Polypharmacy and Medication Adherence in Patients With Type 2 Diabetes

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OBJECTIVE — To determine medication adherence and predictors of suboptimal adherence in a community cohort of patients with diabetes and to test the hypothesis that adherence decreases with increased number of medicines prescribed.

RESEARCH DESIGN AND METHODS — A total of 128 randomly selected patients with type 2 diabetes from a single community health center responded to a pharmacist-administered questionnaire regarding medication use. Survey data were linked to clinical data available from the electronic medical record. We assessed self-reported adherence rates for each diabetes-related medicine, barriers and attitudes regarding medication use, and HbA_{1c}, total cholesterol, and blood pressure levels.

RESULTS — Patients were taking a mean of 4.1 (±1.9) diabetes-related medicines. The average 7-day adherence was 6.7 ± 1.1 days. Total number of medicines prescribed was not correlated with medication adherence. Adherence was significantly lower for medicines not felt to be improving current or future health (6.1 vs. 6.9 days out of 7, $P < 0.001$). Among patients on three or more medicines, 71% (15 of 21 patients) with suboptimal adherence were perfectly adherent with all but one medicine. Side effects were the most commonly reported problem with medication use. Of 29 medicines causing side effects that interfered with adherence, 24 (83%) did so for >1 month, and only 7 (24%) were reported to the patient's primary care physician.

CONCLUSIONS — In this sample, patients reported very high medication adherence rates regardless of number of medicines prescribed. Among patients on multiple medicines, most patients with suboptimal adherence were perfectly adherent to all but one medicine. Unreported side effects and a lack of confidence in immediate or future benefits were significant predictors of suboptimal adherence. Physicians should not feel deterred from prescribing multiple agents in order to achieve adequate control of hyperglycemia, hypertension, and hyperlipidemia.

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Polypharmacy is the natural consequence of providing evidence-based medical care to patients with type 2 diabetes (1). Typically, multidrug regimens are required to control hyperglycemia and the associated metabolic risk factors of hypertension and hyperlipidemia (2). Patient adherence to prescribed medications is crucial to the goal of reaching metabolic control.

Previous research on medication adherence in type 2 diabetes has focused primarily on adherence to hypoglycemic medicines, the association of adherence to glycemic control, and interventions to improve adherence to insulin and oral hypoglycemic agents (3–7). Less is known about medication adherence in the setting of polypharmacy (8,9). Widely used self-report instruments for measuring adherence in diabetes, such as the Summary of Diabetes Self-Care Activities (10), do not ask about medication adherence on an individual medicine-by-medicine basis. Results from studies that have assessed concurrent adherence in multidrug therapy for HIV disease (11–13) and for tuberculosis treatment (14,15) may not be generalizable to the treatment of patients with type 2 diabetes, who tend to be older, are often asymptomatic, and take medicines largely for preventive purposes.

To better understand the impact of polypharmacy on medication adherence, we undertook a detailed survey of medication use among patients with type 2 diabetes. On a medicine-by-medicine basis, we measured self-reported adherence, elicited attitudes and barriers to use, and correlated our results to levels of metabolic control. Previous studies have demonstrated that for an individual medicine, adherence declines comparing once-daily to multiple-daily dosing regimens (16,17). It is less clear whether adherence declines in patients taking multiple different medicines. Two recent studies using large pharmacy record databases have found that decreased adherence to HMG-CoA reductase inhibitors (statins) is associated with prescription of multiple other medicines in the prior year (18,19). We tested the specific hypothesis that self-reported adherence per medicine would decline with increasing number of concurrently prescribed diabetes-related medicines.

RESEARCH DESIGN AND METHODS

— We developed a registry of 910 patients with chart-confirmed type 2 diabetes receiving primary care at Massachusetts General Hospital Revere HealthCare Center, an academically affiliated community health center serving a working class community 10 miles north of Boston. There were 462 patients in this

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Abbreviations: PCP, primary care physician.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

registry with at least one HbA_{1c} and one cholesterol level measured in the previous year and at least one clinic visit in the previous 6 months. From this group, we randomly selected 231 patients to be interviewed. Patients were excluded if they had a terminal illness or cognitive deficits (determined from the medical record) or could not communicate in spoken English (either directly or through family members). Of the selected patients, 71 patients (33%) were unable to be contacted by phone despite repeated calls at different times of day, 17 patients (7%) were found to be ineligible because of language barriers or infirmity, and 9 declined consent (4%). The remaining 128 patients are the subject of this analysis.

