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Patterns of Adherence to Oral Hypoglycemic Agents: Patterns, Correlates, and Outcomes

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Patterns of Adherence to Oral Hypoglycemic Agents: Patterns, Correlates, and Outcomes

Abstract

Despite the development of effective pharmacological therapy to prevent both macrovascular and microvascular complications and adverse events, diabetes control remains sub-optimal. Poor adherence to recommended regimens is a causal factor in preventable morbidity and mortality in diabetic patients. Subgroups of patients with differing longitudinal profiles of adherence may yield differing treatment outcomes. Identifying characteristics associated with longitudinal profiles can potentially alert clinicians to patients at risk for poor clinical outcomes allowing for early intervention and follow-up. Furthermore, few studies have examined the role of adherence improvements as a mediator of intervention effect on glycemic control.

In this work we sought to identify patterns, correlates and outcomes of adherence to oral hypoglycemic agents. We also assessed whether adherence improvements mediated a brief interventions effect on glycemic control. Longitudinal analysis via growth curve mixture modeling was carried out to classify 180 patients who participated in an adherence intervention according to patterns of adherence to oral hypoglycemic agents across 12 weeks. Adherence was assessed using the Medication Event Monitoring System. Hemoglobin A1c assays were used to measure glycemic control as the clinical outcome. Individual patient residential data was geo-coded at the tract level.

Three patterns of adherence to oral hypoglycemic agents were identified: adherent, increasing adherence, and nonadherent. Both individual and neighborhood level factors were identified that were associated with patterns of adherence. Patients with an increasing adherence pattern were more likely to have a Hemoglobin A1c (HbA1c) < 7% (adjusted odds ratio = 14.52, 95% CI [2.54, 82.99]) at 12 weeks in comparison with patients with the nonadherent pattern. 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)]. These findings imply that the identification of patients with type 2 diabetes at risk of nonadherence is important for clinical prognosis and the development and delivery of interventions.

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ADHERENCE TO ORAL HYPOGLYCEMIC AGENTS: PATTERNS, CORRELATES AND OUTCOMES

Heather Faye de Vries McClintock

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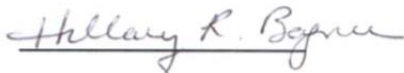Presented to the Faculties of the University of Pennsylvania

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ADHERENCE TO ORAL HYPOGLYCEMIC AGENTS: PATTERNS, CORRELATES AND OUTCOMES

ABTRACT

ADHERENCE TO ORAL HYPOGLYCEMIC AGENTS: PATTERNS, CORRELATES AND

OUTCOMES

Heather Faye de Vries McClintock

Hillary Rohn Bogner

Despite the development of effective pharmacological therapy to prevent both macrovascular and microvascular complications and adverse events, diabetes control remains sub-optimal. Poor adherence to recommended regimens is a causal factor in preventable morbidity and mortality in diabetic patients. Sub-groups of patients with differing longitudinal profiles of adherence may yield differing treatment outcomes. Identifying characteristics associated with longitudinal profiles can potentially alert clinicians to patients at risk for poor clinical outcomes allowing for early intervention and follow-up. Furthermore, few studies have examined the role of adherence improvements as a mediator of intervention effect on glycemic control.

In this work we sought to identify patterns, correlates and outcomes of adherence to oral hypoglycemic agents. We also assessed whether adherence improvements mediated a brief interventions effect on glycemic control. Longitudinal analysis via growth curve mixture modeling was carried out to classify 180 patients who participated in an adherence intervention according to patterns of adherence to oral hypoglycemic agents across 12 weeks. Adherence was assessed using the Medication Event Monitoring System. Hemoglobin A1c assays were used to measure glycemic control as the clinical outcome. Individual patient residential data was geo-coded at the tract level.

Three patterns of adherence to oral hypoglycemic agents were identified: adherent, increasing adherence, and nonadherent. Both individual and neighborhood level factors were identified that were associated with patterns of adherence. Patients with an increasing adherence pattern were more likely to have a Hemoglobin A1c (HbA1c) < 7% (adjusted odds ratio = 14.52, 95% CI [2.54, 82.99]) at 12 weeks in comparison with patients with the nonadherent pattern. 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)]. These findings imply that the identification of patients with type 2 diabetes at risk of nonadherence is important for clinical prognosis and the development and delivery of interventions.

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CHAPTER 1: Patterns of Adherence to Oral Hypoglycemic Agents and Glycemic Control among Primary Care Patients with Type 2 Diabetes

Introduction

Achieving optimal glycemic control is a cornerstone in reducing risk for micro-vascular and macro-vascular complications in type 2 diabetes (American Diabetes Association, 2014). Despite the development of effective diabetes therapies and interventions to prevent both macrovascular and microvascular complications and adverse events, diabetes control remains suboptimal (Stark Casagrande et al., 2013; Stratton et al., 2000; Turner et al., 1999; UK Prospective Diabetes Study Group, 1998b). Oral hypoglycemic adherence is a critical component of diabetes treatment regimens with guideline concordant adherence being associated with improved glycemic control, lower disease-related health-care expenditures, and reduced mortality (Rasmussen et al., 2007; Stuart et al., 2009). However, adherence estimates generally range between 36% and 93% of prescribed medication regimens for adherence to oral hypoglycemic agents, with a significant proportion of patients failing to meet recommended adherence targets (Cramer, 2004).

Cramer and others reviewed factors associated with adherence to diabetes medicines. Identified factors associated with adherence include age, ethnicity, depression, regimen complexity, dosing frequency of medications, adverse effects, medication costs, patient education and beliefs, and social support (Bailey & Kodack, 2011; Cramer, 2004; Odegard & Capoccia, 2007; Rubin, 2005). However, these reviews have not specifically considered the issue of oral hypoglycemic agent adherence in primary care and have not examined factors associated with adherence in the context of an intervention. Education alone is insufficient to produce significant adherence behavior change (Mazzuca, 1982). Interventions tailored to the individual focusing on multiple factors inhibiting adherence have been found to be more effective than interventions that are not individually-focused or focus on a single adherence barrier (Haynes et al., 2008; van

Eijken et al., 2003). Understanding which type 2 diabetes patients are at greatest risk for

nonadherence and subsequently poor clinical outcomes based on clinically identifiable patient

characteristics would help to identify patients who might benefit from interventions in real world

clinical settings.

Investigations attempting to examine individuals at risk for poor adherence share one

major shortcoming, they treat adherence as a discrete outcome despite the varying nature of

adherence over time. Adherence to oral hypoglycemic agents has been assessed through

proportions at singular point(s) in time with little evaluation of variation over time and group

classification. We used an innovative technique for longitudinal data analysis, the general growth

curve mixture model (GGCMM), in order to study individual differences in adherence and change

over time. This technique identifies different subgroups of patients based on their underlying

trends and allows for the examination of membership in the subgroups in relation to baseline

patient characteristics and subsequent clinical outcomes. Prior work examining adherence to oral

hypoglycemic agents has also been limited by recruitment from insurance entities, subjective

adherence assessments, and/or primarily Caucasian samples (e.g.(Kalsekar et al., 2006; Krapek

et al., 2004; Lamberts et al., 2011; van Dijk et al., 2007)). We used an objective assessment of

adherence, electronic monitoring data, and our sample is drawn from primary care practices

serving socioeconomically and ethnically diverse patients.

Our investigation used longitudinal adherence patterns to identify subgroups of type 2

diabetes patients at risk for nonadherence and poor glycemic control at 12 weeks. Our purpose

was to further understand (1) the course of oral hypoglycemic agent adherence patterns over 12

weeks among type 2 diabetes patients in primary care, (2) whether such patterns are related to

patient characteristics; and, (3) whether patterns predict glycemic control at 12 weeks (Figure 1).

We employed data from a primary care randomized controlled trial in which the study intervention

was implemented at the patient level and involved an integrated care specialist working with

physicians to provide care (Bogner et al., 2012). We hypothesized that type 2 diabetes patients

would have distinct patterns of adherence over the 12 week period. We hypothesized based on the literature that patients who were younger, male, non-white, depressed, on a dosing frequency greater than 1 per day, or had a greater medical burden would be more likely than others to have a pattern of nonadherence (Cohen et al., 2010; Hansen et al., 2010; Kalsekar et al., 2006; Paes et al., 1997; Sclar et al., 1999). In addition, we hypothesized that patients in usual care would be less likely to adhere than patients in the intervention condition. Finally, we hypothesized that patients who were adherent or had increasing adherence across 12 weeks would be more likely to have Hemoglobin A_{1c} (HbA_{1c}) in comparison with patients who were nonadherent. Identifying patterns of adherence to oral hypoglycemic agents over 12 weeks linked to the outcome of glycemic control at 12 weeks will set the stage for interventions targeting resources for persons most at risk for nonadherence.

