42)	0.9569
MI	97 (6)	81 (5)	15 (6)	0.6587
Stroke	39 (2)	35 (2)	4 (2)	0.7037
Macrovascular complications	128 (7)	109 (7)	18 (8)	0.9517
Medication adherence	89.89 ± 11.05	93.16 ± 6.96	69.09 ± 9.47	<0.0001
Diabetes self-management	78.82 ± 11.42	80.07 ± 10.90	71.07 ± 11.57	<0.0001
Depression/anxiety medication	319 (18)	271 (18)	47 (20)	0.5570
HbA_{1c}	7.51 ± 0.48	7.51 ± 0.48	7.54 ± 0.46	0.2579
DDS average score	1.68 ± 0.74	1.63 ± 0.71	1.93 ± 0.87	<0.0001
PHQ-8 total score	3.45 ± 3.96	3.20 ± 3.77	4.99 ± 4.73	<0.0001
Treatment satisfaction	5.17 ± 1.19	5.20 ± 1.17	5.00 ± 1.30	0.1919
Specific-Necessity	3.54 ± 0.74	3.57 ± 0.74	3.40 ± 0.74	0.0010
Specific-Concerns	2.59 ± 0.81	2.54 ± 0.80	2.90 ± 0.76	<0.0001
Self-efficacy in diabetes self-care	24.62 ± 2.96	24.57 ± 2.92	24.92 ± 3.18	0.1232
Control of diabetes	20.78 ± 2.43	20.78 ± 2.39	20.81 ± 2.67	0.8713

Data are n (%) or means ± SD. MI, myocardial infarction. †Four participants could not be categorized as adherent or nonadherent at baseline due to missing baseline data. *Groups were compared on these characteristic variables with use of t test (continuous) and χ^2 (categorical).

Statistical Analyses

Baseline characteristics for the EDS cohort and by participant adherence data are summarized in Table 1. We used simple linear regression models to evaluate the associations among baseline characteristics and medication adherence as a continuous variable (Supplementary Table 1).

In all adjusted analyses, we accounted for age, sex, race/ethnicity, randomized treatment group, duration of T2DM, BMI, and HbA_{1c} at baseline and accounted for the within-participant correlation over time using a random effect for participants (36).

To examine whether the PHQ-8 and DDS scores at baseline were correlated with medication adherence over 36 months (aim 1), we ran both unadjusted and adjusted models with medication adherence as a continuous score. Given the skew in the outcome variable, we performed a sensitivity analysis using dichotomized medication adherence with an 80% cutoff, which did not alter results (data not shown). We examined depressive symptoms and diabetes distress at baseline as predictors of medication adherence in separate models, as well as in joint models, to test their individual contributions (14,17,18). Depressive symptom dimensions (cognitive-affective vs. somatic) were also modeled in separate and joint models for examination of their individual contributions given the overlap between somatic symptoms and symptoms associated with diabetes and its treatment (19).

We used linear mixed-effects models to evaluate the association of within-person trajectories of depressive symptoms and diabetes distress captured at each 6-month visit with subsequent medication adherence at the following visit, and vice versa, over 36 months (aim 2). Specifically, we tested whether depressive symptom and diabetes distress scores (at time *t*) predicted subsequent medication adherence (at time $t + 1$) and vice versa. Both unadjusted and adjusted models were fitted. Two linear mixed-effects models were fitted for each emotional distress construct (PHQ-8/DDS) as *1*) a predictor and *2*) an outcome. We examined PHQ-8 and DDS scores in both separate and joint models when these variables were entered as predictors (14,17,18) and similarly examined depressive symptom dimensions (cognitive-affective vs. somatic) (19). When predictors and outcomes were reversed, only separate models were run. (See Supplementary Table 2.)

In testing for mediation (aim 3), linear mixed-effects models were run to model the concurrent trajectory of medication adherence as a function of emotional distress to determine whether the trajectory of each mediator from visit to visit has any mediation effects on the relationship between the trajectories of emotional distress and medication adherence, with adjustment for covariates. The mediation analyses were run in four steps for each potential mediator individually (37): step 1: test the main effects between emotional distress variables and medication adherence (no mediator); step 2: test the effect between emotional distress variables and mediators; step 3: test the effect between emotional distress variables and medication adherence with mediators; and step 4: calculate the percent change for the predictors that meet criteria for mediation (steps 1–3). The percent change is calculated as the relative change in the medication adherence associated with a 1-unit change in emotional distress between the unadjusted and adjusted models.

