A Systematic Review of Adherence With Medications for Diabetes

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OBJECTIVE — The purpose of this study was to determine the extent to which patients omit doses of medications prescribed for diabetes.

RESEARCH DESIGN AND METHODS — A literature search (1966–2003) was performed to identify reports with quantitative data on adherence with oral hypoglycemic agents (OHAs) and insulin and correlations between adherence rates and glycemic control. Adequate documentation of adherence was found in 15 retrospective studies of OHA prescription refill rates, 5 prospective electronic monitoring OHA studies, and 3 retrospective insulin studies.

RESULTS — Retrospective analyses showed that adherence to OHA therapy ranged from 36 to 93% in patients remaining on treatment for 6–24 months. Prospective electronic monitoring studies documented that patients took 67–85% of OHA doses as prescribed. Electronic monitoring identified poor compliers for interventions that improved adherence (61–79%; $P < 0.05$). Young patients filled prescriptions for one-third of prescribed insulin doses. Insulin adherence among patients with type 2 diabetes was 62–64%.

CONCLUSIONS — This review confirms that many patients for whom diabetes medication was prescribed were poor compliers with treatment, including both OHAs and insulin. However, electronic monitoring systems were useful in improving adherence for individual patients. Similar electronic monitoring systems for insulin administration could help healthcare providers determine patients needing additional support.

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Diabetes is a complex disorder that requires constant attention to diet, exercise, glucose monitoring, and medication to achieve good glycemic control. Glasgow (1) conceptualized the complexity of diabetes regimens, creating a model linking disease management and health outcomes with interactions between patients and their healthcare providers. Factors contributing to optimum disease management included age, complexity of treatment, duration of disease, depression, and psychosocial issues (1). Although a variety of terms have been used to describe these self-management or self-care activities (e.g., adherence, compliance, concordance, fidelity, persistence), compliance is the default medical term used in the literature (MEDLINE) to describe medication dosing (2). However, the World Health Organization has promoted the term "adherence" for use in chronic disorders as "the extent to which a person's behavior—taking medication, following diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider" (3).

The incidence of type 2 diabetes is rapidly increasing, largely in older, overweight patients who have concomitant cardiovascular risks (4). However, health care systems often do not have adequate resources to provide support to individuals with chronic diseases. Problems with poor self-management of drug therapy may exacerbate the burden of diabetes.

Several studies suggest that a large proportion of people with diabetes have difficulty managing their medication regimens (oral hypoglycemic agents [OHAs] and insulin) as well as other aspects of self-management (1,5,6). Whereas some studies that have assessed adherence among young people with type 1 diabetes (6,7), little is known about adherence to insulin regimens in patients with type 2 diabetes.

This systematic review was undertaken *1*) to assess the extent of poor adherence and persistence with OHAs and insulin and *2*) to link adherence rates with glycemic control.

RESEARCH DESIGN AND METHODS

Literature search

A systematic literature search was conducted to identify articles containing information on the rate of adherence or persistence with OHAs or insulin. Abstracts captured by the systematic literature search of MEDLINE (1966 to April 2003), Current Contents (1993 to April 2003), Health & Psychosocial Instruments (1985–2003), and Cochrane Collaborative databases were first screened against the protocol inclusion criteria. The Level 1 screen identified papers related to the main topic of interest. Abstracts passing the Level 1 screen were then retrieved for screening against the inclusion criteria (Level 2 screen). Full articles meeting the inclusion criteria were reviewed in detail (Level 3 screen).

Inclusion criteria

Papers were included in this review if *1*) a dosing regimen was evaluated and medication adherence or persistence rates were reported and *2*) study design and methods for calculation of adherence were described. The papers must have included details of the methods used to determine adherence with a hypoglycemic agent (e.g., self-report, physician/nurse estimate, tablet count, prescription refill,

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Abbreviations: MEMS, Medication Event Monitor Systems; MUSE-P, Medication Usage Skills for Effectiveness Program; OHA, oral hypoglycemic agent.

electronic monitoring) and some numeric results. Categorical results were considered a lower level of information than data. The most desirable reports included both adherence rates and HbA_{1c} levels. Reports of interventions that did not include adherence rates were excluded. Reports of adherence with diet or exercise that did not also include medication adherence rates were also excluded. Reports may be retrospective surveys, prospective clinical trials, or prospective studies of adherence interventions. Methods may be database analyses of populations or electronic monitoring of individual patients.

