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Measuring Concurrent Oral Hypoglycemic and Antidepressant Adherence and Clinical Outcomes

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Abstract

Objectives—Many patients experience difficulty in adhering to medication for both physical and mental health. Our objective was to compare self- reported adherence and electronic monitoring of adherence to oral hypoglycemic agents and antidepressants and to examine the relationship of adherence with clinical outcomes.

Study Design—Primary care–based longitudinal study.

Methods—Adherence was assessed in 180 patients prescribed pharmacotherapy for type 2 diabetes mellitus (T2DM) and depression enrolled in a randomized controlled trial of an integrated intervention for depression and T2DM. Adherence data were collected using self report and electronic monitoring. Glycated hemoglobin (A1C) assays were used to measure glycemic control, and the 9-item Patient Health Questionnaire assessed depression.

Results—At 12 weeks, self-reported adherence and electronic monitoring of adherence showed fair agreement (kappa = 0.213, $P = .004$ for oral hypoglycemic agents and kappa = 0.380, $P < .001$ for antidepressants). Patients who achieved ≥80% adherence to oral hypoglycemic agents measured with electronic monitoring were more likely to achieve A1C <7% compared with patients who did not achieve ≥80% adherence at 12 weeks (adjusted odds ratio = 3.52, 95% confidence interval 1.07–11.57). Self-reported adherence to oral hypoglycemic agents was not associated with diabetes outcomes. Measures of adherence for antidepressants were not associated with depression outcomes in models adjusted for potentially influential covariates.

Conclusions—Compared with electronic monitoring of adherence, self-reported adherence tended to overestimate medication adherence. Electronic monitoring of adherence to oral

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hypoglycemic agents predicted glycemic control, but self-reported adherence did not predict clinical outcomes.

Many patients do not take their medications as prescribed.[1] In a systematic review the mean rate of medication adherence among patients with physical disorders was 76 percent, whereas the mean rate of antidepressant adherence was only 65 percent.[2] The clinical effectiveness of interventions is substantially limited by less than optimal adherence, and improving adherence may have a far greater public health impact than any improvements in specific medical treatments.[1,3] Medication nonadherence is associated with high rates of morbidity,[4] mortality,[5] and excess health expenditures.[6]

An accurate measure of patient adherence is essential for both clinicians and researchers to address this significant problem. Self-reported adherence is usually the only means available to clinicians to measure patient adherence to prescribed medication regimens and is an easy and commonly used method for research studies to assess adherence.[7] However, self-report has been found to have low sensitivity for nonadherence and to operate well only over a short time frame.[8,9] Electronic monitoring of adherence using microelectronic monitors on pill bottles that record the date and time of bottle opening has been identified as an informative technique allowing identification of the precise time of container opening. The validity and reliability of electronic monitoring of adherence provides a reference standard by which other adherence assessment methods can be examined.[7,10]

We sought to compare self-reported adherence and electronic monitoring of adherence with oral hypoglycemic agents and antidepressants because our prior work indicated participants think about their physical and mental health differently.[11,12] Examining adherence simultaneously for both antidepressants and oral hypoglycemic agents is relevant to real-world clinical settings in which patients present with both physical and mental health concerns and are treated with multiple medications. No study to date has compared adherence assessment using self-reported adherence and electronic monitoring of adherence for both diabetes and depression. Depression is not only common in patients with diabetes but also contributes to poor adherence to medication and dietary regimens.[13,14] Previous investigations have compared self-reported adherence and electronic monitoring of adherence to a single medication for a physical or mental health condition, but not both in the same people.[15,16] In other work, a single measure of adherence has been used to assess adherence to multiple medications for 1 medical condition[17] or adherence to medications for multiple conditions.[18] In contrast, our study allows for an examination of measurement of adherence using both self-reported adherence and electronic monitoring of adherence in patients who are simultaneously prescribed medications for both a physical and a mental health condition.