We conducted structured telephone-based interviews to determine self-reported adherence to diabetes-related medicines, patient attitudes toward their medicines, and barriers to medication use. While there is no perfect method for assessing medication-taking behavior (20,21), self-report has been demonstrated in previous research to be a specific measure of suboptimal medication adherence (22,23). Methods such as pill counts and use of electronic medication cap monitors are labor intensive and may cause patients to modify their behavior during the study period (24). Moreover, these methods are difficult to use with patients who rely on filling weekly pillboxes to keep track of their medication use (25), as many older diabetic patients do (26). Research assessing concurrent adherence to multiple medicines in HIV therapy has found that although self-report likely overestimates adherence, less-than-perfect self-reported adherence correlates well with suboptimal adherence as measured by electronic medication cap monitors (27). Self-report also correlated well with pill counts (28).

Patients were first called by either the diabetes nurse educator or one of the primary care physicians from the health center in order to obtain verbal consent for a second phone call from the clinical pharmacist. Consenting patients were informed that as part of a quality improvement project, the pharmacist would be calling to ask questions about their medicines. Patients were not specifically aware that they would be asked about medication adherence. Approximately 2–4 weeks later, the clinical pharmacist called consenting patients at home for a detailed assessment of medication use. Patients were asked to bring to the phone the pill bottles of all medicines that they were currently taking and they were then asked medicine-by-medicine about adherence rates and barriers for each medicine pertaining to glycemic or cardiovascular disease management. The classes of medicines in this survey included oral hypoglycemic agents, insulin, antihypertensive agents, lipid-lowering medicines, and aspirin. The pharmacist read from a script and questions were asked in the same way to all patients. Self-reported adherence was assessed for each diabetes-related medicine using the following two questions (adapted from previously standardized instruments) (10): "On how many days in the past week were you able to take all of [specific medicine name] as prescribed by your doctor?" and "Did you take all of this medicine as prescribed by your doctor yesterday?" Patients responded from 0 to 7 days for the first question and yes or no for the second. Interviews generally lasted from 10 to 15 min and were conducted from May 2001 to May 2002.

Demographic information, blood pressure measurements, and laboratory results were collected from computerized databases, including an electronic medical record used exclusively for all clinical care at the health center. Baseline HbA_{1c}, blood pressure, and cholesterol values were taken from the most recent measurement preceding the interview data. To characterize the association between self-reported medication adherence and corresponding risk factor control, we also collected results from the first risk factor measurement following the interview date.

Statistical methods

Categorical variables were compared using χ^2 tests, and normally distributed continuous variables were compared using *t* tests. Spearman's correlation coefficient was used to correlate non–normally distributed adherence rates with number of prescribed medicines. SAS was used for all analyses (version 8.0; SAS Institute, Cary, NC), and $P < 0.05$ was taken to indicate statistical significance.

The study was approved by the Massachusetts General Hospital/Partners Health Care System Institutional Review Board. All patients participating in the study provided informed consent to be interviewed by the clinical pharmacist. In accordance with section 903C of the Public Health Service Act (42 units S.C0.299a-1), confidentiality of all patient information was strictly maintained. The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the study for publication.

RESULTS

Patient characteristics

Of the 128 patients in this cohort, 61% were women, most were white (88%), and the mean age was 66 (±12) years (Table 1). Almost two-thirds of this cohort was insured by Medicare, while only 10% were uninsured or on Medicaid. The remainder were covered by private insurance plans. Most patients reported receiving medication prescriptions from a single provider (96 of 128, 75%), with 26 patients (20%) treated by two providers and 6 patients receiving prescriptions from more than two providers. All patients were prescribed at least one diabetes-related medicine.

Self-reported medication adherence

The 128 patients surveyed were taking a mean of 4.1 (±1.9) medicines per patient to control diabetes and related comorbidities for a total of 523 medicines for the cohort. Altogether 111 patients (87%) were taking medicines for glycemic control (including 42 patients on insulin), 102 patients (80%) were taking antihypertensive medicines, and 73 patients (57%) were taking lipid-lowering medicines. The majority of oral medicines (81%) were dosed once daily, with metformin accounting for over two-thirds of those medicines dosed more than once daily. Including over-the-counter medicines and prescriptions for other medical problems, patients were taking an overall average of 5.8 (±2.8) different medicines per day.

Patients reported very high levels of adherence. For each diabetes-related medicine, all prescribed doses were taken 6.7 (±1.1) out of the previous 7 days. Adherence was less than perfect in the previous week for 40 medicines (7.6%). When asked about taking all doses in the previous day, patients reported missing doses for 21 of 523 medicines (4%).