Search strategy

Key words for the database search were "patient adherence" and "patient compliance" cross-linked with "diabetes mellitus," "hypoglycemic agents," and "insulin." The term "adherence" was linked automatically to the term "compliance" in MEDLINE as the preferred term. Within the terms, sub-items were selected as: Administration & Dosage, Adverse Effects, Therapeutic Use, Prevention & Control, Drug Therapy, Psychology, Statistics & Numerical Data, and Economics, as available for each term. The databases identified 186,188 publications.

Level 1 searches combining terms identified 242 publications that appeared to relate to the topic of interest.

Level 2 was a review of abstracts from the reports identified in Level 1, using the inclusion criteria. This stage identified 38 reports as potentially having relevant data.

Level 3 was a review of the papers identified in Level 2. These citations were supplemented with selected references from articles. This stage identified 19 papers and one abstract (with additional information from the authors) that met the inclusion criteria.

The systematic search resulted in 20 publications with adequate data on measurement of adherence with an OHA or insulin.

Adherence assessment

Definitions. For this review, medication adherence was operationalized as "taking medication as prescribed and/or agreed between the patients and the health care provider." No studies provided information about the level of the patient's agreement with the regimen. The "adherence rate" was the proportion of doses taken as prescribed. Some reports used categorical endpoints (e.g., 90%), below which patients were considered "noncompliant" with the regimen. Adherence with "dose intervals" was defined as the proportion of doses taken within the appropriate window (e.g., 24 + 12 h for once-daily regimens, 12 + 6 h for twice-daily regimens).

Treatment "persistence" was defined as either the proportion of patients who remained on treatment for a specified period (e.g., 12 months) or the mean number of days to treatment discontinuation.

Retrospective database assessment. Prescription benefit organizations (PBOs) that manage prescriptions and health maintenance organizations (HMOs) that manage the overall healthcare of patients have databases containing information about use of prescription medications. Records of new prescriptions and refills can be tabulated using unique patient identifiers. Some databases also are linked to diagnostic codes as well as laboratory and medical visit data that describe health service utilization for a cohort. Searches can be made to ascertain the types of medications, prescribed dose and regimen, and number of times the patient obtained a refill. These population-based surveys provide an overview of drug utilization during a period of time.

Prospective monitoring. Electronic monitoring technology collects events based on taking medication from a monitored container, stores events, and lists medication dosing for an individual. Medication Event Monitor Systems (MEMS; APREX, Division of AARDEX, Union City, CA) were used in some prospective studies. MEMS are standard medication container bottle caps with a microprocessor that records every bottle opening. Patients are given bottles with a MEMS cap and instructions to take all doses of the oral medication from that bottle. Data are downloaded for display as a calendar of events (8). Electronic monitoring provides information about medication usage at the level of the individual patient. Some researchers do not inform patients that they are being monitored to avoid an effect of observation (Hawthorne effect). Cramer (9,10) developed a method, the Medication Usage Skills for Effectiveness Program (MUSE-P), that uses electronic monitoring data displayed on a computer screen as a teaching tool to enhance medication adherence.

Analyses. Descriptive statistics (means, ranges) present data from the selected reports tabulated by methodology (retrospective database review, prospective monitoring), and class of medication (OHA, insulin).

RESULTS

— The systematic review was based on 20 reports that included quantitative information on adherence or persistence with diabetes medications (11–30). The few studies that included laboratory data all showed HbA_{1c} levels >7%.