The objective of our study was to compare self-reported adherence and electronic monitoring of adherence to oral hypoglycemic agents and antidepressants over time and to examine the relationship between the 2 methods of measuring adherence and glycemic control and depressive symptoms at 12 weeks in real-world practices with limited resources and competing demands. To accomplish these goals, we employed data from the randomized trial of a brief intervention to improve adherence through integrated

management of type 2 diabetes mellitus (T2DM) and depression treatment. The study intervention was implemented at the individual level and involved an integrated care manager collaborating with physicians to offer education and guideline-based treatment recommendations, and monitor adherence and clinical status.[19] Adherence, the percent of prescribed doses taken, was assessed at the ≥80% threshold because this cut point has been used as a standard with which other measures are compared.[20,21] The study sample was an ethnically diverse sample of primary care patients. We hypothesized that: (1) self-reported adherence would overestimate adherence compared with electronic monitoring of adherence for both oral hypoglycemic agents and antidepressants; (2) patients with ≥80% adherence to an oral hypoglycemic agent using electronic monitoring would be more likely to achieve glycated hemoglobin (A1C) <7% at 12 weeks compared with patients who did not achieve ≥80% adherence at 12 weeks; and (3) patients with ≥80% adherence to an antidepressant medication measured using electronic monitoring would be more likely to achieve remission of their depression (9-item Patient Health Questionnaire <5) at 12 weeks compared with patients who did not achieve ≥80% adherence at 12 weeks.

METHODS

Recruitment Procedures

Patients were recruited from 3 primary care practices in Philadelphia, Pennsylvania. From April 2010 to April 2011, patients were identified through an electronic medical record with a diagnosis of T2DM, a prescription for an oral hypoglycemic agent within the past year, and a prescription for an oral antidepressant within the past year. Patients identified with an upcoming appointment were approached for further screening. The inclusion criteria were: 1) 30 years and older; 2) a diagnosis of T2DM and a current prescription for an oral hypoglycemic agent; and 3) a current prescription for an antidepressant. Exclusion criteria were: 1) inability to give informed consent; 2) significant cognitive impairment at baseline (Mini-Mental State Examination [MMSE] <21)[22]; 3) residence in a care facility that provides medications on schedule; and 4) unwillingness or inability to use the Medication Event Monitoring System (MEMS). Details of the study design are available elsewhere.[19] The study protocol was approved by the University of Pennsylvania, Perelman School of Medicine Institutional Review Board.

Measurement Strategy

We used standard questions to obtain information from the patients on baseline age, self-reported ethnicity, gender, marital status, and education. Functional status was measured using the Medical Outcomes Study Short Form (SF-36).[23] Patients brought all prescription bottles to the baseline visit. From each medication bottle, the name of the medication and the dose and frequency of the prescription were recorded. Patients were asked if they have received oral instructions to change the dose or frequency. If such a change was made without a change in the prescription bottle, the patient's self-report was recorded. Medical comorbidity was assessed by self-report at baseline. Cognitive status was measured using the MMSE, a short standardized mental status examination widely employed for clinical and research purposes.[24]

Adherence—Adherence to oral hypoglycemic agents and antidepressants was measured during a 2-week run-in phase to obtain a baseline measurement, and at 6 and 12 weeks, using self reports and electronic monitoring. Self-reported adherence was measured using the Brief Medication Questionnaire 5-item Regimen Screen. Patients were asked if they took their oral hypoglycemic agent and antidepressant in the past week. For each medication 4 questions were then asked: "How many days did you take it?"; "How many times per day did you take it?"; "How many pills did you take each time?"; and "How many times did you miss taking a pill?".[25] Patients were regarded as adherent if they reported taking 80% or more of their prescribed medications in the past week. Electronic monitoring of adherence was performed using microelectronic monitors (MEMS) (Figure 1). Use of MEMS on pill bottles allows identification of the precise date and time of container opening. Adherence measured using electronic monitoring was examined as the proportion of medication vial cap openings in a given week relative to the prescribed doses for the week. As in prior investigations,[26–29] the final week of self-reported adherence was examined in order to minimize recall bias and elicit more accurate responses. Patients were blinded to which week of participation was being employed for analysis in order to avoid potential bias.