Patients in our cohort reported having problems with 10% of the prescribed

Table 1—*Patient characteristics* (n = 128)

Characteristic	Mean ± SD or *n* (%)
Age (years)	66 ± 11.7
Women	78 (61)
Marital status	
Married	73 (57)
Widowed	23 (18)
Single or divorced	32 (25)
Race	
White	113 (88)
Other	15 (12)
Insurance status	
Medicare	81 (63)
Private insurance/HMO	34 (27)
Medicaid	8 (6)
Free care/uninsured	5 (4)
HbA_{1c} (%)	7.7 ± 1.5
Patients >7.0	77 (60)
Total cholesterol (mg/dl)	180 ± 37
Patients >200	30 (23)
Blood pressure (mmHg)	136/73 ± 18/10
Patients >140/90	45 (35)

HMO, health maintenance organization.

medicines that we inquired about (51 of 523, representing 19 unique medicines). The single most common reason for having a problem taking a particular medicine was "side effects" (29 of 51 problem medicines, 58%), followed by difficulty remembering to take all doses (12 medicines, 23%), and cost (four medicines, 8%). Among the 29 medications for which side effects were specifically identified as a barrier to adherence, the majority caused symptoms for >1 month (24 of 29, 83%). Patients had reported these significant side effect problems to their primary care physician for only 7 of 29 medicines (23%). Self-reported 7-day adherence rates were significantly lower among problem medicines compared with medicines not causing any problems (5.4 vs. 6.9 days out of 7, $P < 0.001$).

For each medicine, patients were asked: "Do you feel that this medicine is helping to improve your symptoms?" and "Do you feel that this medicine is helping to protect your future health?" Patients could answer "yes," "no," or "unsure." Of the 523 medicines, 82% were considered to be helping with symptoms, and 83% to be protecting future health. Patients' perceptions of the immediate and future benefit of prescribed medications had a significant impact on their adherence. Self-reported 7-day adherence was 6.1 days for medicines that patients felt were either not helping with current symptoms or not protecting future health compared with 6.9 days ($P < 0.001$) for medicines patients deemed to be helpful and protective.

We also assessed patients' perceptions and self-reported adherence rates according to class of medicine prescribed, comparing medicines for glycemic, blood pressure, and lipid control and aspirin. Patients reported the highest 7-day adherence for agents related to treatment of hypertension and hyperlipidemia (6.8 of 7 days for both) and slightly lower rates for glycemic agents (6.7 of 7 days). Compared with either blood pressure– or cholesterol-lowering medicines, adherence to aspirin treatment was significantly lower (6.3 of 7 days, $P = 0.03$ for either comparison).

Patterns of suboptimal adherence among patients on multiple medicines

There was little correlation between total number of medicines taken and average medication adherence (Spearman's correlation coefficient 0.07, $P = 0.4$). Patients reporting perfect adherence to all medicines were taking slightly more diabetes-related medicines (4.1 vs. 3.9 medicines, $P = 0.5$) and more overall medicines of any type (5.3 vs. 4.4, $P = 0.3$) than patients with suboptimal medication adherence.

We assessed whether patients with suboptimal medication adherence would have equally decreased adherence to each of their prescribed medicines. We found the opposite to be true (Table 2). Among patients taking three or more diabetes-related medicines (median 5 medicines, interquartile range ±2), most patients with suboptimal adherence reported perfect adherence for all but one medication (15 of 21 patients, 71%). Only one patient reported less than perfect adherence for all medicines.

Correlation between self-reported adherence and metabolic control

Overall, patients in this cohort were under fairly good metabolic control. At baseline, the average HbA_{1c} was 7.7 (±1.5), with 77 patients (60% of cohort) above 7.0 and 40 patients (31%) above 8.0. The average total cholesterol was 180 (±37) mg/dl, with 29 patients (23%) above 200 mg/dl. The average blood pressure was 136 (±18) mmHg for systolic and 73 (±10) mmHg for diastolic. Among patients prescribed antihypertensive medicines ($n = 102$), the average blood pressure was 137 (±18) mmHg for systolic and 73 (±10) mmHg for diastolic. A total of 74 patients (58% of the cohort) were above the American Diabetes Association target of 130/80 mmHg, and 45 patients (35%) were above the less stringent target of 140/90 mmHg.

Patients with perfect self-reported adherence had consistently lower corresponding risk factor levels than patients reporting suboptimal adherence, although due to small sample sizes this difference was statistically significant only for diastolic blood pressure. Thus, perfect adherence to glucose-controlling medi-

Table 2—*Patterns of suboptimal adherence in patients taking 3 or more diabetes-related medications* (n = 98)

Medications prescribed per patient (*n*)	Patients (*n*)	Medications per patient with less-than-perfect 7-day self-reported adherence rates (*n*)				
		None	One	Two	Three	Four or more
3	22	17	3	1	1	N/A
4	24	16	7	—	1	—
5	23	19	4	—	—	—
6	16	13	1	2	—	—
7	8	7	—	1	—	—
8	4	4	—	—	—	—
9	1	1	—	—	—	—
Total	98	77	15	4	2	0