To our knowledge, no study has examined patient characteristics, pattern of time-varying adherence, and outcome in a primary care trial of diabetes management among type 2 diabetes with the ultimate goal of translating the knowledge into improving clinical outcomes. The Global Burden of Disease Study 2010 and the World Health Organization (WHO) list diabetes as a leading cause of disability (Vos et al., 2012). According to the WHO, the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments (World Health Organization, 2003). Identifying type 2 diabetes patients at risk for poor adherence is key to identifying groups of patients at greatest need for intervention and follow-up.

Methods

Recruitment

A Brief Intervention to Improve Adherence through Integrated Management of type 2 Diabetes Mellitus and Depression Treatment was a randomized controlled trial designed to assess whether an intervention in primary care improved glycemic control and depressive

symptoms in type 2 diabetes patients. Patients were recruited from three primary care practices

in Philadelphia, Pennsylvania. Patients were randomly assigned to the integrated care

intervention or usual care. Electronic medical records were screened between April 2010 to April

2011 for patients with a diagnosis of type 2 diabetes and a prescription for an oral hypoglycemic

agent within the past year. The study is described in detail elsewhere (Bogner et al., 2012).

Study Design

　　　　The purpose of the 2-week run-in phase was to assess the feasibility of use of Medication

Event Monitoring System (MEMS) caps and to allow for the collection of pre-intervention

adherence rates. Data collected during this phase also included baseline demographics and

glycated hemoglobin (HbA$_{1c}$) assays to measure glycemic control. After the two-week run-in

phase, phase 2 of the study began in which patients were randomized to the integrated care

intervention or usual care.

Intervention and Usual Care

　　　　The integrated care manager worked individually with patients to address factors

resulting in nonadherence including depression, chronic medical conditions, function, cognition,

social support, cost of medications, side effects, and past experiences with medications. Through

in person sessions and telephone conversations the integrated care manager provided education

about depression and type 2 diabetes, emphasizing the importance of controlling depression to

manage diabetes; help to identify target symptoms; explanations for the rationale for

antidepressant and oral hypoglycemic agent use; assessment for side-effects and assistance in

their management; assessment for progress (e.g. reduction in depressive symptoms and

improvement in finger stick results); assistance with referrals; and monitoring and response to

life-threatening symptoms (e.g. chest pain, suicidal thoughts and actions).

　　　　The intervention was presented to patients as a supplement to, rather than a replacement

for, existing primary care treatment. Over a three month period patients had three 30 minute in-

person sessions (baseline, 6 weeks and 12 weeks) and two 15-minute telephone monitoring

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contacts. Usual care patients underwent in-person assessments at the same time points as the intervention. Research assistants conducted all assessments blinded to patient's randomization status.

Adherence to Oral Hypoglycemic Agents

Adherence to oral hypoglycemic agents was measured using electronic monitoring data obtained from the Medication Event Monitoring System (MEMS) Caps. MEMS caps on pill bottles record the precise date and time of container opening. Electronic drug monitoring data were assessed as the proportion of medication MEMS cap openings in a given week relative to the prescribed doses for the week. Our adherence calculation did not include excessive bottle openings or openings that exceeded the number of prescribed doses for the week.

Glycemic control

In accordance with American Diabetes Association Guidelines (American Diabetes Association, 2014) blood glycemic control was assessed at baseline and 12 weeks. The in2it A1C Analyzer provides point of care testing and was used to obtain Hemoglobin A_{1c} (HbA$_{1c}$) assays. This device has acceptable precision and agreement in comparison with laboratory services (Moridani et al., 2003).

Baseline Covariates

Standard questions were employed to obtain patient information on age, gender, ethnicity, marital status, and education. Consistent with prior investigations age was dichotomized as $\geq$ 60 years and less than 60 years (Beverly et al., 2013). Medical comorbidity was assessed by self-report at baseline. The Mini-Mental State Examination (MMSE) assessed cognitive status and has been widely employed for clinical and research purposes.(Folstein et al., 1975) The MMSE is a short standardized instrument that assesses orientation to time and place, registration, memory, attention and concentration, praxis, and constructional and language capacity (Tombaugh & McIntyre, 1992). As in prior work, MMSE scores were analyzed as a

dichotomous variable with a clinical threshold of 27 (O'Bryant et al., 2008; Spering et al., 2012). Functional status was measured using the Medical Outcomes Study Short Form (SF-36) (Stewart et al., 1988). Depressive symptoms were assessed using the nine-item Patient Health Questionnaire (PHQ-9). The PHQ-9 is a self-administered version of the PRIME-MD diagnostic instrument for mental disorders (Kroenke et al., 2001).

Analytic strategy

In the first phase of this analysis, general growth curve mixture models (GGCMMs) were applied to indicators of adherence to oral hypoglycemic medication over the 12-week period to identify different adherence patterns (McCutcheon, 1987). Binary indicators were adherence measurements assessed by MEMS caps at weekly intervals over a 12-week period. For each adherence assessment patients were categorized as adherent if they took at least 80% of their pills in the interval. Otherwise, patients were considered to be nonadherent. Greater or equal to 80% adherence was used because the 80% cut-point has been used as a standard to which other measures are compared (Winkler et al., 2002). The model for the adherence patterns included random intercepts and slopes to account for within-subject correlations and separate fixed effect intercepts and fixed effects slopes for time within each latent class or pattern of adherence. We compared the results of this longitudinal linear model to models that accommodated nonlinear changes in adherence across time. The classifications into different patterns of adherence were similar across the different models, so we based our results on the simpler linear model. Number of classes was determined through examination of fit indices (AIC and BIC) as well as for clinically interpretable results. The Rubin-Lo-Mendell test was employed to determine if additional classes added further information to the model (Lo et al., 2001).

In the second phase of this analysis, we examined differences in baseline patient characteristics across adherence profile types (adherent (n=67), increasing adherence (n=52), and nonadherence (n=61)) using χ^2 for binary variables and analysis of variance (ANOVA) for continuous variables. We added patient characteristics and practice indicators to the GGCMM,

one at a time to evaluate their association with class membership. Covariates that were significant at the p<0.10 level were included in the final model. Next, the relationship between the baseline covariates significant at the p<.10 level and latent classes or patterns of adherence was simultaneously assessed. The results were reported as odds ratios and corresponding confidence intervals. The baseline covariates were selected on the basis of previous literature on patient characteristics associated with adherence to oral hypoglycemic agents. We also examined interaction terms for which we had an *a priori hypothesis*: intervention by cognition and an intervention by education.

In the third phase, patients were classified into categories of longitudinal adherence profile types based on the largest posterior probability of membership in a certain class. Logistic regression related latent class variables to the clinical outcome of glycemic control at 12 weeks. Glycemic control was examined both continuously and categorically. As recommended by clinical guidelines, the categorical outcome was assessed using a cutoff of $HbA_{1c} < 7\%$ at 12 weeks (American Diabetes Association, 2014). The results of the categorical outcome are presented in the form of odds ratios and 95% confidence intervals. Consistent with prior work, the model included terms to adjust for age, ethnicity, gender, marital status, educational attainment, functional status, frequency of medication administration, number of medications, number of medical conditions, cognitive status, intervention condition, pre-intervention adherence and baseline clinical outcome (Bogner et al., 2013). 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 the Brief Intervention to Improve Adherence through

Integrated Management of type 2 Diabetes Mellitus and Depression Treatment trial has been published elsewhere (Bogner et al., 2012). The protocol was approved by the University of Pennsylvania Institutional Review Board. In brief, out of 715 patients identified by electronic medical records with type 2 diabetes, 265 were eligible and were approached for screening. Among type 2 diabetes patients who were approached, 190 were enrolled (71.7% participation rate). Patients who participated and patients who refused were similar in terms of key demographic characteristics such as age, gender, and ethnicity. After consent was obtained patients were assessed over a 2-week run-in phase in which medication adherence was examined. At the two-week visit, six patients had their medication discontinued, two patients were lost to follow-up and 182 patients were randomized to the integrated care intervention or usual care. In addition, two patients in the integrated care intervention were lost to follow-up subsequent to randomization. The remaining 180 patients completed all study visits.

The mean age of our sample was 57.4 years (standard deviation (s.d.) 9.5 years, range 32 to 84 years), and 122 (67.8%) of the patients were women. The self-identified ethnicity 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 MMSE score was 28.2 (s.d. 2.3). Baseline patient characteristics across adherence profile types (adherent (n=67), increasing adherence (n=52), and nonadherence (n=61)) are displayed in Table 1. White respondents and patients assigned to the intervention condition were more likely to show an adherent or increasing adherence pattern (p<.05). Physical functioning SF-36 score and mini-mental state examination (MMSE) scores significantly differed by adherence profile type (p<.05).