Glycemic Control—At baseline and 12 weeks blood glycemic control was assessed in accordance with American Diabetes Association Guidelines.[30] The 3-month time frame was assessed because of its significance for diagnostic accuracy of glucose titration for A1C assessment.[30] A1C assays were performed employing the in2it A1C Analyzer. Point of care testing using this device has acceptable precision and agreement compared with laboratory services.[31]

Depression—Depressive symptoms were measured using the 9-item Patient Health Questionnaire (PHQ-9) at baseline and 12 weeks. The PHQ-9 is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders. The PHQ-9 depression module, which scores each of the 9 *DSM-IV* criteria as "0" (not at all) to "3" (nearly every day), is a reliable tool for screening and monitoring designed for primary care settings.[32] A PHQ-9 score of 10 or greater was associated with a high sensitivity and a high specificity for major depression.[33] In order to include as many persons who were willing and able to participate as possible we chose to include participants with a range of depressive symptoms reflecting the concept of the relapsing, remitting nature of depression in primary care.[34]

Analytic Strategy

Adherence was defined as the percent of prescribed doses taken and was calculated as the number of doses taken divided by the number of doses prescribed over the preceding 1-week period × 100%. Adherence was dichotomized at a threshold of 80% because the proportion of pills taken was highly skewed and failed normality assumptions. Adherence, the percent of prescribed doses taken, was assessed at the ≥80% threshold because this cut point is both conservative in detecting nonadherence and is aligned with adherence assessments in prior investigations from mental health[16,35] and diabetes.[18,36] Because only 2 participants (1.1%) had extra bottle openings, these openings were excluded from our analysis.

Our analysis proceeded in 2 phases. In the first phase, using adherence dichotomized at a threshold of 80%, the kappa coefficient was used to assess the magnitude of agreement between self-reported adherence and electronic monitoring. The kappa coefficient was used because it assesses the chance-corrected agreement between these 2 methods of measuring adherence.

In the second phase, using adherence dichotomized at a threshold of 80%, our goal was to examine the relationship of ≥80% adherence, measured using both self-reported adherence and electronic monitoring, with clinical outcomes. As recommended by the American Diabetes Association clinical guidelines, an indicator of whether a participant achieved A1C <7% at 12 weeks was calculated.[30] Depression remission was defined by a PHQ-9 score <5 at follow-up.[32] We employed logistic regression to assess the relationship between the categorical diabetes outcome and adherence to the oral hypoglycemic agent and to assess the relationship between depression remission and adherence to the antidepressant. For both models, we report the odds ratio and 95% confidence interval. Our final multivariate logistic regression models were adjusted for potentially influential variables including age, ethnicity, gender, marital status, educational attainment, functional status, frequency of medication administration, number of medications, number of medical conditions, cognitive status, intervention condition, and baseline clinical outcome. Analyses were conducted using SAS version 9.2 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Sample Characteristics

The CONSORT flow diagram for flow of participants through the trial has been published elsewhere.[19] Baseline patient characteristics are shown in Table 1. A total of 138 patients (76.7%) were prescribed an oral hypoglycemic agent once a day, 40 (22.2%) twice a day, 1 (0.6%) 3 times a day, and 1 (0.6%) 4 times a day. A total of 160 patients (88.9%) were prescribed an antidepressant once a day, 19 (10.6%) twice a day, and 1 (0.6%) 3 times a day.

Adherence

Figure 2 depicts the mean adherence to oral hypoglycemic agents (upper panel) and to antidepressants (bottom panel) assessed with self report and electronic monitoring using the MEMS at baseline, 6 weeks, and 12 weeks. Table 2 presents the kappa coefficient results for the proportion of patients who were ≥80% adherent by each method and for oral hypoglycemic agents and antidepressants separately. At baseline and 6 weeks, self-reported adherence and electronic monitoring of adherence showed slight agreement (eg, kappa = 0.155, P = .038 for oral hypoglycemic agents at 6 weeks and kappa = 0.179, P = .009 for antidepressants at 6 weeks). At 12 weeks, self-reported adherence and electronic monitoring of adherence showed fair agreement (kappa = 0.213, P = .004 for oral hypoglycemic agents and kappa = 0.380, P <.001 for antidepressants). At 12 weeks, adherence rates for oral hypoglycemic agents measured with self report and electronic monitoring were 72.8% versus 65.6%, respectively. At 12 weeks, adherence rates for anti-depressants measured with self report and electronic monitoring were 70.6% versus 58.3%, respectively.

