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Costs of Medication Nonadherence in Patients with Diabetes Mellitus: A Systematic Review and Critical Analysis of the Literature

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ABSTRACT

Objectives: Information on the health care costs associated with nonadherence to treatments for diabetes is both limited and inconsistent. We reviewed and critically appraised the literature to identify the main methodological issues that might explain differences among reports in the relationship of nonadherence and costs in patients with diabetes.

Methods: Two investigators reviewed Medline, EMBASE, Cochrane library and CINAHL and studies with information on costs by level of adherence in patients with diabetes published between January 1, 1997 and September 30th 2007 were included.

Results: A total of 209 studies were identified and ten fulfilled the inclusion criteria. All included studies analyzed claims data and 70% were based on non-Medicaid and non-Medicare databases. Low medication possession ratios were associated with higher costs. Important differences were found in the ICD-9/ICD-9 CM codes used to identify patients and their diagnoses, data sources, analytic window period, definitions of adherence measures, skewness in cost data and associated statistical issues, adjustment of costs for inflation, adjustment for confounders, clinical outcomes and costs.

Conclusions: Important variation among cost estimates was evident, even within studies of the same population. Readers should be cautious when comparing estimated coefficients from various studies because methodological issues might explain differences in the results of costs of nonadherence in diabetes. This is particularly important when estimates are used as inputs to pharmacoeconomic models.

Keywords: costs, diabetes, economics, medication adherence, medication compliance.

Introduction

Nonadherence has a significant impact on the cost-effectiveness of pharmaceuticals [1], and has been estimated to cost the US economy up to $100 billion per year [2]. In diabetes, nonadherence to oral hypoglycemic medications [3,4] may partly explain why only 43% of patients with diabetes mellitus have glycosylated hemoglobin (HbA1c) below the 7% level [5,6] recommended by the American Diabetes Association [7].

Studies of adherence in diabetes have focused on its economic burden [8–10], its complications [11,12] and the cost-effectiveness of antidiabetic drugs [13–18]. Many have reported wide variation in the percent of patients being "nonadherent," ranging from 13% to 64% for oral agents and from 19% to 46% for users of insulin [19–21]. Additionally, important variations in the coefficient estimations for costs have been reported [21,22], which might be related to differences in the design, population, variables included in the analysis and statistical analyses. Therefore, we reviewed and critically appraised the literature to identify the main methodological issues that might explain differences among reports in the relationship of nonadherence and costs in patients with diabetes.

Methods

Search Strategy

We conducted a systematic literature review using Medline, EMBASE, Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) from January 1, 1997 to September, 30 2007.

The key terms used included: (compliance, adherence, persistence, nonadherence, concordance) AND (economics, costs, value, expenditures, resource utilization) AND (diabetes, hyperglycemia, diabetes-related complications, antidiabetic medications, insulin, oral hypoglycemic agents). We also hand-searched medical journals and reviewed the reference lists of other reviews.

Selection Criteria

Studies that reported costs by different levels of medication adherence or persistence were included. Adherence and persistence definitions were according to previous studies [23]. We also included studies that used HbA1c as a proxy of medication adherence because HbA1c is a well-established measure of glycemic control [22,24,25] and a proxy for adherence [26]. Non-English studies, articles with insufficient data, and those without costs or adherence information were excluded.

Extracted Information

Abstracts and full publications were reviewed by two researchers and disagreements were resolved by consensus. The extracted information included the study design, data source(s), methods of adherence measurement, statistical analysis, and results. Study designs were classified as trials, cohort, case-control, or cross-sectional studies. Data sources for patient demographics, adherence, resource utilization, and costs, as well as observation and follow-up periods, were recorded (Table 1). For statistical analysis, we included information on any statistical method used to assess the relationship or association between medication

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Table I Studies identified with costs reported by adherence level in diabetic patients