Patterns of adherence

Corresponding to the first phase of the analysis, we examined patterns of oral hypoglycemic agent adherence over 12 weeks. In order to delineate these patterns a series of GGCMMs were fitted to the MEMS data. The three-pattern model presented in Figure 2

improved the model fit over the two- and four-pattern models. The Rubin-Lo-Mendell test

indicated that the three-pattern model of longitudinal adherence trajectories improved the model

fit over the two-pattern model (p<0.001), with the four-pattern model providing no additional

improvement in fit (p>0.99). Entropy, a measure of classification uncertainty, was 96.7%

indicating a clear delineation of classes.

Figure 2 shows the patterns of adherence represented by the categorical indicators of

adherence at weekly intervals over the 12-week interval. The number of persons assigned to

each pattern is presented at the bottom of Figure 2. Patients were assigned to each pattern

according to their maximal posterior probabilities in each pattern. The first pattern (n= 67, 37.0%

of the entire sample, "adherent") represents patients with a high probability of adherence at each

time point. Patients with an "adherent" pattern had a probability of adherence at baseline of

72.1% and strongly increasing adherence over time (model slope: 1.54 (95% confidence interval

(CI): 0.90, 2.17)), with adherence reaching near 100% by the 5th week.

The second pattern represents patients who have a low level of adherence at baseline

and improve ("increasing adherence;" n = 52, 29.2% of the sample). Patients with "increasing

adherence" had a modeled probability of adherence of 30.3% at baseline with a statistically

significant increase in adherence over time (model slope of .22 (95% CI: 0.12, 0.32)). Modeled

adherence reached over 80% by the end of the 12 week period. The third pattern (n=61, 33.8%

of the entire sample, "nonadherent") represents patients with a near zero probability of adherence

at each time point. Patients with the nonadherent pattern had a near zero probability of

adherence at baseline which remained near zero. To provide a more stable model, the slope

parameters were fixed at zero for the third pattern of "nonadherent."

Baseline Type 2 DM patient characteristics and patterns of adherence

Corresponding to the second phase of our analysis, we examined whether patient

characteristics were associated with patterns of adherence to oral hypoglycemic agents (Table 2).

Odds ratios were employed to estimate the association of baseline patient characteristics with

patterns of adherence. Two comparisons of patterns of adherence were examined: adherent vs. nonadherent and increasing adherence vs. nonadherent. Patients with MMSE score greater than or equal to 27 were more likely to have an adherent pattern compared to a nonadherent pattern (odds ratio (OR) = 1.29, 95% (CI) [1.06, 1.57]). Patients in the intervention condition were more likely to have an adherent pattern compared to a nonadherent pattern (OR = 11.6, 95% CI [4.08, 32.9]). In addition, 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]). In our final model, no associations between age, gender, ethnicity, education, depression status, dosing frequency, number of medications, functional status, or medical comorbidity and classes of adherence were found. We considered potential interaction terms: intervention by cognition and intervention by education, but none reached the level of significance of $p < .05$.

Clinical outcome of patterns of adherence: Hemoglobin A_{1c} (HbA_{1c}) at 12 weeks

Corresponding to the third phase of our analysis, we examined whether longitudinal profiles of adherence were associated with glycemic control as assessed by Hemoglobin A_{1c} (HbA_{1c}) at 12 weeks (Tables 3 and 4). HbA_{1c} at 12 weeks was strongly related to adherence patterns (χ^2 (2)= 12.82, p<0.01). Patients with an increasing adherence pattern were significantly more likely to have an $HbA_{1c} < 7\%$ (unadjusted OR = 4.39, 95% CI [1.91, 10.12]); adjusted OR = 14.52, 95% CI [2.54, 82.99]) at 12 weeks in comparison with patients with the nonadherent pattern. Patients with an adherent pattern were not significantly more likely to have an $HbA_{1c} < 7\%$ (unadjusted OR = 1.86, 95% CI [0.92, 3.76]; adjusted OR = 2.24, 95% CI [0.51, 9.92]) at 12 weeks in comparison with the nonadherent pattern. Patients with an increasing adherence pattern were significantly more likely to have achieved an $HbA_{1c} < 7\%$ (unadjusted OR = 2.36, 95% CI [1.03, 5.41]); adjusted OR = 6.47, 95% CI [1.52, 27.51]) at 12 weeks in comparison with patients with the adherent pattern. Patients with a nonadherent pattern were not significantly less likely to have achieved an $HbA_{1c} < 7\%$ (unadjusted OR = 0.59, 95% CI [0.27, 1.09]; adjusted OR = 0.45, 95% CI [0.10, 1.97]) at 12 weeks in comparison with the adherent pattern. The model included terms to adjust for baseline differences in age, ethnicity, gender, marital status,

educational attainment, functional status, frequency of medication administration, number of medications, number of medical conditions, cognitive status, primary care practice, baseline HbA_{1c}, pre-intervention adherence and intervention condition.

Discussion

Examination of adherence over 12 weeks revealed three patterns: adherent, increasing adherence, and nonadherent. Patients who had a MMSE score greater than or equal to 27 were more likely to have an adherent pattern than the nonadherent pattern compared to patients with a MMSE less than 27. Patients in the intervention condition were more likely to have an adherent pattern than a nonadherent pattern in comparison with patients in usual care. Similarly, patients in the intervention condition were more likely to have an increasing adherence pattern than a nonadherent pattern in comparison with patients in usual care. Patients with an increasing adherence pattern were also more likely to have an $HbA_{1c} < 7\%$ at 12 weeks in comparison with patients with the nonadherent pattern. Similarly, patients with an increasing adherence pattern were more likely to have achieved an $HbA_{1c} < 7\%$ at 12 weeks in comparison with patients with the adherent pattern. Our use of general growth curve mixture models allows us to assess 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. Our finding that patterns of adherence were differentially related to covariates of interest demonstrates the significance of delineating patterns of adherence over time.

Before discussing our findings, the results must first be considered in the context of some potential study limitations. First, we obtained our results from three primary care sites whose patients may not be representative of other primary care practices. However, the three practices were probably similar to other primary care practices in the region as they were diverse and varied in size. Second, there are limitations for all methods for assessing adherence. MEMS

caps were our primary measure of adherence because as an objective measure of adherence they have a low failure rate and are more sensitive than other adherence measures.(Farmer, 1999) Any influence of MEMS caps on medication adherence would be experienced equally in both the intervention and usual care groups. Third, while research has assessed the 80% threshold for some medications(Winkler et al., 2002), the clinical significance of this threshold has not been tested for many medications. Fourth, the length of follow-up for this trial was 12 weeks. However, significant intent-to-treat effects have been found in diabetes studies for a 12 week time period (Haynes et al., 2008). Finally, even with confidence in our assessments of exposure, misspecification of the model relating adherence and blood glycemic control is still a possibility, such as when important variables have not been included in our model. We have tried to take care in adjusting our estimates of association for potentially influential characteristics that may relate to the outcome.

Despite these limitations, our results deserve attention because we attempted to characterize patterns of adherence over 12 weeks and the association of patient characteristics, intervention condition, and glycemic control with patterns of adherence. Assessment of a single point in time is insufficient to understand variations in adherence over time. The three patterns of adherence we observed suggest a possible need for more intensive interventions targeting individuals, particularly those with MMSE less than 27. Our results suggest that the intervention condition increased the number of patients with an increasing adherence pattern that might have otherwise have had a nonadherent pattern.

Our results were not wholly consistent with our initial hypotheses. We did not find an association of age, sex, ethnicity, dosing frequency or medical burden with patterns of adherence. The lack of significant associations of age, sex, ethnicity, dosing frequency, depression status, or medical burden in patients suggests that the effects of these variables did not appear to influence patterns of adherence. In terms of depression status, the onset and nature of clinical diagnosis of depression as well the influence of these diagnoses on functioning may be more important in

adherence than symptom presentation. In the examination of medical burden more careful assessment of the type of medical conditions and everyday related tasks that include medication-taking related items may be necessary to find a clear association with medical co-morbidity. Given a lack of identification of clear risk profiles for nonadherence, physicians may only be able to suspect nonadherence during the course of treatment for diabetes. If nonadherence is suspected, reasons for nonadherence should be examined and addressed to mitigate poor health prognoses and adverse clinical outcomes (Bogner et al., 2013).

Of note, in examining the relationship between patterns of adherence and achieving glucose control adjusting for potentially influential covariates increased the effect size of our estimates. Adjustment of the odds ratio for imbalance in the distribution of baseline covariates assessed at baseline can be expected to yield estimates closer to the true estimate of the effect (Buyse, 1989; Lu et al., 2005). For example, a larger proportion of patients with the adherent pattern in comparison with the nonadherent pattern may have had multiple medical conditions which may have influenced glucose control. When controlling for medical conditions the effect of medical conditions on the patterns of adherence and glucose control relationship was taken away. We did not find an association with the adherent pattern and glucose control. This lack of an association may be indicative of dosing inadequacy of oral hypoglycemic agents. Patients who are adherent to an inadequate dosage of oral hypoglycemic agents would not be expected to achieve targets for glycemic control.