We explored whether associations over time differed among the randomly assigned treatment groups (aim 4) using linear mixed-effects models associating longitudinal emotional distress scores (PHQ-8/DDS) with longitudinal medication adherence. An interaction term between emotional distress score and treatment group was included to examine whether the association differed across the treatment groups. Models were adjusted for the same covariates listed above and accounted for within-participant correlation.

All analyses were conducted with use of R 4.2.1. Given the exploratory nature of our analyses, we did not adjust for multiplicity. However, we did use a more stringent significance level of 0.01 a priori.

Data and Resource Availability

This manuscript is based on follow-up data and outcome assessments from the 1,739 participants enrolled into EDS. The GRADE and EDS database will be available in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository in 2024.

RESULTS

Participant Cohort Characteristics

A total of 1,739 GRADE participants were enrolled in EDS. The majority of the participants were male (68%), and mean ± SD participant age was 58.0 ± 10.2 years. Mean diabetes duration for participants was 4.2 ± 2.8 years, BMI 34.1 ± 6.5 kg/m^2, HbA_{1c} of 7.5% ± 0.5%. The sample was racially and ethnically diverse; 56% of participants were non-Hispanic/Latino White, 17% Hispanic/Latino, and 18% non-Hispanic/Latino Black/African American. Overall, sample characteristics of EDS and non-EDS GRADE participants were similar; details have previously been reported (17). Baseline demographic characteristics are summarized in Table 1. Variables associated with lower medication adherence included lower income, younger age, female sex, and Hispanic/Latino and Black race/ethnicity (see Supplementary Table 1). Of participants, 9% had a positive screening result on the PHQ-8 and 25% indicated elevated levels of diabetes distress (17). Mean ± SD baseline medication adherence was 89.9 ± 11.1 on the 0–100 scale, with a median score of 92.2 (interquartile range 84.4, 100).

Baseline Emotional Distress and Medication Adherence Over 36-Month Follow-up

As shown in Table 2, both baseline depressive symptoms and diabetes distress predicted medication adherence at follow-up with adjustment for covariates at baseline. Specifically, a 1-unit increase in baseline PHQ-8 total score was associated with a 0.43-point decrease in medication adherence over the follow-up ($P < 0.0001$). Similarly, a 1-unit increase in the baseline DDS mean score was associated with a 2.07-point decrease in medication adherence over the follow-up ($P < 0.0001$). This indicates a similar magnitude of effect between depressive symptoms and diabetes distress; meeting the threshold for either depression (score $\geq$10) or diabetes distress ($\geq$2) was associated with a 4-point decrease in medication adherence in comparisons with those who did not meet this threshold. When depressive symptoms and diabetes distress were modeled together, each continued to independently predict lower medication adherence over the follow-up ($P < 0.0001$).

When examining depressive symptom dimensions, significant relationships were

Table 2—Association of depression symptoms and diabetes distress at baseline with medication adherence over 36-month follow-up

	Unadjusted		Adjusted	
	Estimate (95% CI)	*P*	Estimate (95% CI)	*P**
Separate models				
Depressive symptoms at baseline				
PHQ-8 total score	−0.48 (−0.60, −0.37)	**<0.0001**	−0.43 (−0.54, −0.31)	**<0.0001**
PHQ-8 somatic score	−3.52 (−4.37, −2.67)	**<0.0001**	−3.23 (−4.05, −2.40)	**<0.0001**
PHQ-8 cognitive-affective score	−2.91 (−3.81, −2.01)	**<0.0001**	−2.30 (−3.16, −1.43)	**<0.0001**
Diabetes distress at baseline				
DDS average score	−2.74 (−3.35, −2.12)	**<0.0001**	−2.07 (−2.67, −1.47)	**<0.0001**
DDS emotional burden	−2.16 (−2.68, −1.64)	**<0.0001**	−1.49 (−2.00, −0.98)	**<0.0001**
DDS regimen-related distress	−2.20 (−2.68, −1.72)	**<0.0001**	−1.85 (−2.31, −1.39)	**<0.0001**
DDS physician-related distress	−1.38 (−1.94, −0.83)	**<0.0001**	−0.99 (−1.52, −0.46)	**0.0003**
DDS interpersonal distress	−1.55 (−2.08, −1.01)	**<0.0001**	−1.11 (−1.63, −0.60)	**<0.0001**
Joint models				
Depressive symptoms and diabetes distress				
PHQ-8 total score	−0.31 (−0.44, −0.19)	**<0.0001**	−0.30 (−0.43, −0.18)	**<0.0001**
DDS average score	−2.12 (−2.78, −1.46)	**<0.0001**	−1.46 (−2.10, −0.82)	**<0.0001**
Depressive symptom dimensions				
PHQ-8 somatic score	−3.03 (−4.20, −1.86)	**<0.0001**	−3.19 (−4.32, −2.07)	**<0.0001**
PHQ-8 cognitive-affective score	−0.75 (−1.97, 0.47)	0.2293	−0.05 (−1.21, 1.12)	0.9350