All medicines in this table are related to diabetes management, including agents for treatment of hyperglycemia, hypertension, and hyperlipidemia.

cines was associated with lower HbA_{1c} levels (7.6 vs. 7.9, $P = 0.5$), perfect lipid-lowering adherence with lower cholesterol levels (175 vs. 203, $P = 0.1$), and perfect antihypertensive adherence with lower blood pressure levels (135 vs. 145 for systolic, $P = 0.1$, and 73 vs. 88 for diastolic, $P < 0.001$). Testing occurred a mean of 84.6 (±64.3) days after the interview for HbA_{1c} ($n = 121$), 134.6 (±102.7) days for cholesterol ($n = 109$), and 69.8 (±57) for blood pressure ($n = 126$).

The differences in self-reported adherence rates between patients at or below goal and patients above goal were small and not statistically significant. Patients above risk factor goal reported high corresponding adherence rates (6.6 of 7 days for glucose-controlling medicines among patients with $HbA_{1c} > 8.0$, 6.5 of 7 for lipid-lowering medicines among patients with cholesterol >200, and 6.5 of 7 for antihypertensive medicines among patients with blood pressure >140/90 when measured next).

CONCLUSIONS — From our detailed assessment of multiple medication use in 128 patients with type 2 diabetes, we determined that despite the complexity of medical regimens, patients reported very high 7-day medication adherence rates. Moreover, a higher number of prescribed medicines was not associated with poorer per-medicine adherence. Rather, patients with suboptimal overall adherence tended to have problems with one specific medicine out of their overall medical regimen. Among patients on three or more diabetes-related medicines, we found that the majority of those patients with less than perfect adherence were perfectly adherent to all but one medicine.

Correlates of poor adherence included problems with side effects and a lack of conviction on the patient's part that the medicine was helping either current symptoms or future health. Our finding confirms the importance of the patient's health beliefs in effective disease management (29–31). Previous studies of adherence in chronic disease have found that patients frequently stop taking their medications because they consider them ineffective or because they experience unpleasant side effects. In asymptomatic conditions, patients may believe that they do not need the medication and may not even fill their prescription (32). Of note, the side effects that patients identified as interfering with medication adherence in our study tended to be chronic and not generally reported by the patient to his or her primary care physician.

The association between self-reported adherence and corresponding metabolic control was weak but in the expected direction of worse control with less-than-perfect adherence. This finding supports the use of self-reported adherence as a valid measure of medication use and underscores the importance of medication adherence in lowering corresponding risk factor levels. There are two potential explanations for the finding that adherence was generally high in our cohort among patients above goal for glycemia, cholesterol, or blood pressure. Either patients were significantly overreporting their adherence or physicians were not prescribing sufficiently potent doses of medicines in order to achieve metabolic control (33). Given both the tremendous burden of diabetes and its complications on society (34–36) and the low overall rates of metabolic control reported nationally (37), a greater emphasis on adequate potency of medication prescription may be indicated.

Our study is unique in several ways. We used structured interviews to measure simultaneous medication adherence for patients on multiple drug regimens, we used type 2 diabetes as the model disease, and we included assessment of hypertension and hyperlipidemia (both medication adherence and metabolic control) in addition to hyperglycemia. Because patients were not expecting to be asked about their previous week's medication adherence, there was also less chance for patients to modify their pill-taking behavior in anticipation of the interviews. There are several limitations to our study. Our patient cohort was relatively well engaged with the medical system in that eligible patients had had laboratory testing in the previous year and a clinic visit in the previous 6 months. From this randomly selected group, we were unable to contact approximately one-third of the patients for interviews despite repeated phone calls at various times of the day. These patients may have had different (perhaps worse) adherence behaviors. Thus, actual self-reported adherence rates in the general population may be lower than in our patient sample. In addition, patients in the study were informed that their responses and specific concerns about their medical regimens would be communicated to their primary care physician (PCP). This may have lead to overestimation of self-reported adherence, but we believe it may have also enabled patients to express concerns about side effects and other medication-related problems that had not been previously communicated with their PCPs. Also, our patients were predominantly white and did not report significant financial barriers to medication use. Future research is warranted to assess the relation between polypharmacy and medication adherence in other patient populations.

We conclude that in a group of patients with good overall adherence, polypharmacy alone does not lead to reduced medication adherence. Rather, patients with suboptimal adherence tend to have problems with one specific medicine, either because of unreported side effects or because the patient feels that medicine is not of value to current or future health. Physicians should not feel deterred from prescribing multiple agents in order to achieve adequate control of hyperglycemia, hypertension, and hyperlipidemia. More effective patient-physician communication, particularly with regards to actively eliciting medication side effects and patient conceptions of the impact of prescribed medicines on current and future health, may lead to improved overall adherence.

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