OHA: retrospective analyses

Adherence rates among 11 retrospective studies (19 cohorts) (11,14–16,18–22,24,25) using large databases ranged from 36 to 93% (excluding the study with categorical adherence rates) (17) (Table 1). The mean age of patients in all these studies was >50 years, indicating that these were older patients with type 2 diabetes. The open observational (noncomparative) studies (11,20,22,24,25) had similar results, ranging from 79 to 85% adherence with OHAs during 6–36 months of observation. Several studies compared cohorts with different regimens. Depressed patients had lower adherence rates than nondepressed patients (85 vs. 93%) (14). Once-daily regimens had higher adherence than twice-daily regimens (61 vs. 52%) (16). Monotherapy regimens had higher adherence than polytherapy regimens (49 vs. 36%) (14) or a higher proportion of patients achieving high adherence rates (35 vs. 27% at 90% or higher adherence rates) (17). Patients converting from monotherapy or polytherapy to a single combination tablet improved their adherence rates by 23 and 16%, respectively (19). The only report with adherence rates <50% was a survey of California Medicaid (MediCal) patients newly treated with OHAs (15). Other studies included patients with chronic treatment.

Seven reports (nine cohorts) of OHA treatment persistence ranged from 16 to 80% in patients remaining on treatment for 6–24 months. Four studies reported 83–300 days to discontinuation (Table 1). The methodology differed among studies, so that cross-overs to an alternative OHA or insulin might not have been counted as discontinuation. Two reports with large proportions (58 and 70%) of patients remaining on treatment for

Table 1—*Retrospective database studies of OHA for type 2 diabetic patients*

Reference	Population	Medications	Follow-up (months)	HbA_{1c}	Age (years)	*n*	Adherence rate	Persistance (percent)	Persistance (days)
Boccuzzi et al. (11)	PBO, new start	OHA monotherapy	12	—	60 ± 14	79,498	79%	58%*	83 ± 71
Brown et al. (12)	HMO, new start	OHA + Insulin	(10 years)	—	—	693 all	—	70%†	—
Catalan et al. (13)	Canada	Acarbose	12	—	51 ± 9	216 young		16%*	83
				—	72 ± 5	677 elderly		20%*	105
Chlechanowski et al. (14)	HMO, all	OHA + Insulin	12	7.4 ± 1.4	64 ± 11	119 not depressed	93%	—	—
				8.0 ± 1.5		121 depressed	85%	—	—
Dailey et al. (15)	Medicaid, new start	Monotherapy	18	—	—	37,431	49%	36%*	—
		Polytherapy					36%	22%*	—
Dezii and Kawabata (16)	PBO	Glipizide, o.d.	12	—	55 ± 13	992	61%	44%*	—
		Glipizide, b.i.d.					52%	36%*	—
Donnan et al. (17)	Scotland	Monotherapy	12	—	68	2,849	(35% > 90%)	—	300
		Polytherapy					(27% > 90%)	—	—
Evans et al. (18)	Scotland	Sulfonylurea	6	—	67	2,275	87%	—	—
		Melformin			64	1,350	83%	—	—
Mellkian et al. (19)	PBO	Monotherapy	6	—	63 ± 15	105	54%	—	—
		Mono to combination					77%	—	—
		Polytherapy	6	—		59	71%	—	—
	PBO	Poly to combination					87%	—	—
Morningstar et al. (20)	Canada	OHA	36	—	—	3,358	86%	—	—
Rajagopalan et al. (21)	PBO	OHA + Insulin	24	—	53	195,400 all	81%	—	—
						28,001 new start	81%	—	—
Scheclman et al. (22)	Clinic	OHA + Insulin	15	8.1 ± 2.0	50 ± 11	810	80 ± 21%	—	—
Sclar et al. (23)	Medicaid	OHA	12	—	59 ± 10	975		39%‡	—
Spoelstra et al. (24)	Netherland	OHA	12	—	63	411	85 ± 15%	—	—
Venturini et al. (25)	HMO	Sulfonylurea	24	—	59 ± 11	786	83 ± 22%	—	—

*Persistance for 12 months; †persistance for 24 months; ‡persistance for 6 months, §adherence rates excluding categorical data. HMO, health maintenance organization; PBO, pharmacy benefit organization.

