

A brief adherence intervention that improved glycemic control: mediation by patterns of adherence

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Abstract This study examined whether longitudinal adherence profiles mediated the relationship between a brief adherence intervention and glycemic control among patients with type 2 diabetes. Adherence was assessed using the Medication Event Monitoring System. Longitudinal analysis via growth curve mixture modeling was carried out to classify patients according to patterns of adherence to oral hypoglycemic agents. Hemoglobin A_{1c} assays were used to measure glycemic control as the clinical outcome. Across the whole sample, longitudinal adherence profiles mediated 35.2 % (13.2, 81.0 %) of the effect of a brief adherence intervention on glycemic control [from odds ratio (OR) = 8.48, 95 % confidence interval (CI) (3.24, 22.2) to 4.00, 95 % CI (1.34, 11.93)]. Our results suggest that patients in the intervention had better glycemic control largely due to their greater likelihood of adherence to oral hypoglycemic agents.

Keywords Primary health care · Type 2 diabetes · Adherence · Randomized controlled trials · Mediation

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Introduction

Interventions targeting adherence to medications for diabetes have been successful in improving clinical outcomes (Vermeire et al., 2005). However, the factors comprising an effective adherence intervention have yet to be fully elucidated. Evidence suggests that interventions tailored specifically to the individual which address a wider range of barriers may be the most effective in producing clinically meaningful results [e.g. (Haynes et al., 2008)]. Education alone has not been found to be sufficient for producing significant behavior change (Mundt et al., 2001). While many adherence enhancing interventions have succeeded in improving glycemic control, it remains unclear whether improved glycemic control results from improved patient adherence.

The focus of intervention research on “do they work?” not “why do they work?” leaves a substantial gap in understanding what comprises a successful adherence intervention. Mediation analysis is an important method for examining the mechanism of intervention trials. A mediator accounts for the variation between a predictor and an outcome, while moderators indicate when effects might be seen, mediators specify how or why an effect occurred (Baron & Kenny, 1986). Given findings that interventions improve adherence, and interventions improve clinical outcomes, the investigation of whether improvements in a clinical outcome are due to improvements in adherence occasioned by the intervention is an important next step in scientific inquiry (Stratton et al., 2000; Turner et al., 1999). Prior work has found that diabetes adherence interventions improve adherence and glycemic control but these studies have not examined mediation by medication adherence (e.g. (Aliha et al., 2013; Piette et al., 2000)). Determinants of behavior change (e.g. socio-ecological resources and

self-efficacy) have been examined in relation to diabetes intervention effects on behaviors and clinical outcomes (Barrera et al., 2008; Sweet et al., 2009; Trief et al., 2009). Mediation of diabetes intervention effects on clinical outcomes by behavior (e.g. insulin use and self-monitoring practices) has also been investigated (Brega et al., 2012; Piette et al., 2013). Only one identified study examined the influence of adherence behavior to diabetes self-care as a mediator of an intervention's effect on glucose control (Trief et al., 2013). To our knowledge, no known studies have examined mediation of a diabetes intervention effect by longitudinal profiles of oral hypoglycemic agent adherence.

Our goal was to examine longitudinal profiles of oral hypoglycemic adherence as a mediator of a brief adherence intervention on glycemic control. The model in Fig. 1 represents a set of testable hypotheses about how the intervention and improved glucose control may be related to one another through their association with oral hypoglycemic agent adherence profile type. Our model was tested in four stages: (1) the association of intervention assignment and glucose control; (2) the association of intervention assignment with oral hypoglycemic agent adherence profile type; (3) the association of adherence profile type and glucose control; and 4) the association of intervention and improved glucose control with terms representing oral hypoglycemic agent adherence profile type in the model to test for mediation.