Patients with MMSE greater than or equal to 27 were more likely to have an adherent than a nonadherent pattern. Past work has demonstrated that individuals with type 2 diabetes show accelerated cognitive decline, particularly in information-processing speed and executive function, compared with individuals without diabetes (Spauwen et al., 2013). While the association between cognition and diabetes is supported by a number of biologically plausible mechanisms, successful diabetes management is largely determined by self-care behaviors such as adherence. Lower cognitive functioning is associated with reduced health literacy(Nguyen et

al., 2013) and understanding of diabetes management (Hewitt et al., 2011), and greater

dependency (Sinclair et al., 2000) in persons with diabetes. Furthermore, lower cognitive

functioning is also linked to increased risk of poor glycemic control (Okura et al., 2009), severe

hypoglycemia (Punthakee et al., 2012), and mortality (McGuire et al., 2006) in patients with type 2

diabetes. Patients with lower cognition scores on the MMSE are at risk for a pattern of

nonadherence and may need special attention for adherence management.

Our results suggest that the intervention increased the number of patients with an

adherent and increasing adherence pattern that might have otherwise have had a nonadherent

pattern. The strong association between intervention assignment and adherence pattern

substantiates evidence that intervention strategies targeting multiple adherence barriers and

which are tailored to the needs of each patient are successful in improving adherence (Haynes et

al., 2008). The interventionist worked individually with patients to address the factors involved in

adherence that related to their specific characteristics and medical co-morbidity. The high

recruitment rates and retention of minorities in this intervention has particularly significance given

the disportionate burden of diabetes among minority groups (Office of Minority Health, 2014).

This is aligned with prior work demonstrating that integrated interventions are more engaging and

acceptable to minorities than other intervention approaches (Ayalon et al., 2007; Bogner et al.,

2008; Unutzer et al., 2002). Furthermore, this intervention was both brief and simple in

comparison with other diabetes interventions suggesting it may be a sustainable strategy for

improving patient adherence that can be implemented in primary care or other settings (Leeman,

2006; Renders et al., 2001).

Our findings hold particular clinical significance by demonstrating an increased likelihood

of patients with $HbA_{1c} < 7\%$ at 12 weeks among patients with an increasing adherence pattern.

However, we did not find an association with the adherent pattern and glycemic control. As more

is discovered regarding factors influencing adherence over time, we may be able to more

accurately identify predictors of glycemic control. The lack of a significant association between

the adherent pattern and glycemic control may be indicative of the severity of underlying disease or dosing inadequacy of oral hypoglycemic agents. Patients who are adherent to an inadequate dosage of oral hypoglycemic agents would be less likely to have glycemic control. In the future, longitudinal models may be used to link patient characteristics and patterns of adherence to the likelihood of adequate glycemic control in order to guide clinical treatment. Interventions tailored to the cognitive functioning of patients might have a substantial public health impact on glycemic control. A simple and brief adherence intervention was strongly related to adherence patterns and clinical outcome. Our results highlight the need for the development, implementation, and dissemination of clinical interventions to enhance medication adherence.

Figures and Tables

Figure 1. Conceptual framework of baseline covariates, patterns of adherence, and glycemic control.
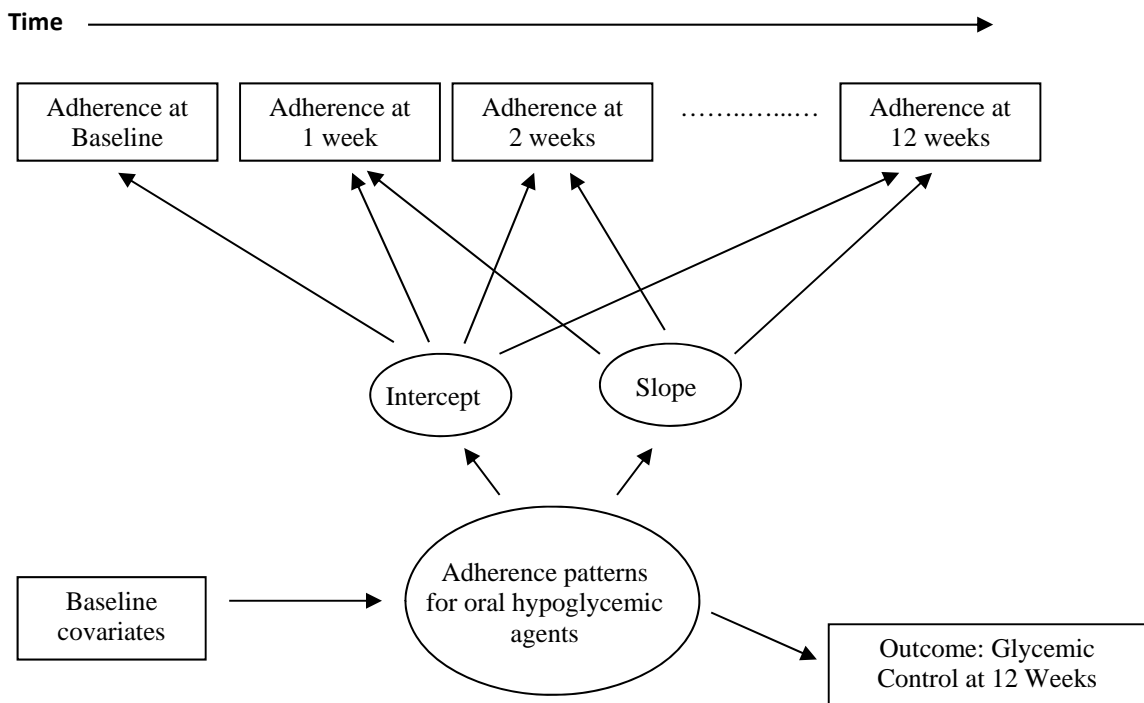
Note: Patterns of adherence based on Medication Event Monitoring System (MEMS) data.
Glycemic control at 12 weeks based on Hemoglobin A_{1c} (HbA_{1c}).

Figure 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).
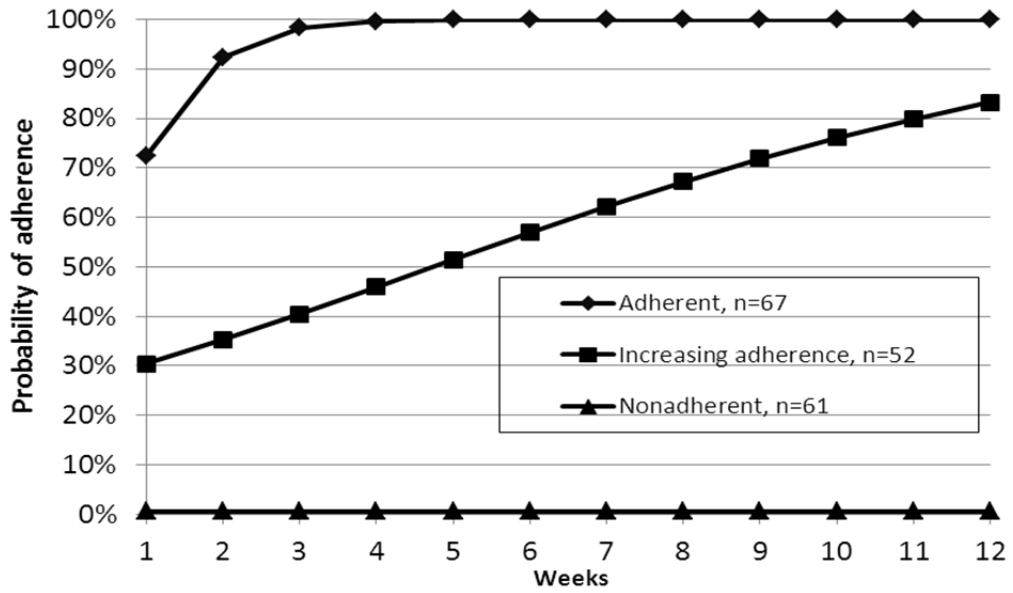
Note: Data gathered from 2010-2011.

Table 1. Baseline patient characteristics by adherence profile type (n=180).