Table 2—*Prospective studies of OHA for type 2 diabetic patients using electronic monitoring*

Reference	*n*	Population	Age (years)	Medications	Follow-up	HbA_{1c}	Adherence rate	Dose interval*
Mason et al. (26)	21	Clinic	—	Sulfonylurea	3 months	>8%	74.5%	
Matsuyama et al. (27)	15	Intervention	84 ± 8	OHA	3 months	12.7 ± 1.9	85.1%	
	17	Control				12.1 ± 2.6	82.8%	
Paes et al. (28)	91	Community	69	OHA	6 months	—	67.2 ± 30%	
						(40 o.d.)	79.1 ± 19%	77.7 ± 21%
						(36 b.i.d.)	65.6 ± 30%	40.7 ± 28%
						(15 t.i.d.)	38.1 ± 36%	5.3 ± 5%
Rosen et al. (29)	77	Clinic	65	Metformin	4 weeks	7.9 ± 1.1	77.7 ± 18%	
Rosen et al. (30)	16	Intervention	63 ± 11	Metformin	6 months		79.3 ± 13%	
	17	Control					60.7 ± 13%	

*Dose interval = proportion of dose taken within the prescribed number of hours between doses (e.g., b.i.d. = 12 ± 6–h interval).

12–24 months included all OHAs in the analyses (11,12). However, a study of Medicaid recipients in South Carolina showed low treatment persistence (39% at 6 months) (23). Three reports (four cohorts) with smaller proportions (16–49%) of patients remaining on treatment for 6–12 months focused on specific drug treatments (13,16) and monotherapy/polytherapy (15). Persistence expressed as days to discontinuation was similar in the two reports using similar methodology (83–105 days) (11,13) but was longer (300 days) in the report with descriptive data (17).

OHA: prospective studies

Three groups performed small prospective studies with electronic dose monitoring, with two centers each publishing two reports describing different aspects of the studies. Adherence rates were more consistent than was found in the retrospective database analyses (Table 1). Mean adherence with OHAs was in a narrow range of 61–85% during up to 6 months' observation (Table 2). All of the prospective studies used MEMS electronic monitoring to determine when doses were taken. Electronic monitoring also demonstrated that adherence rates decreased with larger numbers of OHA doses to be taken daily. One report showed mean adherence of 79.1 ± 19% for once-daily regimens, 65.6 ± 30% for twice-daily regimens, and 38.1 ± 36% for three-times daily dosing regimens ($P < 0.05$) (28). The accuracy of taking doses at appropriate time intervals also decreased (77.7 ± 21% for once-daily regimens, 40.7 ± 28% for twice-daily regimens, 5.3 ± 5% for three-times daily regimens; $P < 0.01$).

The adherence rate for patients taking sulfonylurea was 74.5% using electronic monitoring, compared with 92.4% for self-reported adherence (26). Matsuyama et al. (27) used electronic monitoring reports to guide clinical decision making. Adherence reports for a subset of patients were provided to their doctors to assist in making treatment decisions. The information revealed a need for additional patient education because of inconsistent dosing (47% of reports). The control group had several instances of dose increases because the clinician was not aware that erratic dosing was the problem rather than low dose.

Rosen et al. (29,30) used electronic monitoring with the MUSE-P medication enhancement program (29) to demonstrate that poor adherence can be improved when patients and clinicians are aware of the frequency of missed doses. They monitored a series of patients (mean adherence 78%) (29) to find a group of poor OHA compliers (mean 61%) in order to start with a cohort needing improvement. The control group remained unchanged, whereas the group receiving the intervention improved to 79% adherence ($P < 0.05$) with their OHA regimen (Table 2) (30).