Methods

Study sample

A Brief Intervention to Improve Adherence through Integrated Management of type 2 Diabetes Mellitus and Depression Treatment was a randomized controlled trial designed to examine whether an integrated care intervention (IC intervention) improved adherence to oral hypoglycemic

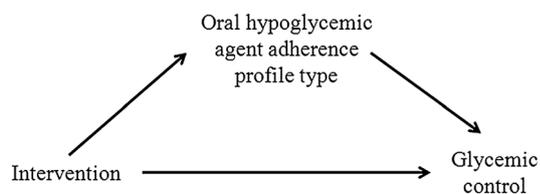


Fig. 1 Model of the potential relationship of the intervention, oral hypoglycemic agent adherence profile type, and glycemic control. *Note:* Oral hypoglycemic agent adherence profile types were obtained from general growth curve mixture models in which patients were classified into categories of longitudinal adherence profile types based on the largest posterior probability of membership across the classes. Three longitudinal adherence profile types were: adherent, increasing adherence, and nonadherent

agents, glycemic control, and depression among primary care patients with type 2 diabetes mellitus (type 2 DM). The study protocol was approved by the University of Pennsylvania Institutional Review Board. The intervention is described in detail elsewhere (Bogner et al., 2012).

Recruitment

Patients were recruited from three primary care practices in Philadelphia, Pennsylvania. From April 2010 to April 2011, patients with a diagnosis of type 2 DM and a prescription for an oral hypoglycemic agent within the past year were identified through electronic medical records. Patients with an upcoming appointment who met initial criteria were approached for further screening. Eligibility criteria included: (1) aged 30 years and older; (2) a diagnosis of type 2 DM; (3) a current prescription for an oral hypoglycemic agent; and (4) a current prescription for an antidepressant. The age cut-off of 30 years and older was chosen because of its significance for the detection, screening, and intervention for diabetic patients (Kahn et al., 2010). Patients with a current prescription for an antidepressant were included because diabetes and depression are two of the most common co-morbid problems seen in primary care settings (Eaton, 2002). Exclusion criteria included: (1) inability to give informed consent; (2) significant cognitive impairment at baseline (Mini-Mental State Examination (MMSE) < 21) (Crum et al., 1993); (3) residence in a care facility that provides medications on schedule; and (4) unwillingness or inability to use the Medication Event Monitoring System (MEMS). The intervention aimed to address adherence to patients' entire medication treatment regimen including insulin use, and thus insulin users were not excluded from participation. Patients whose caregivers assisted with their medications were not excluded from participation. MEMS caps on pill bottles record the exact data and time of medication container opening. Patients were randomly assigned to the IC intervention or usual care.

Study design

This trial consisted of two phases: the run-in phase and the randomized controlled trial phase. The purpose of the 2-week run-in phase was to collect pre-intervention adherence rates for all patients. During this phase data were also collected on demographics, depressive symptoms, and glycosylated hemoglobin. No intervention was performed during this phase. Following completion of the 2-week run-in phase, patients entered phase 2 of the study in which they were randomized within each practice by flip of a coin to either the IC intervention or usual care. Physicians were told which patients were enrolled in the IC intervention to

allow for collaboration with the IC manager, but were blinded to enrollment in the usual care group.

Integrated care intervention (IC intervention)

For patients assigned to the intervention, integrated care managers offered education, guideline-based treatment recommendations, and monitored adherence and clinical status in collaboration with physicians. The integrated care manager worked with patients individually to address patient-level factors involved in adherence to oral hypoglycemic agents including depression, chronic medical conditions, function, cognition, lack of social support, cost of medications, experiencing side effects, and past experiences with medications. Patient-level factors were addressed through a variety of activities including in person sessions, telephone contacts, and collaborating with the physician. Through in person sessions and telephone conversations the IC manager provided education about type 2 DM; helped patients identify target symptoms; provided a rationale for the rationale for use of oral hypoglycemic agents; assessed for side-effects and needed assistance with self-management; assessed for progress (e.g. improvement in finger stick results); assisted with referrals; and monitored and responded to life-threatening symptoms (e.g. chest pain). The intervention was presented to patients as a supplement to, rather than a replacement for, existing primary care treatment.

Over a 3-month period patients had three 30-min in person sessions (baseline, 6 and 12 weeks) and two 15-min telephone monitoring contacts. Integrated care managers were two research coordinators (one Master's level and one bachelor's level) who administered all intervention activities. Prior to trial initiation, the integrated care managers received training on pharmacotherapy for type 2 DM management during weekly clinical sessions with the principal investigator.