Text in bold indicates a statistically significant relationship ($P < 0.01$). *The adjusted linear mixed-effects model estimates the medication adherence at subsequent follow-up visit as a function of the emotional distress factors with adjustment for age, sex, race/ethnicity, randomized treatment group, duration of T2DM, BMI, and HbA_{1c} at baseline.

observed for both somatic and cognitive-affective symptoms of depression ($P < 0.0001$). In a joint model, only somatic symptoms independently predicted lower adherence over 36 months. For diabetes distress, relationships were generally consistent across DDS subscales ($P < 0.001$). (See Table 2.)

Bidirectional Visit-to-Visit Relationships Among Emotional Distress and Medication Adherence

We found that with separate models, higher total depressive symptoms and mean diabetes distress scores significantly predicted lower medication adherence 6 months later (Table 3). Specifically, a 1-unit increase in PHQ-8 total score at one visit was associated with a 0.1-point decrease in medication adherence at the subsequent visit ($P = 0.0028$). Similarly, a 1-unit increase in the DDS mean score at one visit was associated with a 0.76-point decrease in medication adherence at the next visit ($P < 0.0001$). When depressive symptoms and diabetes distress were modeled together, only diabetes distress

Table 3—Association of depressive symptoms and diabetes distress with next-visit medication adherence

	Unadjusted		Adjusted	
	Estimates (95% CI)	*P**	Estimates (95% CI)	*P**
Separate models				
Depressive symptoms				
PHQ-8 total score	−0.12 (−0.19, −0.05)	**0.0004**	−0.10 (−0.16, −0.03)	**0.0028**
PHQ-8 somatic symptom score	−0.79 (−1.27, −0.32)	**0.0011**	−0.71 (−1.19, −0.24)	**0.0031**
PHQ-8 cognitive-affective score	−0.79 (−1.28, −0.31)	**0.0013**	−0.56 (−1.04, −0.09)	0.0210
Diabetes distress				
DDS average score	−0.98 (−1.33, −0.62)	**<0.0001**	−0.76 (−1.12, −0.41)	**<0.0001**
DDS emotional burden	−0.88 (−1.19, −0.58)	**<0.0001**	−0.70 (−1.01, −0.40)	**<0.0001**
DDS regimen-related distress	−0.81 (−1.08, −0.54)	**<0.0001**	−0.65 (−0.92, −0.39)	**<0.0001**
DDS physician-related distress	−0.19 (−0.52, 0.13)	0.2436	−0.12 (−0.45, 0.20)	0.4645
DDS interpersonal distress	−0.55 (−0.84, −0.26)	**0.0002**	−0.41 (−0.70, −0.12)	**0.0057**
Joint models				
Depressive symptoms and diabetes distress				
PHQ-8 total score	−0.07 (−0.14, 0.00006)	0.0498	−0.06 (−0.13, 0.01)	0.0952
DDS average score	−0.86 (−1.23, −0.48)	**<0.0001**	−0.66 (−1.04, −0.29)	**0.0005**
Somatic and cognitive-affective depressive symptoms				
PHQ-8 somatic symptom score	−0.50 (−1.12, 0.11)	0.1099	−0.60 (−1.22, 0.01)	0.0548
PHQ-8 cognitive-affective score	−0.47 (−1.09, 0.16)	0.1429	−0.18 (−0.80, 0.44)	0.5742

Text in bold indicates a statistically significant relationship ($P < 0.01$). *The adjusted linear mixed-effects model estimates the medication adherence at a subsequent follow-up visit as a function of the emotional distress factors with adjustment for age, sex, race/ethnicity, randomized treatment group, and longitudinal duration of T2DM, BMI, and HbA_{1c}.