Reference	Design	Source of data				Inclusion criteria	Observation period	Follow-up period
		Population	Diagnosis	Adherence	Costs			
Balkrishnan R, 2003 [28]	Retrospective cohort	Medicare HMO in North Carolina	ICD-9 codes 250.xx	Prescription refills	Reimbursement by the HMO	Patients aged ≥65 years, enrolled in a Medicare HMO in North Carolina who received ≥1 antidiabetic prescription dispensed every 6 months	1996–2002	Up to 5 years
Cobden D, 2007 [29]	Retrospective cohort	Pharmetrics	ICD-9 CM code 250.xx excluding type 1 subcodes	Prescription refills	Payments made by third-party payers to health care providers (reimbursement)	≥18 years, type 2 diabetes who converted to BIAsp 70/30 pen device and previously treated with human or analog insulin	January 1, 2001 to April 30, 2005	At least 2 years
Balkrishnan R, 2004 [30]	Retrospective cohort	North Carolina Medicaid program	ICD-9	Prescription refills	Reimbursement	Type 2 diabetes who were newly started on thiazolidinedione therapy or other oral antidiabetic drug	July 2001 to June 2002	2 years
Hepke, 2004 [31]	Retrospective cohort	Blue Cross Blue Shield of Michigan	ICD-9 250, 352.2, 362, 366.41, 648	Prescription refills	Reimbursement	Non-Medicare eligible Michigan residents enrolled continuously in 1999, at least 1 inpatient or Emergency room claim, ≥2 professional or outpatient facility claims with diabetes diagnosis and a filled prescription for antidiabetic drug.	1999	1 year
Lee WC, 2006 [17]	Retrospective cohort with pre and post analysis	Integrated medical and pharmacy claims database: Pharmetric	ICD-9 code 250.xx excluding type 1 subcodes	Prescription refills	Payments to the health insurance: reimbursement	≥18 years of age, type 2 diabetes who initiated treatment with insulin analogue pen device between July 1, 2001 and Dec 31, 2002, and whose treatment was converted from conventional human or analogue insulin injection (vial/syringe) to a prefilled insulin analogue pen.	January 2001–April 2005	Up to 4 years
Shenolikar RA, 2006 [32]	Retrospective cohort	North Carolina Medicaid database	ICD-9 CM code 250.xx	Prescription refills	Total health care costs: medical and dental care, regular checkups, office visits, home health care, inpatient and outpatient care, long term care facility care and prescription drugs.	At least one ICD9 code for diabetes, and one for antidiabetic medication and Medicaid eligibility for 36-month follow-up period. African Americans were analyzed vs. other	July 1, 2000 to June 30, 2003	1 year
Sokol MC, 2005 [33]	Retrospective cohort	Administrative claims database maintained by a health plan organization	ICD-9 codes 250.xx, 357.2, 362.0x, 366.41, 648.0	Prescription refills	All-cause costs and disease-related costs.	Patients aged 65 and older with diagnosis of diabetes	June 1997 to May 1999	1 year
Wagner EH, 2001 [34]	Retrospective cohort	Automated diabetes registry from the Group Health Cooperative of Puget Sound, Seattle Washington	Diagnosis of diabetes and HbA1c from diabetes registry	Prescriptions refills and HbA1c	Decision support system that is automated, step-down cost accounting for health care provided to members.	Diabetics older than 18 years, with at least one HBA1c, and continuously enrolled from 1992–1996	January 1, 1992 to March 31, 1996	4 years
White, TJ 2004 [35]	Retrospective cohort	Managed care organization database	ICD-9 for type 2 diabetes	Percentage of adherence	Claims data	Patients receiving an oral antidiabetic medication and have a diagnosis of CVD, continuously enrolled in the health plan, and ≥30 years of age	April 1, 1998 to March 31, 2000	1 year
Shetty S, 2005 [36]	Retrospective cohort	US Managed care organization	ICD-9 CM codes 250.x0 or 250.x2	Not reported	Reimbursement	Had ≥2 claims for type 2 diabetes in either the primary or secondary position, had at leas one prescription for an oral hypoglycemic agent and/or insulin, had at least one available HbA1c, were commercially insured with a drug benefit, and had at least 6 months of continuous enrollment.	January–December 2002	1 year

CVD, cardiovascular disease; HMO, Health Maintenance Organization; ICD-9, International Classification of Diseases, 9th Revision; ICD-9 CM, International Classification of Diseases Clinical Modification. HbA1c, glycosylated hemoglobin.