Usual care

Patients in the usual care group underwent the same assessments at the same time points (baseline, 6, and 12 weeks) as the patients in the IC intervention. As in the intervention group, assessments were conducted in person. Research assistants conducted all assessments and were blinded to patients' randomization status.

Measurement strategy

Potential study patients were screened for cognitive impairment using the MMSE, a short standardized mental status examination widely employed for clinical and research purposes (Folstein et al., 1975). Patients were

asked whether they resided in a care facility that provided medications on schedule and whether they were unwilling or unable to use MEMS. At baseline sociodemographic characteristics were assessed using standard questions. Functional status was measured using the Medical Outcomes Study Short Form (SF-36) (Stewart et al., 1988). Adherence to oral hypoglycemic agents was measured during the 2-week run-in phase, and at 6 and 12 weeks, using electronic monitoring data obtained from MEMS Caps.

At baseline and 12 weeks blood glyceemic control was assessed in accordance with American Diabetes Association Guidelines (American Diabetes Association, 2014). Hemoglobin A_{1c} (HbA_{1c}) assays were performed with the in2it A1C Analyzer. Point of care testing using this device has acceptable precision and agreement in comparison with laboratory services (Moridani et al., 2003).

Analytic strategy

We calculated descriptive statistics to compare baseline patient characteristics in the intervention group to usual care using the Fishers' exact test and Wilcoxon rank sum test (for categorical and continuous variables respectively). For the analysis of mediation, we used our prior classifications of patients into latent longitudinal adherence profile (de Vries McClintock et al., in press). To obtain these profiles, we employed recent developments in statistical assessment of treatment effects or of course of depression in primary care, especially the general growth curve mixture model (GGCMM) (Jo & Muthen, 2001; Muthen et al., 2002; Muthen, 2001; Muthen & Shedden, 1999) as in prior work [e.g. (Elliott et al., 2005; Lin et al., 2007)]. Binary indicators of adherence measurements were assessed by MEMS caps at weekly intervals over a 12-week period. Patients were categorized as adherent if they took at least 80 % of their pills in the interval (George et al., 2000). Otherwise, patients were considered to be nonadherent. The GGCMM analyses produced parameters that describe the adherence profiles of each class as well as estimated posterior probabilities of unobserved class membership for each patient. Patients were classified into categories of longitudinal adherence profile types based on the largest posterior probability of membership across the classes. Longitudinal adherence profile types identified were: adherent, increasing adherence, and nonadherent. We analyzed the resulting categorical variable for longitudinal oral hypoglycemic agent adherence profile types as a mediator.

The four-step approach of Baron and Kenny provides a theoretical and practical foundation for the assessment of mediation (Baron & Kenny, 1986). The definition of mediation is met if the following conditions hold: (1) the

IC intervention improves the clinical outcome (blood glucose control); (2) the IC intervention improves the potential mediator (longitudinal oral hypoglycemic agent adherence profile type); (3) improvements in the mediator are associated with improvements in the clinical outcome, controlling for the intervention's effect on the outcome; and (4) adjusting for the mediator, the clinical outcome is attenuated and no longer significant. Partial mediation is present if the intervention coefficient is attenuated but there is still a significant effect of the intervention on glucose control. An additional requirement of causal mediation is that changes in the mediators occur in time before changes in the outcome. Adherence is measured over time before the outcome of interest, blood glucose control. Following MacKinnon et al., we used a threshold of 15 % for sufficient change in the coefficients of intervention as assessment of attenuation for mediation (MacKinnon et al., 2000, 2002). The first three conditions have been examined in prior work, and meet sufficient criteria for mediation (Bogner et al., 2012; de Vries McClintock et al., in press). For condition 2, patients in the intervention condition were more likely to have an adherent pattern compared to a nonadherent pattern [odds ratio (OR) = 11.6, 95 % confidence interval (CI) (4.08, 32.9)]. Patients in the intervention condition were more likely to have an increasing adherence pattern compared to a nonadherent pattern [OR = 41.31, 95 % CI (13.87, 123.03)] (de Vries McClintock et al., in press). For this analysis we are examining whether criteria for condition number 4 is met.