Table 4—Estimates and percent change in the estimate for the mediator effects of the emotional distress variables on longitudinal medication adherence over 36 months

		With mediators							
		Treatment satisfaction		Specific necessity		Specific concerns		Self-efficacy	
Emotional distress factors	Without mediators: estimate	Estimate	%Δ	Estimate	%Δ	Estimate	%Δ	Estimate	%Δ
PHQ-8 total score	−0.35	−0.33	5.16	†	†	−0.31	11.94*	†	†
PHQ-8 somatic symptom score	−2.28	−2.17	4.51	†	†	−2.00	12.07*	†	†
PHQ-8 cognitive-affective score	−2.19	−2.05	6.50	†	†	−1.92	12.34*	†	†
DDS average score	−2.19	−2.17	1.18	−2.25	−2.69	−1.85	15.50*	−2.27	−3.59
DDS emotional burden	−1.27	−1.22	3.22	−1.34	−5.74	−0.87	31.46*	−1.36	−7.70
DDS regimen-related distress	−2.48	−2.50	−0.71	−2.51	−1.12	−2.30	7.42	†	†
DDS interpersonal distress	−1.23	−1.15	6.34	−1.27	−3.62	−1.01	17.25*	−1.28	−4.64

Data are shown first unadjusted (no mediators) and then adjusted for potential mediators one at a time, with the percent change (%Δ) (% mediation) of the emotional distress effect. All results are based on linear mixed-effects models with random effect for participant with adjustment for age, sex, race/ethnicity, randomized treatment group, and longitudinal duration of T2DM, BMI, and HbA_{1c}. All coefficients have P values <0.0001. *Factors with a percent change (mediation) of at least 10%. †No mediation, as the predictor was not associated with the proposed mediator; because "control over diabetes" and DDS physician-related distress did not show any mediation, they were not included in the table.

continued to independently predict lower medication adherence at the next visit ($P < 0.0001$).

When considering depressive symptom dimensions, significant relationships were only found for somatic symptoms (estimate −0.71 [95% CI −1.19, −0.24], $P = 0.0031$); however, this effect was not independent of cognitive-affective symptoms in a joint model. Relationships were generally consistent across DDS subscales emotional burden ($P < 0.0001$), regimen-related distress ($P < 0.0001$), and interpersonal distress ($P = 0.0057$) but not physician-related distress ($P = 0.464$) (Table 3).

Lower medication adherence did not predict depressive symptoms or DDS scores at the next visit (Supplementary Table 2); lower adherence did predict subsequent increases in DDS regimen-related distress subscale scores ($P = 0.004$).

Mediation by Treatment Satisfaction, Beliefs About Medication, Self-efficacy for Self-care, and Perceived Control Over Diabetes

We examined potential mediators of the visit-to-visit association between emotional distress and subsequent medication adherence. Adjustment for the trajectory of concerns about negative effects of prescribed medications for diabetes from visit to visit mediated the largest percentage of the association between total depressive symptoms and lower medication adherence from visit to visit; concerns about medication were also the most robust mediator of relationships between diabetes distress and medication nonadherence (Table 4). Adjustment for changes in treatment satisfaction over time also accounted for a modest portion of the associations of depressive symptoms and diabetes distress with medication nonadherence. The pattern was similar for somatic and cognitive-affective depressive symptoms and for DDS subscales. No evidence was observed for beliefs about the necessity of taking prescribed diabetes medications, diabetes care self-efficacy, or perceived control as significant mediators of the associations between depressive symptoms or diabetes distress with medication nonadherence over time.

Moderation by Treatment Arm of Distress and Adherence Relationship

There was no statistically significant support for treatment group effect on the association of depressive symptoms and diabetes distress with lower medication adherence over the 36-month follow-up period with use of the prespecified cutoff of $P < 0.01$ (results not shown).