Insulin

Adherence rates among the three studies that assessed insulin use were not comparable because of different methods of analysis (Table 3). The retrospective database method (21) showed a mean 63 ± 24% adherence for large cohorts of long-term and new-start adult type 2 diabetic insulin users. Adherence rates were lower for insulin use than for OHA use (73–86%) in both populations (21). A 10-year follow-up of a large cohort of patients newly started on insulin found that 80% of patients persisted with insulin treatment for 24 months (12). Fewer patients in the insulin-only group (20%) than pa-

Table 3—*Retrospective database studies of insulin use*

Reference	*n*	Population	Age (years)	Follow-up	HbA_{1c}	Adherence rate
Brown et al. (12)	102	HMO new start	—	10 years	—	Persistence 79.6% at 24 months
Morris et al. (7)	89	Scotland	16 ± 7	12 months	9.4 ± 1.7	33–86% days supply*
					9.0 ± 1.5	87–116% days supply*
Rajagopalan et al. (21)	27,274 all	PBO	53	24 months	—	62 ± 24%
	1,323 new start					64 ± 24%

*Days supply = number of tablet dispensed per prescribed number of times to be taken daily. HMO, health maintenance organization; PBO, pharmacy benefit organization.

tients taking an OHA (31%) discontinued treatment (obtained no refill) during the second year of follow-up (11). A study of children and adolescents presented evidence that poorer compliers had higher mean HbA_{1c} levels ($R^2 = 0.39$) (7). They calculated an index of days with insulin obtained from the pharmacy, based on the prescribed dose. HbA_{1c} levels ranged from 9.44 ± 1.7 for the lowest amount of insulin obtained to 8.98 ± 1.5, 7.85 ± 1.4, and 7.25 ± 1.0 for the higher categories of adherence, respectively ($P < 0.001$). Additional information about clinical status demonstrated that 36% of patients with poorest adherence were admitted to the hospital for diabetic ketoacidosis ($P = 0.001$ compared with patients with higher adherence rates) and other complications related to diabetes ($P = 0.02$ compared with patients with higher adherence rates). Adolescents (10–20 years of age) were significantly more likely to be in the lowest adherence category and have the highest HbA_{1c} levels compared with younger and older patients (both $P < 0.001$).

CONCLUSIONS — This systematic review confirms that many patients with diabetes took less than the prescribed amount of medication, including both OHA and insulin. Given the central importance of patient self-management and medication adherence for health outcomes of diabetes care (31), surprisingly few studies were found that adequately quantified adherence to diabetes medication. The overall rate of adherence with OHA was 36–93% in retrospective and prospective studies. Previous surveys have found that people took ~75% of medications as prescribed, across a variety of medical disorders (32,33). Decreasing adherence related to polytherapy and multiple daily dosing schedules also matched reports from other medical disorders (32,33).

This survey adds to the general finding that adherence rates are not related to the simplicity of regimen, the severity of the disorder, or the possible consequences of missed doses. The persistence with OHAs of 6–24 months, as seen in this survey, suggests that brief treatment persistence is a major issue that could lead to deleterious health outcomes. These data parallel other chronic medical disorders in which persistence often is <1 year (34,35). Even with good OHA adherence, the natural progression of type 2 diabetes eventually leads many patients to require insulin treatment. The study that evaluated type 2 diabetic patients receiving insulin showed 63% of doses taken as prescribed (21). In one cohort, only 80% of patients persisted with insulin for 2 years despite the need for long-term glycemic control (12). The detailed analysis of a group of children and adolescents showed that poor adherence with the prescribed insulin regimens resulted in poor glycemic control, as well as more hospitalizations for diabetic ketoacidosis and other complications related to diabetes (7). Self-reported insulin use (not included in this analysis) showed that patients frequently omit injections. In 31% of women who reported intentionally omitting doses (8% frequently), weight gain was the reason (36). One-fourth of adolescents reported having omitted some injections during the 10 days before a clinic visit (37). Therefore, clinicians cannot assume that patients with either type 1 or type 2 diabetes are fully compliant with insulin regimens, even if the consequences might be hazardous.