Based on our prior work examining the relationship between intervention condition and glucose control, patients were analyzed according to the treatment to which they were randomized (intent-to-treat). Practice site was included in the model to account for unmeasured factors related to clustering by practice. The model adjusted for baseline HbA_{1c}. Logistic regression related latent class variables to the clinical outcome of glucose control at 12 weeks for the entire sample. To assess whether stratified analysis was warranted we examined baseline interactions (Baron & Kenny, 1986). Based on the presence of a significant interaction ($P < .001$), we then conducted stratified analysis of patients with and without HbA_{1c} \geq 8 % at baseline. As recommended by clinical guidelines, our outcome of glucose control was assessed using a cutoff of HbA_{1c} $<$ 7 % at 12 weeks (American Diabetes Association, 2014). The results are presented in the form of odds ratios and 95 % confidence intervals. As recommended by Hayes (2009), we have modernized the application of Baron and Kenny by applying the bootstrapping technique, one of the more valid and powerful methods for testing intervening variable effects and generating bias-corrected confidence intervals for indirect effects. The size of the indirect effect and bias-corrected 95 % CI was obtained through the bootstrap techniques with

5,000 replications (Preacher & Hayes, 2008; Vanderweele & Vansteelandt, 2010). We set α at 0.05, recognizing that tests of statistical significance are approximations that serve as aids to inference. The GGCMM was fitted using Mplus version 7 (Muthén & Muthén, 1998) and other analyses were conducted in STATA version 12 for Windows (STATA Corporation, College Station, TX).

Results

Study sample

The CONSORT flow diagram for this trial has been published elsewhere (Bogner et al., 2012). In brief, of 715 patients with type 2 DM were identified by electronic medical records. In all, 265 were eligible based on initial inclusion criteria and approached, and 190 were enrolled based on additional inclusion criteria (71.7 % participation rate). After a 2-week run-in phase in which adherence to medications was assessed, consent was obtained. At the 2-week visit, eight patients were no longer eligible for participation (five physicians had discontinued antidepressants, one physician had discontinued an oral hypoglycemic agent, and two patients were lost to follow-up). The remaining 182 patients were randomized to the IC intervention or usual care. Subsequently, 2 patients in the IC intervention were lost to follow-up leaving 180 patients who completed all study visits. For these 180 patients complete information on baseline covariates and on the clinical outcome of glucose control at 12 weeks was obtained. The mean age of our sample was 57.4 years [standard deviation (s.d.) 9.5 years, range 32 to 84 years]. One hundred and twenty-two (67.8 %) of the patients were women. The self-identified race of patients was 65 white (36.1 %), 102 African-American (56.7 %), 7 Hispanic (3.9 %), and 6 (3.3 %) who self-identified as 'other.' In all, 69 persons (38.33 %) were married and 29 persons (16.1 %) had less than a high school education. The mean number of medical conditions was 7.3 (s.d. 3.2) and the mean MMSE score was 28.2 (s.d. 2.3). The baseline patient characteristics of the study sample are shown in Table 1.

Mediation of intervention group effect on glycemic control by adherence profile type

In our prior work, a series of GGCMMs were fitted to the MEMS data. The three-pattern model presented in Fig. 2 improved the model fit over the two- and four-pattern models yielding three adherence profile types. The three adherence profile types identified and employed for this analysis were: adherent ($n = 67$), increasing adherence