Clinical Outcomes

At 12 weeks, 81 patients (45%) had a PHQ-9 <5 indicating depression remission and 110 (61.1%) had A1C <7%. Table 3 examines the relationship of clinical outcomes, A1C <7%, and depression remission at 12 weeks, with ≥80% adherence, measured both using self-reported adherence and electronic monitoring. Patients who achieved ≥80% adherence to oral hypoglycemic agents measured with electronic monitoring were more likely to achieve A1C <7% compared with patients who did not achieve ≥80% adherence at 12 weeks (adjusted odds ratio [OR] = 3.52, 95% confidence interval [CI] 1.07–11.57). Patients who achieved ≥80% adherence to oral hypoglycemic agents measured using self-reported adherence were no more likely to achieve A1C <7% compared with patients who did not achieve ≥80% adherence at 12 weeks (adjusted OR = 0.94, 95% CI 0.33–2.66). Patients who achieved ≥80% adherence to antidepressants measured with electronic monitoring were more likely to achieve remission of depression in comparison with patients who did not achieve ≥80% adherence at 12 weeks (PHQ-9 <5, unadjusted OR= 1.88, 95% CI 1.03–3.46), but the results did not remain significant in the final model after adjusting 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, and baseline clinical outcome (PHQ-9 <5, adjusted OR = 0.76, 95% CI 0.27–2.20).

DISCUSSION

The principal finding of this study is that self-reported adherence overestimates adherence over time compared with electronic monitoring. Patients who were adherent to oral hypoglycemic agents assessed using electronic monitoring had improved glycemic control at the end of the study period. However, self-reported adherence did not predict clinical outcomes for T2DM. Adherence to oral hypoglycemic agents was slightly greater than adherence to antidepressants in our sample of patients simultaneously prescribed oral hypoglycemic agents and antidepressants. Self-reported adherence and electronic monitoring for antidepressants did not predict depression remission.

Before discussing our findings, the results must be considered in the context of potential limitations. First, our sample was obtained from patients who received care at 3 primary care practices that might not be representative of most primary care sites. However, the 3 practices varied in size and were diverse and probably similar to other primary care practices in the region. Second, the healthy adherer bias is an important issue when examining any association of adherence with clinical outcomes. The patients who achieved A1C <7% may follow healthier lifestyles other than just taking their medications. We do not have information on lifestyle factors such as diet and physical activity. Third, we chose to use electronic monitoring as our reference standard for our measure of adherence. While electronic monitoring may overestimate adherence because the events captured by it (date/time of bottle opening) do not ensure medication ingestion, electronic monitoring has been shown to have a low failure rate and may be more sensitive than other adherence measures.[21,37] Fourth, self-reported adherence was assessed by non-clinician research assistants and therefore might differ from self-reported adherence assessed by a clinician.

Fifth, for some medications the 80% threshold has not been assessed. However, patients were taking a broad range of antidepressants and oral hypoglycemic agents in this study and the 80% threshold has been assessed for the majority of these medications.[16–18,21,36] Sixth, the Hawthorne effect may have influenced patient behavior, making patients more likely to adhere to their medical regimens than they would if they were not participating in the study.[38] However, even with careful monitoring of adherence in the study setting, adherence rates have been shown to be poor in numerous settings.[39–41] Finally, patients with significantly elevated A1C are an important target for resources and intervention and our study population did not consist solely of this patient profile. However, while patients may experience periods of stringent regimen adherence, relapse into poorer control is common and thus targeting patients with a range of glycemic control is essential and highly applicable to real-world settings. As a result, patients with diabetes and a range of A1C scores have been the target of many adherence investigations and interventions. Despite these limitations our results deserve attention because this is the first known study to compare adherence assessment using self-reported adherence and electronic monitoring of adherence for both oral hypoglycemic agents and antidepressants. Adherence to treatment is essential for improving care among patients with comorbid diabetes and depression.[42] Integrating management of physical and mental health has special significance in the primary care setting where patients commonly present for treatment of both physical and mental health.