Sociodemographic characteristics	Adherent (n=67)	Increasing Adherence (n=52)	Non-adherent (n=61)	P-value
Age, mean in years (s.d.)	56.7 (9.3)	59.3 (8.9)	56.7 (10.1)	.25
White, n (%)	33 (49.3)	13 (25)	19 (31.2)	.02
Gender, women n (%)	40 (59.7)	42 (80.8)	40 (65.6)	.05
Married, n (%)	30 (44.8)	21 (40.4)	18 (29.5)	.19
Less than HS education, n (%)	5 (7.5)	11 (21.2)	13 (21.3)	.05
Functional status (SF-36)				
Physical function score, mean (s.d.)	60.8 (30.1)	44.6 (32)	49.1 (32.6)	.02
Medications				
Frequency of oral hypoglycemic agent per day, mean (s.d.)	1.3 (.5)	1.3 (.6)	1.2 (.4)	.77
Number of medications, mean (s.d.)	9.5 (4.5)	9.4 (4.4)	11 (5.4)	.12
Health status				
Medical conditions, mean (s.d.)	6.6 (2.5)	7.6 (3.4)	7.8 (3.7)	.09
Cognitive status				
MMSE, mean (s.d.)	28.8 (1.6)	28.1 (2.2)	27.6 (2.8)	.01
Randomization assignment				
Intervention, n (%)	40 (59.7)	44 (84.6)	8 (13.1)	<.001
Depression status				
PHQ-9, mean (s.d.)	9.5 (7.2)	11.5 (8.3)	10.1 (7.3)	.35
Type 2 diabetes				
HbA_{1c}, mean (s.d.)	7.1 (1.7)	7.2 (1.9)	7.1 (2.0)	.87

Abbreviations: 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 χ^2 for binary variables and analysis of variance (ANOVA) for continuous variables for categorical or continuous data, respectively.

Table 2. Multivariate logistic regression of baseline patient characteristics among the three patterns of adherence generated from the general growth curve mixture model (GGCMM) (n= 180).

Patient characteristics	Adherent vs. Nonadherent OR [95% CI]	Increasing Adherence vs. Adherent OR [95% CI]	Increasing Adherence vs. Nonadherent OR [95% CI]
Education (reference: less than high school education)	.54 [.16, 1.83]	2.86 [.66, 12.38]	1.53 [.34, 6.82]
Ethnicity (reference: minority)	.87 [.55, 1.38]	1.21 [0.82, 1.80]	1.06 [.71, 1.56]
Cognition (reference: MMSE < 27)	1.29* [1.06, 1.57]	0.93 [0.75, 1.15]	1.19 [.96, 1.47]
Intervention (reference: usual care)	11.6* [4.08, 32.9]	3.56* [1.30, 9.79]	41.31* [13.87, 123.03]

Note: OR = Odds Ratio; CI = Confidence Interval. MMSE= mini-mental state examination.* p< .05

Table 3. Outcome glycemic control at 12 weeks for the three patterns of adherence

(n=180, reference: non adherent).

	$HbA_{1c} < 7\%$ vs. $HbA_{1c} \geq 7\%$ at 12 weeks	
Patterns of adherence (0-12 weeks)	**Unadjusted OR [95% CI]**	**Adjusted OR** ** **[95% CI]**
Adherent (n=67)	1.86 [0.92, 3.76]	2.24 [0.51, 9.92]
Increasing adherence (n=52)	4.39* [1.91, 10.12]	14.52* [2.54, 82.99]
Non adherent (n=61)	1.00	1.00

Note: Hb = hemoglobin; OR = odds ratio; CI = confidence interval; * p< .05
** adjusted for age, ethnicity, gender, marital status, educational attainment, functional status, frequency of medication administration, number of medications, number of medical conditions, cognitive status, practice, baseline $HbA_{1c,}$ pre-intervention adherence and intervention condition.

Table 4. Outcome glucose control at 12 weeks for the three patterns of adherence

(n=180, reference: adherent).

Patterns of adherence (0-12 weeks)	Achieved HbA$_{1c}$ < 7% vs. Did Not Achieve HbA$_{1c}$ < 7% at 12 weeks	
	Unadjusted OR [95% CI]	**Adjusted OR** ** **[95% CI]**
Increasing adherence (n=52)	2.36* [1.03, 5.41]	6.47* [1.52, 27.51]
Non adherent (n=61)	0.59 [0.27, 1.09]	0.45 [0.10, 1.97]
Adherent (n=67)	1.00	1.00

Note: OR = odds ratio; CI = confidence interval; * $p < .05$
** adjusted for age, ethnicity, gender, marital status, educational attainment, functional status, frequency of medication administration, number of medications, adherence, number of medical conditions, cognitive status, practice, baseline Hba$_{1c}$ and intervention condition.

CHAPTER 2: Neighborhood Social Environment and Patterns of Adherence to Oral Hypoglycemic Agents among Patients with Type 2 Diabetes Mellitus

Introduction

Despite the development of effective pharmacological therapy to prevent both macrovascular and microvascular complications and adverse events (Stratton et al., 2000; Turner et al., 1999; UK Prospective Diabetes Study Group, 1998a, 1998b) diabetes control remains sub-optimal (Egede et al., 2011; Saaddine et al., 2006; " U.S. Department of Health and Human Services. Healthy People 2020,"). Poor adherence to recommended regimens is a causal factor in preventable morbidity and mortality in diabetic patients (Rasmussen et al., 2007). While individual characteristics are important contributors to medication adherence, much of the observed variation in adherence rates remains unexplained by these factors (Geraghty et al., 2010; Laraia et al., 2012; Long et al., 2010). Neighborhood environment may shape medication adherence through many factors such as socioeconomic resources, perceptions, expectations and beliefs. Individuals living in the same neighborhood may be more similar to each other than persons living in other neighborhoods because they share common social, economic, systemic, and lifestyle characteristics. Thus there may be common health behaviors that persist over and above individual variation relate to living environment (Diez-Roux, 2000; Groenewegen et al., 1999). The assessment of this collective phenomenon is needed to fully elucidate and understand adherence behaviors. However, little empirical knowledge exists about the nature and size of these collective or contextual neighborhood level effects on health behaviors such as medication adherence (Berkman & Kawachi, 2000).

Neighborhood social environment is an important construct in discerning how neighborhood contextual effects influence health behavior (Kawachi & Berkman, 2000). With a movement to examine neighborhood effects beyond the influence of poverty, a focus on social characteristics, organization and culture in relation to behaviors and outcomes has become

essential (Browning & Cagney, 2003). The concepts of social affluence, neighborhood advantage and residential stability, derived from the work of Sampson et al. (Sampson et al., 1999; Sampson & Raudenbush, 1999; Sampson et al., 1997), have been the subject of much research and have been established as important explanatory factors in understanding the role of neighborhood social environment in health (Boardman, 2004; Matthews & Yang, 2010; Yang et al., 2011). These measures tap into both the influence of poverty as well as social mechanisms and processes hypothesized to link neighborhood environment to health. We seek to understand whether these constructs are related to medication adherence, a critical predictor of prognostic outcomes particularly for patients with diabetes. Our conceptual framework, shown in Figure 1, depicts the key constructs assessed in this study relating key features of the neighborhood social environment to patterns of adherence over time.

Prior work has found that neighborhood residence is associated with medication adherence (Billimek & August, 2013; Groenewegen et al., 1999; Merlo et al., 2003) and other self-care behaviors (Adams et al., 2013; Deshpande et al., 2005; Gary et al., 2008), even when controlling for individual characteristics. However, these studies have been limited by their cross-sectional designs, reliance on subjective adherence assessments and/or lack of a representative sampling frame due to regional variations in culture, context and available resources. Few identified studies investigated this relationship among diabetic patients, a population in which the environment may have a particularly salient role. Our work extends current findings by employing a longitudinal study design to examine adherence with medication regimens as assessed by an objective and time-varying measure of adherence among a diverse sample of primary care patients with diabetes. Demonstrating a relationship between features of neighborhood social environment and patterns of adherence to oral hypoglycemic agents will set the stage for interventions targeting resources for persons and neighborhoods most at risk for poor health.

Within a prospective randomized controlled trial we sought to investigate whether indicators of neighborhood social environment (social affluence, neighborhood advantage and

residential stability) would be associated with patterns of adherence to oral hypoglycemic agents. Our aim was to examine whether residents in neighborhoods with high social affluence, high neighborhood advantage, and/or high residential stability would be more likely to have a pattern of adherence or increasing adherence over time. We hypothesized that residents in neighborhoods with two or three features present (high social affluence, high neighborhood advantage and high residential stability) would be more likely to have a pattern of adherence or a pattern of increasing adherence than residents in neighborhoods with one or none of these features present. To our knowledge, this is the first investigation to examine social affluence, neighborhood advantage and residential stability in relation to longitudinal patterns of adherence among primary care patients with diabetes.

Methods

Recruitment

The randomized controlled trial, A Brief Intervention to Improve Adherence through Integrated Management of Type 2 Diabetes Mellitus and Depression Treatment, was designed to assess whether an integrated care intervention in primary care improved glucose control and depressive symptoms in type 2 diabetes mellitus (type 2 DM) (Bogner et al., 2012). In all, 180 patients were recruited from three primary care practices in Philadelphia, Pennsylvania and were randomly assigned to the intervention or usual care. 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 from April 2010 to April 2011. Patients with an upcoming appointment were approached for additional screening. Eligibility criteria were: 1) aged 30 years and older; 2) a diagnosis of type 2 DM; and 3) a current prescription for an oral hypoglycemic agent. Exclusion criteria were: 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 study protocol was approved by the University of

Pennsylvania, Perelman School of Medicine Institutional Review Board. The intervention is

described in detail elsewhere (Bogner et al., 2012).