Table 1 Baseline characteristics

	Usual care (n = 88)	Intervention (n = 92)	P value
Sociodemographic characteristics			
Age, mean in years (s.d.)	57.1 (9.6)	57.8 (9.4)	.75
African American [n (%)]	48 (54.5 %)	54 (58.7 %)	.28
White [n (%)]	36 (40.9 %)	29 (31.5 %)	
Hispanic [n (%)]	3 (3.4 %)	4 (4.3 %)	
Other [n (%)]	1 (1.1 %)	5 (5.4 %)	
Gender, women [n (%)]	58 (65.9 %)	64 (69.6 %)	.64
Less than HS education [n (%)]	15 (17.0 %)	14 (15.2 %)	.84
Type 2 diabetes mellitus			
Years of diabetes, mean (s.d.)	12.0 (11.8)	10.5 (10.2)	.37
HbA _{1c} , mean (s.d.)	7.0 (1.9)	7.2 (1.8)	.22
Depression			
PHQ-9, mean (s.d.)	9.9 (7.2)	10.6 (7.9)	.65
Medications			
Number of medications, mean (s.d.)	10.1 (5.1)	9.8 (4.5)	.71
≥80 % adherent to oral hypoglycemic agent [n (%)]	37 (42.0 %)	33 (35.9 %)	.45
Functional status (SF-36)			
Physical function score, mean (s.d.)	53.6 (31.7)	50.8 (32.6)	.57
Social function score, mean (s.d.)	67.7 (39.9)	76.6 (36.9)	.09
Role physical score, mean (s.d.)	49.4 (46.7)	59.5 (46.6)	.15
Role emotional score, mean (s.d.)	65.9 (46.0)	67.8 (44.6)	.82
Bodily pain score, mean (s.d.)	42.3 (31.4)	50.9 (31.7)	.06
Cognitive status			
MMSE, mean (s.d.)	28.2 (2.3)	28.2 (2.3)	.80

s.d. standard deviation, HS high school, SF-36 Medical Outcomes Study Short Form, MMSE Mini-Mental State Examination, PHQ-9 nine-item Patient Health Questionnaire, Hb hemoglobin
P values represent comparisons according to Fisher’s exact test and the Wilcoxon rank sum test for categorical or continuous data, respectively

(n = 52), and nonadherent (n = 61) (de Vries McClintock et al., in press). Table 2 shows the effect of the intervention on glycemic control in models with and without mediation by adherence profile types. Patients randomized to the IC intervention were more likely to achieve a HbA_{1c} < 7 % in comparison with patients in the usual care group at 12 weeks (p < 0.001). When including the mediator (adherence profile type) in the model evaluating achievement of HbA_{1c} < 7 % at 12 weeks, 35.2 %, [95 % CI

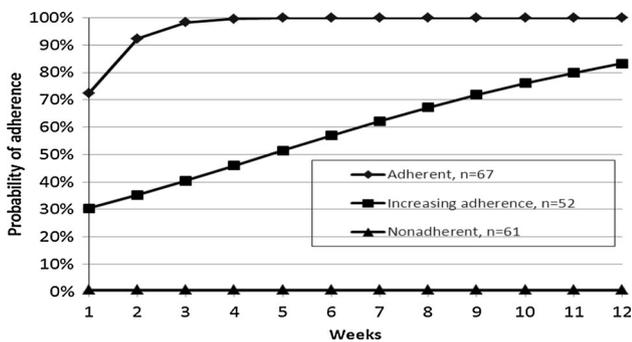


Fig. 2 General growth curve mixture model analysis of adherence to oral hypoglycemic agents (number of patients in each class with plotted conditional probabilities) (n = 180). Note: Data gathered from 2010–2011

(13.2, 81.0 %)] of the effect was mediated by adherence profile type [from odds ratio (OR) = 8.48, 95 % CI (3.24, 22.2) to 4.00, 95 % CI (1.34, 11.93)] (Table 2).

Mediation of intervention group effect on glycemic control by adherence profile type stratified by HbA_{1c} ≥ 8 %

Additional multivariate analyses were performed to examine mediation by patients with and without HbA_{1c} ≥ 8 %. Among patients with HbA_{1c} ≥ 8 %, patients randomized to the IC intervention were more likely to achieve an HbA_{1c} < 7 % in comparison with patients in the usual care group at 12 weeks (intervention 25.0 % vs. usual care 4.8 %; P < 0.05). When including the mediator (adherence profile type) in the model evaluating achievement of HbA_{1c} < 7 % at 12 weeks, 63.5 % of the effect was mediated by adherence profile type and the relationship between the intervention and glucose control was no longer significant [from OR = 12.41, 95 % CI (1.21, 654.35) to 2.51, 95 % CI (0.12, 159.82)].