Participants consistently overestimated adherence with self-report compared with electronic monitoring. In the literature, reasons for overestimation of self-reported adherence include poor physician-patient communication, lack of comprehension of required medication-taking regimens, cognitive decline, social desirability of responses, interviewing conditions, and data collection methods.[43,44] In our study, overestimation of adherence with self-report may be the result of patients truly believing that they are taking their medications as prescribed. Prior work has found that patients may believe they took their medication while unknowingly having missed prescribed treatment regimens due to factors such as recall time frame, age, medical comorbidity, and interviewing circumstances.[45] Of note, adherence measured using electronic monitoring increased throughout the course of the study while the overestimation of self-reported adherence in relation to electronic monitoring slightly decreased. The former is likely due to the effect of the intervention. The latter may be explained by social desirability or the “desire to please,” which is a tendency of individuals to respond in a manner consistent with societal norms or beliefs[46] and has also been identified as a major cause of overstated medication adherence in self-reported adherence assessments.[47] As the study progressed, participants became increasingly aware that their adherence was consistently and accurately being monitored, thus making it more socially desirable to improve the accuracy of their reporting.

Our results were not wholly consistent with our initial hypotheses. We found that patients who were adherent to oral hypoglycemic agents assessed using electronic monitoring had significantly improved glycemic control compared with patients who were nonadherent at the end of the study period. This is consistent with previous findings that found an association between greater electronic monitoring adherence and improved diabetes outcomes in primary care patients.[48] However, we did not find an association between

electronic monitoring and outcomes for depression. Our sample did comprise a large portion of participants with minor depression, and findings regarding the efficacy for antidepressant use for the treatment of minor depression are inconclusive. While some studies have indicated that antidepressants may reduce depressive symptoms in minor depression,[49,50] a recent systematic review of studies to examine the efficacy of antidepressants for the treatment of minor depression reported that there is unlikely to be a clinically important advantage for antidepressants over placebo in individuals with minor depression.[51]

We found adherence to oral hypoglycemic agents appeared to be greater than adherence to antidepressants, highlighting differing medication taking–related behaviors for physical health conditions compared with mental health conditions as well as being consistent with previous research suggesting that the rate of medication adherence among patients with physical disorders is greater than the rate of antidepressant adherence.[2] This may be due to a myriad of factors such as greater perceived stigma associated with medications for mental disorders,[52] systemic factors such as insurance coverage,[53] or patient-provider dynamics in which medical comorbidity may complicate the management of mental illness.[54]

Poor adherence is a major obstacle to the benefit of medication regimens in the treatment of comorbid T2DM and depression. Regular monitoring and discussion of adherence is an important aspect of clinical encounters. 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 depression and diabetes. Our data demonstrated that over time self-reported adherence more closely approximated electronic monitoring. However, heavy reliance on self-reported adherence in practice could affect the quality of clinical care. If nonadherence is suspected, reasons for nonadherence should be examined and addressed to mitigate poor health prognoses and adverse clinical outcomes. Improved management of both T2DM and depression through improved adherence could have an important public health impact on patient functional status and mortality.[55]

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Take-Away Points

Poor adherence is a major obstacle to the benefit of medication regimens in the treatment of comorbid type 2 diabetes mellitus and depression.

- An accurate measure of patient adherence is essential for both clinicians and researchers to address this significant problem. Heavy reliance on self-reported adherence in practice could affect the quality of clinical care.
- Regular discussion of adherence is an important aspect of clinical encounters. 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 depression and diabetes.