CONCLUSIONS

This study provides strong evidence that elevations in depressive symptoms and diabetes distress each predict subsequent medication nonadherence in T2DM. Significant associations between initial levels of depressive symptoms and diabetes distress and medication adherence over the subsequent 36 months were largely independent of each other in this large sample. In contrast, lagged associations, which were analyzed from one visit to the subsequent visit 6 months later over the 36-month follow-up, showed more evidence for an independent role of diabetes distress in subsequent nonadherence. These longitudinal findings largely mirror cross-sectional relationships observed at baseline in GRADE-EDS (17). These effects were mediated by associated increases in concerns about the diabetes medications prescribed through GRADE and, to a lesser degree, by treatment satisfaction. Of note, the association between emotional distress and medication nonadherence was robust when modeled as a lag from emotional distress to subsequent medication adherence; however, when this lag was reversed from adherence to subsequent emotional distress, little evidence of a meaningful association was found. To the extent that these lagged relationships indicate causal associations, which cannot be addressed directly with the current data, these findings suggest that interventions aimed at improving emotional distress among adults with T2DM would likely generate positive effects on diabetes treatment adherence. Finally, GRADE treatment assignment was not found to significantly moderate the relationship between emotional distress variables and lower medication adherence, suggesting that these associations are robust across T2DM treatment regimens.

Examination of results from subscales of these multifaceted emotional distress constructs provided further information for clarification of the nature of these problems with respect to diabetes treatment adherence. Results from analyses modeling somatic and cognitive-affective depressive symptoms together suggest that somatic symptoms are uniquely associated with medication nonadherence. This finding is consistent with baseline results from GRADE-EDS (17), and with results from a small study of adults with T2DM where electronic monitoring was used to track medication adherence over time (14), raising the possibility that the association between depressive symptoms and medication nonadherence may be at least partially explained by overlapping symptoms of diabetes (19). Alternatively, our results suggest that the somatic experience of depressive symptoms is the "active ingredient" that is most closely linked with problems taking diabetes medications as prescribed. Our mediation findings suggest that these somatic symptoms may also lead to increased concerns about the negative effects of diabetes treatments and less satisfaction with those treatments, contributing to less adherence over time. Examination of DDS subscales revealed relationships that were largely consistent with the overall DDS score. Although regimen distress was the only DDS subscale showing a significant association with prior medication adherence in lagged analyses, it is likely that this association is at least partly explained by the content of items comprising this subscale (e.g., "Feeling that I am often failing with my diabetes routine").

Results suggest that depressive symptoms and diabetes distress are linked to reduced medication adherence in the early stages of diabetes diagnosis even in a sample with a relatively low prevalence of elevated emotional distress. While the strength of the relationships among emotional distress constructs and medication adherence was smaller over 6-month time frames, the strength of these associations increased over 3 years with a 1-point increase in depressive and diabetes distress symptoms associated with 0.4- and 2.1-point decrease in adherence, respectively. This suggests a cumulative effect over time and translates to 9.6%–12.6% lower medication adherence over 3 years for those with the highest scores on the PHQ-8 and DDS compared with those reporting no symptoms of emotional distress. If this relationship is causal, a clinically meaningful decrease in depressive symptoms of 50% (38) among individuals with high distress could improve medication adherence to a degree similar to that of educational and behavioral intervention trials (e.g., 39) targeting medication adherence (4%–11%). At the same time, these effects observed longitudinally and at baseline did not translate to meaningful effects on HbA_{1c} in GRADE-EDS (40).

This study has both strengths and limitations. Strengths include the large sample size and its racial/ethnic and socioeconomic diversity. Another strength is the comprehensive measurement of depressive symptoms, diabetes distress, and potential confounders. Important strengths in relation to the research aims are randomized treatment assignment and the inclusion of participants who were relatively homogenous with respect to diabetes severity and duration. The large sample size also allowed us to explore moderation by treatment arm. Limitations include use of self-reports for medication adherence, which is vulnerable to bias. However, self-ratings for diabetes medication adherence have previously been shown to have equivalent relationships with glycemic control in comparisons with electronic monitoring (14). Another limitation is that the presence of clinical depression was not assessed by a clinician. Further, with this large sample we are powered to detect small effects, and the clinical significance of the observed effects between emotional distress variables and medication adherence remains unclear. Finally, the levels of medication adherence, depressive symptoms, and diabetes distress in this clinical trial may not be representative of usual care populations. Finding these associations even within a trial suggests that depressive symptoms and diabetes distress are robustly associated with medication nonadherence, even when medications are provided at no cost to patients and there is extensive support for medication adherence.

Given the notable frequency of elevated emotional distress in adults recently diagnosed with T2DM (1–4), findings support further research on the benefits of regular screening and providing treatment to help alleviate emotional distress, including at subclinical levels, among individuals with T2DM.

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