Among patients with an HbA_{1c} < 8 %, patients randomized to the IC intervention were more likely to achieve HbA_{1c} < 7 % in comparison with patients in the usual care

Table 2 Clinical outcomes of glyceemic control in usual care and in the integrated intervention at 12 weeks

	Usual care (n = 88)	Intervention (n = 92)	Without mediator (adherence profile type)		With mediator (adherence profile type)	
			Estimated between-group odds ratio ^a (95 % CI)	P value	Estimated between-group odds ratio ^b (95 % CI)	P value
Type 2 diabetes mellitus						
Achieved HbA _{1c} < 7 %, n (%)	43 (48.9)	67 (72.8)	8.48 (3.24 to 22.2) [†]	<0.001	4.00 (1.34, 11.93) [†]	.013

CI confidence interval, Hb hemoglobin

Estimates, 95 % confidence intervals, and P values from the statistical models

[†] Odds ratio (95 % CI) from a logistic regression model

^a Adjusted for baseline glycosylated hemoglobin and primary care practice

^b Adjusted for baseline glycosylated hemoglobin, primary care practice and pattern of adherence

group at 12 weeks (intervention 89.7 % vs. usual care 62.7 %; $P < 0.01$). When including the mediator (adherence profile type) in the model evaluating achievement of HbA_{1c} < 7 % at 12 weeks, only 26.4 % of the effect was mediated by adherence profile type [from OR = 4.77, 95 % CI (1.87, 12.17) to 3.16, 95 % CI (1.05, 9.49)].

Discussion

The principal finding of this study is that the relationship between a brief adherence intervention and glyceemic control was partially mediated by oral hypoglycemic agent adherence profile type over 12 weeks across the entire sample. Among patients with a HbA_{1c} \geq 8 % at baseline, the relationship between the brief adherence intervention and glyceemic control was fully mediated by oral hypoglycemic agent adherence profile type over 12 weeks. A brief intervention's effect on improved glyceemic control among patients with a HbA_{1c} \geq 8 % was due to their greater likelihood of adherence to oral hypoglycemic agents. To our knowledge, this is the first report of mediation by adherence of an association between a diabetes adherence intervention and glyceemic control.

Before discussing the implications of our findings, the limitations of our study must be considered. First, our results were obtained from patients who received care at three primary care sites that might not be representative of most primary care practices. However, the three practices were diverse and varied in size and were probably similar to other primary care practices in the region. Second, all methods for assessing adherence have limitations. We chose to use microelectronic monitors on pill bottles as our primary measure of adherence because microelectronic monitors have a low failure rate (George et al., 2000) and may be more sensitive than other adherence measures (Farmer, 1999). The validity and reliability of electronic monitoring of adherence provides a reference standard by

which other adherence assessment methods can be examined (Nakonezny et al., 2008; Osterberg & Blaschke, 2005). Third, while the 80 % threshold for adherence has been assessed in some clinical research [e.g.(George et al., 2000)], the clinical relevance of this threshold has not been tested for many medications. Fourth, we utilized only one method of mediation analysis. Other approaches to mediation analysis (Hayes, 2009) with different assumptions may yield different results (Mackinnon, 2008). Fifth, a current prescription for an antidepressant was part of our inclusion criteria. Therefore, our findings may be most relevant to patients with diabetes as well as depression. Finally, point-of-care testing for HbA_{1c}, is imperfect in its assessment (Lenters-Westra & Slingerland, 2010). However, misclassification would likely be non-differential thus biasing estimates toward the null. Drawbacks of point of care testing for HbA_{1c} must be weighed in relation to other factors such as cost-effectiveness and practicality of use in the clinical setting.