The second goal of this study was to estimate the strength of the association between adherence and glycemic control. Too few studies included HbA_{1c} levels to allow a precise conclusion, although interventions that improve self-management have been associated with better clinical outcomes (38). Further research is needed to quantify the specific improvement in glycemic control that might be obtained from improved medication adherence. Such studies should demonstrate the health benefits that may be derived from more convenient therapeutic regimens that are being developed for diabetes.

A bright spot among these reports of poor adherence and persistence was the finding that electronic monitoring tools exist to help enhance medication adherence for individual patients. One study demonstrated that doctors and pharmacists were able to adjust treatment plans more appropriately when they had electronic monitoring data than when they used the usual mode of employing only laboratory data (27). The difference was in understanding that elevated glucose or HbA_{1c} levels were related to missed doses and not underprescribing. This information avoided changing prescriptions, increasing drug dose, and switching or adding medication. Rosen et al. (30) screened a clinic population to select patients with low adherence rates for randomization to a control group or the MUSE-P intervention. MUSE-P consists of a dialogue between the patient and health care provider about daily medication dosing structured around their personal record of electronic monitoring data (39). This simple technique resulted in a significant improvement in adherence rates compared with the control subjects, who received the same amount of personal attention but not focused on adherence. This program has been effective in enhancing adherence in other medical disorders (39–41). However, electronic monitoring is not a readily available tool. Several simple measures usually are helpful in clinical practice, such as once-daily dosing and combining multiple medications into the same regimen (e.g., several drugs premeal rather than some before and some with meals). Patients should be given information about what to do if a dose is missed or if adverse effects are bothersome, in addition to the purpose of the medication (9,10).

Similar electronic monitoring systems for insulin administration are needed to record patterns of insulin use by individual patients. This information could help healthcare providers determine which patients need additional support to achieve consistent glycemic control. Further studies with electronic monitoring of diabetes medications may identify and define the characteristics of poorly compliant patients to improve treatment outcomes. Improved understanding of the way patients use medication could also affect healthcare utilization. Improved glycemic control could reduce overall healthcare costs (42). This has important implications because of the potential to improve the currently poor adherence with all aspects of diabetes self-management. Inadequate adherence to medication and lifestyle recommendations by patients with diabetes may play an important role in adding to the economic burden of the disease.

The major drawback of this survey is the methodology used for adherence analyses in the reports reviewed. A shortcoming in the literature is the lack of studies evaluating interventions to improve adherence in which adherence was measured using appropriate methods. The retrospective analyses used various defi-

nitions of adherence and persistence and different durations of follow-up. Some included all patients, whereas others censored cohorts based on arbitrary conditions. Analyses did not always account for patients who changed to another hypoglycemic agent or were no longer eligible for observation because of a change in health insurance. Attempts are underway to define optimum analytic methods for retrospective database studies (43). Electronic monitoring studies suffered from small size and observation limited to one OHA. An overall drawback to this review is the lack of an electronic method to monitor insulin use. Such devices are commonly used to record blood glucose measurements. The development of an electronic monitoring system for insulin dosing would be an important step toward proving better support for individuals with poor insulin adherence and improving the dialogue between patients and their healthcare providers.

The finding that patients prescribed an OHA or insulin take less than the prescribed number of doses over long periods of follow-up indicates an urgent need for prescribers to understand that failure to reduce HbA_{1c} levels might be related to inadequate self-management. The implication is that instead of increasing the dose, changing the medication, or adding a second drug when glucose and HbA_{1c} levels are high, clinicians should consider counseling patients on how to improve medication adherence. A first step to improving adherence is being able to assess it. Developing methods that properly assess medication adherence as a behavior that can be modified could provide a clinically significant improvement in glycemic control for some patients. Although methods are not yet available for routine use, such information could enhance patient-clinician relationships by providing information to guide individualized self-management to support patients.

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