Study Design

The trial was conducted in two phases: the run-in phase and the randomized controlled

trial phase. The run-in phase of this trial consisted of a 2-week period in which pre-intervention

adherence data for all patients was collected. Baseline demographics and glycated hemoglobin

(HbA$_{1c}$) assays to measure glycemic control were also collected at this time. Phase 2 of the

study, where patients were randomized to the integrated care intervention or usual care,

commenced after the 2-week run-in phase and occurred over 12 weeks.

Intervention

Integrated care managers worked with patients individually in the intervention group to

offer education, guideline-based treatment recommendations, and monitor adherence and clinical

status in collaboration with physicians. The integrated care manager addressed factors involved

in adherence to oral hypoglycemic agents presented in the conceptual model, adapted from

Cooper and colleagues (Cooper et al., 2003), and previously published (Bogner & de Vries,

2010). The patient-level factors hypothesized to result in nonadherence included higher levels of

depression, greater numbers of chronic medical conditions, lower functioning, impaired cognition,

poor social support, higher cost of medications, more side effects, and negative past experiences

with medications.   We chose this multi-faceted approach because education alone has not been

found to be effective for improving adherence (Mundt et al., 2001).

The intervention was presented to patients as a supplement to, rather than a replacement

for, existing primary care treatment. Over a three month period participants had three 30-minute

in person sessions (baseline, 6 weeks and 12 weeks) and two 15-minute telephone monitoring

contacts. Integrated care managers were two research coordinators (one Master's level and one

bachelor's level) who administered all intervention activities. The integrated care managers

received training on pharmacotherapy for type 2 DM management during five weekly clinical

sessions with the principal investigator prior to trial initiation.

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 integrated care intervention. Research

assistants conducted all assessments in-person and were blinded to patients' randomization

status.

Measurement Strategy

Patient Characteristics

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). At baseline, sociodemographic characteristics were assessed using

standard questions. Address data was obtained for participants at baseline. Electronic

monitoring data obtained from the MEMS Caps were used to measure adherence to oral

hypoglycemic agents. Adherence was assessed as the proportion of medication MEMS cap

openings in a given week relative to the prescribed doses for the week. Blood glycemic control

was assessed at baseline and 12 weeks in accordance with American Diabetes Association

Guidelines (American Diabetes Association, 2014). The in2it A1C Analyzer provides point of care

testing and was used to obtain glycated hemoglobin (HbA_{1c}) assays. This device has acceptable

precision and agreement in comparison with laboratory services (Moridani et al., 2003).

Neighborhood Social Environment

Neighborhoods fortify their residents by providing an infrastructure of privacy, protection, resources, and/or social networks. Neighborhoods characterized by social affluence may have extensive networks or one-on-one interactions. Benefits may be achieved when information, knowledge, content, and ideas are disseminated within social space. Neighborhood advantage taps into experiences which may manifest in higher educational attainment, occupation, and/or income. Advantage is often re-created through generations. Neighborhood stability refers to the amount of transitions (people who come into or out of a neighborhood) within neighborhoods, with fewer transitions corresponding better well-being for residents. These constructs were derived from the Sampson et al. and have been widely operationalized in the literature using Census data as we have done in this work (Boardman, 2004; Brusilovskiy & Salzer, 2012; Long et al., 2010; Matthews & Yang, 2010; Sampson et al., 1997; Yang et al., 2011).

Analysis

This analysis was conducted employing classifications of patients into patterns of adherence to oral hypoglycemic agents, as per our prior work (de Vries McClintock et al., in press). In brief, we employed general growth curve mixture models (GGCMM) (Elliott et al., 2005; Jo & Muthen, 2001; Lin et al., 2007; Muthen et al., 2002; Muthen, 2001; Muthen & Shedden, 1999; Ten Have et al., 2004) to generate estimated posterior probabilities of unobserved class membership for each patient. This seminal approach improves precision by accounting for both intervention effects and baseline covariates on adherence over time. Longitudinal patterns of adherence to oral hypoglycemic agents were created by classifying patients based on the largest posterior probability of membership across the classes. The resulting categorical variable, patterns of adherence to oral hypoglycemic agents (adherent, increasing adherence, and nonadherent), was employed as the dependent variable for this analysis.

Individual patient residential data was geo-coded at the tract level and then was merged with 2010 tract-level Census data. Factor analysis was conducted on 10 variables as done in

prior work by Sampson et al. and others to assess key constructs of the social environment: social affluence, neighborhood advantage and residential stability (Boardman, 2004; Brusilovskiy & Salzer, 2012; Long et al., 2010; Matthews & Yang, 2010; Sampson et al., 1997; Yang et al., 2011). Factor analysis examines the nature of the relationships between variables by identifying the smallest number of factors explaining composites of the observed variables. To decrease collinearity between resulting factors we required that variables loaded above 0.55 on a single factor. All 10 variables loaded above 0.55 on one of three factors resulting in three single composite factors/variables. Conventional diagnostics such as scree plots also confirmed these three identified factors. These factors represented constructs of neighborhood social environment: social affluence, neighborhood advantage, and residential stability. Factor scores for neighborhood social environment (social affluence, neighborhood advantage and residential stability) were dichotomized as high or low based on the sample median. Composites of these constructs were created representing three high features present (high social affluence, high advantage, and high stability), two high features present (high social affluence and high advantage, high social affluence and high stability, and high advantage and high stability), one high feature present (high social affluence only, high advantage only, and high stability only), and no high features present. Due to the small number of persons in neighborhoods with no high features present, the groups of one high features present groups and no high features present group were collapsed to serve as the reference group for our analysis.

Multinomial logistic regression related neighborhood social environment (social affluence, neighborhood advantage and residential stability) to patterns of adherence to oral hypoglycemic agents. Results are presented in the form of odds ratios and 95% confidence intervals. Neighborhood social environment was assessed both continuously and categorically. We have only presented our results from our categorical assessment for purposes of brevity. Consistent with prior work, the model included terms to adjust for age, ethnicity, gender, educational attainment, financial status, employment, frequency of medication administration, number of medical conditions, cognitive status, practice, baseline HbA_{1c}, and intervention condition (Bogner

et al., 2013). 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) (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 the Brief Intervention to Improve Adherence through Integrated Management of Type 2 Diabetes Mellitus and Depression Treatment trial has been published elsewhere (Bogner et al., 2012). In brief, of 715 patients with type 2 DM identified by electronic medical records, 265 were eligible and were approached and 190 were enrolled (71.7% participation rate). Consent was followed by a 2-week run-in phase in which adherence to medications was assessed. At the 2-week visit, 5 physicians had discontinued the antidepressant, 1 physician discontinued the oral hypoglycemic agent, and 2 patients were lost to follow-up. In all, 182 patients were randomized to the integrated care intervention or usual care. After randomization at the 2-week meeting, 2 patients in the integrated care intervention were lost to follow-up leaving 180 patients who completed the final study visit for our study sample.

In all, 179 patients had complete data on residential address and covariates of interest and were included in the present analysis. The mean age of our sample was 57.4 years (standard deviation (s.d.) 9.5 years). One hundred and twenty-one (67.6%) of the patients were women. The self-identified ethnicity of patients was 65 white (36.3%), 101 African-American (56.4%), 7 Hispanic (3.9%), and 6 (3.4%) who self-identified as 'other.' In all, 69 patients (38.6%) were married, and 29 patients (16.2%) had less than a high school education. The mean number of medical conditions was 7.3 (s.d. 2.4) and the mean MMSE score was 28.2 (s.d. 2.3).

Neighborhood social environment (residential stability, social affluence, and neighborhood advantage

Social affluence was derived from five variables: percent of households with resident/room ratio greater than 1 (factor loading = 0.57), percent of female-headed households (0.84), percent unemployed (0.77), percent of people below the poverty line (0.87), and percent of people receiving public assistance (0.73). Neighborhood advantage was derived from three variables: percent of residents with at least a bachelor's degree (0.87), percent of people in professional occupations (0.75), and percent of people with a household income greater than $75,000 (0.67). Finally, residential stability was derived from two variables: the percent of house owners (0.86) and the percent of residents living at the same address over 5 years (0.86). These results are shown in Table 1. Social affluence, residential stability, and neighborhood advantage stratified by median factor score as High and Low are depicted in Table 2.