Despite limitations, our results deserve attention because we attempted to characterize the relationship between a brief adherence intervention, oral hypoglycemic agent adherence profile type and glyceemic control. Our work is consistent with Trief et al. who found that a telemedicine case management intervention among patients with type 2 DM was mediated by self-reported adherence to diabetes self-care. Trief and colleagues examined mediation by self-reported adherence to recommended blood glucose testing, dietary control, exercise, and foot care. In contrast, the focus in our study was on adherence to medications for diabetes because of the clinical significance of diabetes medication taking in clinical prognosis (Rasmussen et al., 2007). Our use of general growth curve mixture models allowed us to distinguish distinct patterns of adherence over time instead of assessing adherence through proportions at singular point(s) in time with no assessment of variation over time and group classification. Furthermore, this approach utilizes all adherence data

producing estimated posterior probabilities of unobserved class membership for each patient, thus improving precision by accounting for effects of the intervention and baseline covariates on adherence. In summary, our findings build and expand on prior work by demonstrating that longitudinal adherence profiles assessed by an objective measure of medication adherence mediate the relationship between a brief adherence intervention and glycemic control for patients with $HbA_{1c} \geq 8\%$ at baseline.

Specifically, in our examination across the full sample, our results demonstrate partial mediation. While the intervention coefficient is attenuated, there is still a significant relationship between the intervention and glucose control. Partial mediation may be due to the comprehensive nature of the adherence intervention in which adherence barriers were targeted using a multi-faceted approach. Improved glycemic control may have occurred through mechanisms other than improved adherence (e.g. diet and exercise) as the interventionist aimed to improve through an array of avenues including social support and the development of problem solving skills. In addition, the therapeutic alliance, defined broadly as the collaborative bond between patient and provider, has been identified as a key element of patient-provider relationship not only for psychotherapy, but also for pharmacotherapy. Better therapeutic alliance is associated with better adherence to medications as well as treatment outcomes (Krupnick et al., 1996; McCabe et al., 2012). The therapeutic alliance may be tapping into patient's subjective assessment of the social and personal experiences with their provider or in this case the interventionist. If patients had a stronger bond with an interventionist, they may be more willing to follow the interventionist's advice on treatment adherence and, in turn, may have been more adherent leading to better clinical outcomes.

Our finding that mediation was present to a greater extent for patients with a $HbA_{1c} \geq 8\%$ compared to patients with a $HbA_{1c} < 8\%$ at baseline supports a more complex conceptualization of mediation effects in which mediators may differ by baseline characteristics of the patient. It may be necessary to develop interventions that incorporate mediators based on individual patients. In other words, some mediators may work for some patients but not for others, and intervention development may need to be customized accordingly. Mediators of intervention effect have been identified as factors that may be critical for tailoring (Small et al., 2012). Methodological developments allow for tailoring over time throughout the interval of intervention deployment, even for covariates that occur post-randomization (Almirall et al., 2012). Further research with such designs (e.g. adaptive trials) may have both important methodological and clinical implications.

Building on prior evidence indicating that interventions targeting adherence improve clinical outcomes [e.g. (Vermeire et al., 2005)], we have sought to help elucidate the mechanism by which interventions may influence outcomes. Our results indicate that patterns of adherence over time are critical in explaining diabetes intervention effects on glycemic control. The prospective design of the study lends strength to the idea that patterns of adherence over time can signal how effective an intervention may be in improving outcomes. Patterns of adherence over time may be an important marker for subsequent clinical outcomes and therefore are an important target for intervention and follow-up.

The National Institutes of Health (NIH) Adherence Research Network has identified improving adherence as a top priority. This inter-disciplinary initiative notes that increased adherence to medication regimens promises substantial improvements in public health as well as savings in healthcare costs. A lack of compliance with recommended treatment regimens has been identified as a causal factor in preventable morbidity and mortality in numerous studies and across many illnesses (Osterberg & Blaschke, 2005). Thus, efforts to improve treatment adherence has been labeled the “next frontier in (health-care) quality improvement” (Heidenreich, 2004). Our study provides additional evidence of the public health importance of addressing adherence. The effectiveness of diabetes interventions in improving clinical outcomes may be substantially mediated by patterns of adherence over time. Collaborative networks between policy initiatives, health-care networks and medical settings are needed to develop sustainable adherence programs.

Conflict of interest De Vries HF, Morales KH, Small DS, Bogner HR declare that they have no conflict of interest.

Human and animal rights and Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or national) and with the Helsinki Declaration 1975, as revised in 2000. Informed consent was obtained from all patients in the study.

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