Figure 1.
MEMS Caps
MEMS indicates Medication Event Monitoring System.

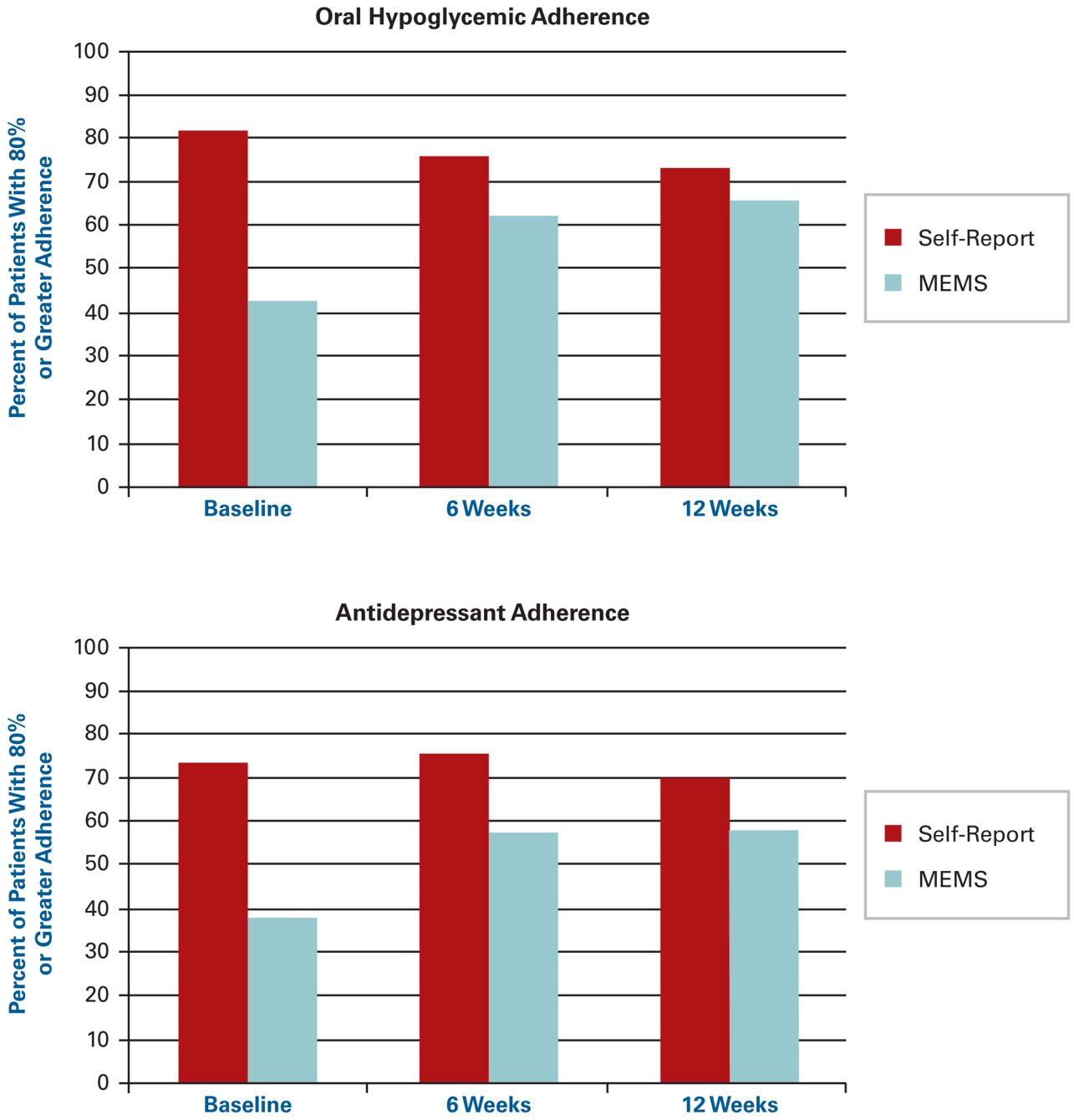

Figure 2.