Neighborhood social environment (residential stability, social affluence, and neighborhood advantage) and patterns of adherence to oral hypoglycemic agents

We examined the relationship between composite neighborhood characteristics and patterns of adherence to oral hypoglycemic agents (Table 3). The column of Table 3 labeled Adherent vs. Nonadherent provides odds ratios estimating the association of neighborhood social environment with patterns of adherence, comparing the adherent pattern to the nonadherent pattern. Compared to residents in neighborhoods with one or no high features present, residents in neighborhoods with high social affluence, high residential stability, and high neighborhood advantage were more likely to have an adherent pattern compared to a nonadherent pattern (adjusted odd ratio (OR)= 8.81, 95% confidence interval (CI) [1.80, 43.05]). The column of Table 3 labeled Increasing Adherence vs. Nonadherent compares the increasing adherence pattern to the nonadherent pattern. Compared to residents in neighborhoods with one or no high features present, residents in neighborhoods with high social affluence, high residential stability, and high neighborhood advantage were more likely to have an increasing adherence pattern compared to

a nonadherent pattern (adjusted OR= 13.00, 95% CI [2.25, 75.06]). There was not a significant

relationship between neighborhoods with two features present and patterns of adherence.

Discussion

The principal finding of this study is that residents in neighborhoods with high social affluence,

high residential stability, and high neighborhood advantage were much more likely to have an

adherent pattern compared to a nonadherent pattern. Similarly, residents in neighborhoods with

high social affluence, high residential stability, and high neighborhood advantage were much

more likely to have an increasing adherence pattern compared to a nonadherent pattern. These

results provide evidence that features of neighborhood social environment may be important

contributors to patterns of adherence to oral hypoglycemic agents, a critical factor in treatment

effectiveness and subsequent outcomes.

Before we discuss our findings, the results must be considered in the context of several

potential study limitations. First, data was collected from three primary care sites whose patients

may not be representative of other primary care practice settings. However, they were similar to

other primary care practices in the region in terms of diversity and size. Second, it is important to

note that all methods for assessing adherence have limitations. We utilized MEMS caps as our

primary measure because they are an objective measure, have a low failure rate (George et al.,

2000), and are more sensitive than other measures (Farmer, 1999). Both groups (intervention

and usual care) would experience any influence of MEMS caps on medication adherence equally.

Third, we solely examined the role of neighborhood social environment on behavioral patterns

(medication adherence). Future research could incorporate other measures of neighborhood

environment (e.g. physical environment: built environment, local food environment) as well as

individual factors (physical health, psychosocial stress, and psychosocial resources) and health

outcomes in order to delve deeper into the complex interplay of mediating or moderating

pathways linking neighborhoods to health across time (Kim, 2008). Finally, we are constrained

by the utilization of an administrative definition of neighborhoods (census tracts), which may not be the most meaningful level of aggregation. It is possible that assessment within a more respondent-derived neighborhood context may elicit the greatest explanatory power in understanding the role of neighborhood environment (Diez Roux, 2001).

Despite these limitations, our results are important to consider given that this study is one of the first examine the relationship between neighborhood social environment, as assessed by social affluence, residential stability, and neighborhood advantage, and patterns of adherence. A growing body of evidence has linked indicators of neighborhood social environment, namely measures of socioeconomic status with morbidity and mortality (Pickett & Pearl, 2001). However, little research has examined more proximal mechanisms to health, health behaviors, which are critical precedents for understanding disease prognosis in diabetes. In our work, we characterize mechanisms shaping the link between neighborhood social environment and health (Matthews & Yang, 2010; Yang et al., 2011) demonstrating that the presence of multiple features (high social affluence, high residential stability, and high neighborhood advantage) may be critical in understanding adherence patterns. Our results support evidence that neighborhoods matter and furthermore help to inform and enhance future research on how neighborhoods matter.

While we found that residents in neighborhoods with three high features present were significantly more likely to have a pattern of adherence or a pattern of increasing adherence, we did not find that residents in neighborhoods with two features present were significantly more likely to have a pattern of adherence or a pattern of increasing adherence. This aligns with work demonstrating that accumulation of exposures to multiple contextual factors may explain the health impact of neighborhoods. While the presence of a few features is somewhat influential, the presence of multiple features for extended periods of time is associated with the greatest health impact (Honold et al., 2012). Because fewer neighborhood features may have only a modest effect, our study may not have been large enough to provide an adequate test of our hypothesis that residents in neighborhoods with two features present were significantly more

likely to have a pattern of adherence or a pattern of increasing adherence than residents in neighborhoods with one or no features present.

Our findings are consistent with the work of Billmek et al. in which nonadherence to medications was examined in relation to neighborhood deprivation among persons with type 2 DM. Billmek and colleagues examined the cross-sectional relationship of neighborhood deprivation, as assessed by the Neighborhood Socioeconomic Status Index comprised of census tract measures, and self-reported adherence. Their findings suggest that social environment as well as related costs may contribute to nonadherence (Billimek & August, 2013). In our work we enrolled patients who already had filled prescriptions for oral hypoglycemic agents and we adjusted for individual financial status, thus minimizing the influence of cost on adherence to medication regimens, and supporting evidence that neighborhood social environment and adherence may be linked by factors other than financial pressure. Our work is further delineated from prior work by a focus on features of neighborhood social environment derived from the work of Sampson et al. (Sampson et al., 1999; Sampson & Raudenbush, 1999; Sampson et al., 1997). Our findings provide insight into the social mechanisms and process that link neighborhood environment to health. Furthermore, we used an objective measure of adherence, and 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. Our findings extend prior work by demonstrating that features of the social environment are associated with longitudinal patterns of adherence as assessed by objective measures of medication adherence among primary care patients with type 2 DM.
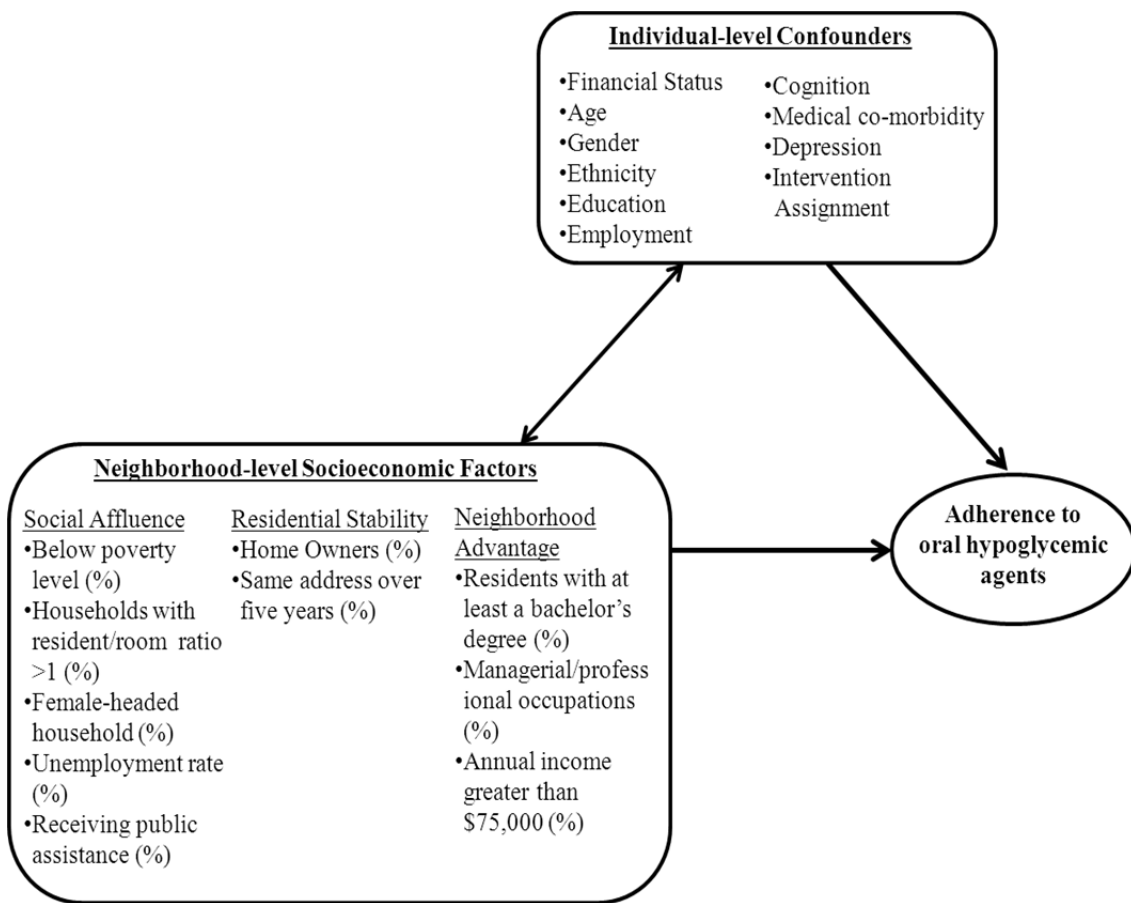
Our results highlight the significance of features of the social environment in shaping patterns of adherence to oral hypoglycemic agents over time, over and above of the effects of individual characteristics. Carpiano RM established a framework through which we can characterize the underlying mechanisms relating neighborhood social environment to adherence

(Carpiano, 2006, 2007). Following this framework, a lack of social capital and/or cohesion may exist in neighborhoods with low social affluence, advantage, and stability (Jencks & Mayer, 1990). Such environments may lack a myriad of health promoting social processes such as social control over deviant health-related behavior and attitudes (e.g. over-eating). These environments may promote unhealthy behaviors through social norms (Macintyre et al., 1993), minimal levels of social trust (Ross & Mirowsky, 2001) and a lack of a supportive community environment (Kawachi & Berkman, 2000). Furthermore, the character of daily routines, shaped by neighborhood environment (e.g. disorder), dictates the availability of temporal windows to engage in health promoting activities such as medication taking (Takahashi et al., 2001). Such windows may be limited in more compromised neighborhoods. All these processes may be at work in shaping patterns of health behavior over time, particularly when multiple features are present cumulatively over the life course (Dannefer, 2003; Ferraro & Shippee, 2009).

This study is among the first to suggest that features of neighborhood social environment may influence medication adherence. While the distinct mechanisms for this association require further examination, this study adds to a growing body of evidence that patient's social environment influences behavioral patterns. While such contextual factors play a critical role in shaping health outcomes, they are seldom addressed or incorporated into treatment plans. As a result, patients who receive guideline concordant care may not achieve treatment targets due to factors related to their daily environmental context. Reliance on a multi-level contextual framework, extending beyond the individual, to promote diabetic self-management activities may be essential for effective intervention deployment and notable public health improvements (Glasgow, 1995; Glasgow et al., 2000; Jack et al., 2004). Ongoing efforts to improve access and quality of care should be accompanied by initiatives to integrate the health care systems within community settings. Collaborative networks between healthcare networks and neighborhood communities are needed to foster effective adherence initiatives.

Figures and Tables

Figure 1. Proposed conceptual model of neighborhood level socioeconomic factors and adherence to oral hypoglycemic agents. This model was adapted from the work of the Translating Research Into Action for Diabetes (TRIAD) study (Gary et al., 2008) and Carpiano RM (Carpiano, 2007),

Individual-level Confounders

- Financial Status
- Age
- Gender
- Ethnicity
- Education
- Employment

- Cognition
- Medical co-morbidity
- Depression
- Intervention Assignment

Neighborhood-level Socioeconomic Factors

Social Affluence
- Below poverty level (%)
- Households with resident/room ratio >1 (%)
- Female-headed household (%)
- Unemployment rate (%)
- Receiving public assistance (%)

Residential Stability
- Home Owners (%)
- Same address over five years (%)

Neighborhood Advantage
- Residents with at least a bachelor's degree (%)
- Managerial/professional occupations (%)
- Annual income greater than $75,000 (%)

Adherence to oral hypoglycemic agents

Note: Patterns of adherence based on Medication Event Monitoring System (MEMS) data.

Table 1. Factor Analysis of 2010 Tract-Level Census Data (n=179).

	Social Affluence	Neighborhood Advantage	Residential Stability
Poverty	.87	-.06	-.21
Households with resident/room ratio >1	.57	.05	-.08
Female-headed households	.84	-.08	.19
Unemployment rate	.77	-.05	-.04
Receiving public assistance	.73	-.08	.01
House owners	.01	-.06	.86
Same address over 5 years	-.02	-.01	.86
Residents with at least a bachelor's degree	-.11	.87	-.15
Managerial/professional occupations	.03	.75	-.01
Annual income greater than $75,000	-.12	.67	.23

Note: Data obtained from 2010 U.S. Census and all measures are defined in accordance with these guidelines.

Table 2. Social affluence, residential stability, and neighborhood advantage stratified by median factor score (High versus Low).

	High	Low
Social Affluence		
Poverty (%), mean (s.d.)	13.52 (1.39)	35.60 (1.22)
Households with resident/room ratio > 1 (%), mean (s.d.)	1.00 (.12)	2.89(.29)
Female-headed households (%), mean (s.d.)	9.87 (.69)	29.71 (.75)
Unemployment rate (%), mean (s.d.)	7.1 (.39)	18.7 (.70)
Receiving public assistance (%), mean (s.d.)	2.22 (.18)	11.03 (.53)
Residential Stability		
House owners (%), mean (s.d.)	60.39 (2.94)	51.77 (1.60)
Same address over 5 years (%), mean (s.d.)	61.49 (1.06)	57.96 (2.06)
Neighborhood Advantage		
Residents with at least a bachelor's degree (%), mean (s.d.)	43.31 (2.21)	11.29 (.79)
Managerial/professional occupations (%), mean (s.d.)	13.85 (.66)	9.2 (.42)
Annual income greater than $75,000 (%), mean (s.d.)	38.70 (1.95)	12.24 (.81)

Note: s.d=standard deviation. Data obtained from 2010 U.S. Census and all measures are defined in accordance with these guidelines.

Table 3. Multinomial logistic regression of neighborhood features (social affluence, neighborhood advantage, and residential stability) and three patterns of adherence (n= 179).

Neighborhood characteristics	Adherent vs. Nonadherent OR [95% CI]		Increasing Adherence vs. Non adherence OR [95% CI]	
	Unadjusted Estimate OR [95% CI]	Adjusted Estimate OR [95% CI]	Unadjusted Estimate OR [95% CI]	Adjusted Estimate OR [95% CI]
Three high features present (n=41)	4.19* [1.51, 11.62]	8.81* [1.80, 43.05]	3.03* [1.08, 8.57]	13.00* [2.25, 75.06]
Two high features present (n=58)	2.11 [0.95, 4.70]	2.47 [0.79, 7.73]	0.97 [0.40, 2.33]	1.26 [0.34, 4.69]
One or fewer high features present (n=80)	1.00	1.00	1.00	1.00

Note: OR = odds ratio; CI = confidence interval; * p< .05
All estimates are adjusted for age, ethnicity, gender, educational attainment, financial status, employment, frequency of medication administration, number of medical conditions, cognitive status, practice, baseline glycated hemoglobin (HbA$_{1c}$), depression, and intervention condition.

CHAPTER 3: A Brief Adherence Intervention that Improved Glycemic Control: Mediation by Patterns of Adherence

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. 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 Figure 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 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 three-month period patients had three 30-minute in person sessions (baseline, 6 weeks and 12 weeks) and two 15-minute 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 glycemic 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 4-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; MacKinnon et al., 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

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condition were more likely to have an adherent pattern compared to a nonadherent pattern (OR = 11.6, 95% 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$_{1c}$ ≥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 (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 5000 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, 8 patients were no longer eligible for participation (5 physicians had discontinued antidepressants, 1 physician had discontinued an oral hypoglycemic agent, and 2 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 general growth curve mixture models (GGCMM) were fitted to the MEMS data. The three-pattern model 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 (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%

confidence interval (CI) (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 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 glycemic 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 glycemic control was mediated by oral hypoglycemic agent adherence profile type over 12 weeks. A brief intervention's effect on improved glycemic 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 glycemic 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 glycemic 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$_{1c}$ ≥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 (healthcare) 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, healthcare networks and medical settings are needed to develop sustainable adherence programs.

Figures and Tables

Figure 1. Model of the potential relationship of the intervention, oral hypoglycemic agent

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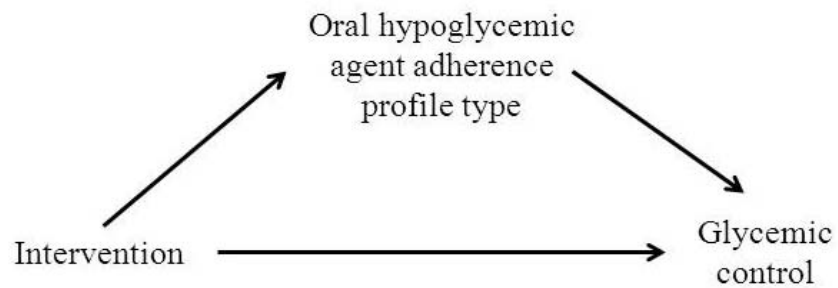
Note: Oral hypoglycemic agent adherence profile types were obtained from general growth curve
mixture models in which patients were classified into categories of longitudinal adherence profile
types based on the largest posterior probability of membership across the classes. Three
longitudinal adherence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

Table 1. Baseline characteristics by intervention condition.

	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%)	
White, n (%)	36 (40.9%)	29 (31.5%)	.28
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
$\geq$ 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

Abbreviations: 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.

Table 2. Clinical outcome of glycemic control in usual care and in the integrated intervention at 12 weeks.

			Without mediator (adherence profile type)		With mediator (adherence profile type)	
	Unadjusted Estimate		Estimated Between-Group Odds Ratio* (95% CI)	*P* value	Estimated Between-Group Odds Ratio** (95% CI)	P value
	Usual Care (n=88)	Intervention (n=92)				
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

Abbreviations: CI, confidence interval; s.d., standard deviation; Hb, hemoglobin.

Estimates, 95% confidence intervals, and p-values from the statistical models.

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

* Adjusted for baseline glycosylated hemoglobin and primary care practice

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

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