Categorical Measure of 80% or Greater Adherence to Oral Hypoglycemic Agents (Upper Panel) and to Antidepressants (Bottom Panel), Assessed With Self-Report and Electronic Monitoring at Baseline, 6, and 12 Weeks (n = 180)

MEMS indicates Medication Event Monitoring System.

Table 1

Patient Characteristics at Baseline (n = 180)

Sociodemographic characteristics	
Age, mean in years (SD)	57.4 (9.5)
African American, n (%)	102 (56.7%)
White, n (%)	65 (36.1%)
Hispanic, n (%)	7 (3.9%)
Other, n (%)	6 (3.3%)
Gender, women n (%)	122 (67.8%)
Less than HS education, n (%)	29 (16.1%)
Medications	
Number of medications, mean (SD)	9.7 (4.8)
Frequency of antidepressant per day, mean (SD)	1.1 (.34)
Frequency of oral hypoglycemic agent per day, mean (SD)	1.3 (.48)
Health status	
Medical conditions, mean (SD)	7.3 (3.2)
Functional status (SF-36)	
Physical function score, mean (SD)	52.1 (32.1)
Social function score, mean (SD)	72.3 (38.5)
Role physical score, mean (SD)	54.6 (46.8)
Role emotional score, mean (SD)	66.9 (45.2)
Bodily pain score, mean (SD)	46.7 (31.8)
Cognitive status	
MMSE, mean (SD)	28.2 (2.3)
Baseline clinical indicators	
A1C, mean (SD)	7.1 (1.9)
A1C <7%, n (%)	71 (39.4%)
PHQ-9, mean (SD)	10.3 (7.6)
PHQ-9 <5, n (%)	52 (29.9%)
Randomization assignment	
Intervention, n (%)	92 (51.1%)

A1C indicates glycated hemoglobin; HS, high school; MMSE, Mini-Mental State Examination; PHQ-9, 9-item Patient Health Questionnaire; SD, standard deviation; SF-36, Medical Outcomes Study Short Form.

Table 2

Cross-Method Agreement of Self-Reported Adherence With Electronic Monitoring Over Time (n = 180)

	Electronic Monitoring Adherence	Self-Reported Adherence	Adherence Agreement Kappa Coefficient	
Oral Hypoglycemic Agent	**n (%)**	**n (%)**	**Kappa**	***P***
Baseline	77 (42.8%)	146 (81.1%)	0.133	.012
6 weeks	112 (62.2%)	137 (76.1%)	0.147	.038
12 weeks	118 (65.6%)	131 (72.8%)	0.210	.004
Antidepressants				
Baseline	69 (38.3%)	133 (73.9%)	0.180	.002
6 weeks	104 (57.8%)	136 (75.6%)	0.179	.009
12 weeks	105 (58.3%)	127 (70.6%)	0.380	<.001

Adherence was operationalized as ≥80% adherence. n = number of participants who were adherent by method of adherence.

Table 3

Self-Reported Adherence and Electronic Monitoring for Oral Hypoglycemic Agents and Antidepressants and Clinical Outcomes at 12 Weeks (n = 180)

	Self-Reported Adherence		Electronic Monitoring Adherence	
	Unadjusted OR [95% CI]	Adjusted OR[a] [95% CI]	Unadjusted OR [95% CI]	Adjusted OR[a] [95% CI]
Type 2 diabetes mellitus				
Achieved A1C <7%	1.41 [0.72–2.74]	0.94 [0.33–2.66]	2.49 [1.32–4.69]	3.52 [1.07–11.57]
Depression				
Achieved remission (PHQ-9 <5)	1.53 [0.79–2.94]	0.71 [0.27–1.86]	1.88 [1.03–3.46]	0.76 [0.27–2.20]

Adherence was operationalized as ≥80% adherence.

A1C indicates glycated hemoglobin; CI, confidence interval; OR, odds ratio; PHQ-9, 9-item Patient Health Questionnaire.

[a]Adjusted 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, and baseline clinical outcome.