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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 1 Studies identified with costs reported by adherence level in diabetic patients

Reference	Design	Source of data: Population	Diagnosis	Adherence	Costs	Inclusion criteria	Observation period	Follow-up period
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.

nonadherence and costs, sample size, adjustment for inflation and/or discounting, adjustment for confounders or for the days when patients were in institutionalized care settings such as hospital, and nursing home (Table 2).

Quality Criteria

A checklist for economic evaluation [27] was modified to assess the quality of studies. The original checklist contained 35 items, but 5 of them were related to health economic models (12, 14 15, 20, and 21), and were not considered applicable to the studies included in the review. We assigned a score of 1 if an article included the required item, and zero if it was not included. Therefore, the maximum score for an article that included all information related to study design, data collection, analysis and interpretation of results was 30.

Results

Search Results

Two hundred nine titles were identified and their abstracts were reviewed. Fifty abstracts included information on both adherence and costs in patients with diabetes, and their full articles were retrieved. Ten studies [17,28–36] fulfilled the inclusion criteria (Fig. 1). All studies analyzed US claims data using retrospective cohort studies designs [17,28–36] (Table 1). Three studies utilized Medicare or Medicaid databases [28,30,32], while all others used commercial or managed care organizations data sets.

Association between Medication Nonadherence and Cost

There were important variations in the items included in order to estimate costs. For example, one study included only claims for physician office visits, outpatient services, and hospital stays [29], while another was more comprehensive, and included: costs for hospitalization, outpatient care, emergency care, clinic visits, laboratory tests, professional services, and pharmaceuticals [31]. Two studies took into account the net cost to the plan but they did not include patients' copayments and deductibles [33,35], while a third study included copayments and deductibles [36]. The study by Wagner used its own internal accounting system that included overhead costs [34]. It was unclear in some studies as to which specific costs were included [17,28,32].

Low medication possession ratios (MPRs) were generally associated with higher costs. For example, one study reported an association of MPR of 60% with mean total costs of \$8699 [29]. Balkrishnan et al. found that a 10% increase in MPR for an antidiabetic medication was associated with an 8.6% reduction in total annual health care costs [28]. Studies generally reported increments of mean annual costs according to baseline HbA1c values. For example, the mean annual costs for patients with baseline HbA1c < 8% were \$4475, while for those with HbA1c > 10 were \$8088 [34] (Table 2).

Methodological Issues

The specific International Classification of Diseases (ICD-9) or ICD-9 Clinical Modification (ICD-9-CM) codes used to identify the study population were not mentioned in three studies [30,34,35], and among those that were reported, there were important variations in the codes included (Tables 1 and 2). For example, some studies included type 1 and type 2 diabetes [28,31,33], while others excluded type 1 diabetes [17,29,36]. The population varied by study, as well by period of observation. The maximum follow-up was 5 years, and half of the studies followed patients for only 1 year.

Table 2 presents measures of adherence, costs, statistical analysis, results of each study, and quality score. All studies used claims data to collect drug utilization information. Five studies used MPR as a measure of medication adherence [17,28–30,32], two studies did not report a specific medication adherence measure [34,36], and three used various measures of medication adherence such as medication adherence rate [31], percentage days supplies [33], and percentage of adherence [35]. All studies used the total follow-up period to calculate adherence and costs, and used charges as proxy for costs. In terms of type of costs, some studies reported total health-care costs [17,28–30,34–36], while others focused on overall costs of health care [31], or costs related with diabetes care [32,33]. Two studies used Poisson regression models for costs [17,29], and the remainder used multivariate regression analysis for costs. Few studies log-transformed costs [32,34,36], and only one study [22] tried to deal with the skewed distribution of both health-care costs and MPRs. Seven studies were able to adjust for some potential confounders [17,28,29,31–33,36], while only one adjusted costs for inflation and duration of hospitalizations [28]. Most studies were assigned a low quality score (<50% of required information), ranging from 8/30 to 14/30.

Discussion

We identified various methodological issues that hinder comparisons from being made across studies, and which might result in significant differences in the reported associations between non-adherence to medicines and costs in patients with diabetes.

Based on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recommendations on improving the quality of adherence studies [37,38], we found that the type of study design was not clearly established, and studies were unable to distinguish prevalent from incident cases. Incident cases are more expensive than prevalent cases in terms of hospitalization rates, length of stay, case mix, and service intensity, and have higher discontinuation rates [39–41]. Studies included different population groups, which has an impact on costs: some focused on codes for type 2 diabetes only, type 1 and type 2, gestational diabetes, and/or diabetes-related complications. For example, gestational diabetes is more expensive than type 2 diabetes because of the frequency and duration of hospitalizations [42]. None of the studies described if primary, secondary, or both codes were used. Previous studies have shown an increase in costs by up to twofold when both primary and secondary ICD-9 codes were used [31].

Contrary to accepted recommendations, none of the studies validated ICD-9/ICD-9-CM codes [43]. Wilchesky et al. showed 64% sensitivity of claims data to detect patients with diabetes [44], which means that an appreciable number of cases may be missed. Similarly, none of the studies validated prescription claims data that are vulnerable to errors from sampling, misidentification of newly treated patients, and misclassification of added versus switched medications [45,46]. ICD-9/ICD-9-CM codes to measure utilization and costs also requires validation, because some studies have found that 9% of discharges incorrectly omit codes for diabetes, and 13% of discharges are registered without any foot-related diagnosis code [47].

Most studies used medication possession ratios, but there were important variation in the definition. For some, MPR was the sum of days of antidiabetic prescription supply dispensed divided by the number of days between prescription refills, from the first date of dispensing within each year until the dispensing

Table 2 Continuation of studies identified with costs reported by adherence level in diabetic patients

		Measures method			Statistical analysis					
Reference	N	Adherence	Resource utilization	Costs/adjustment for inflation	Statistical method	Continuous enrollment in the health insurance	Adjustment by confounders	Adjustment by hospitalization or other location	Results	Quality score
Balkrishnan R, 2003 [28]	775	MPR defined as the days of antidiabetic prescription supply dispensed divided by the number of days between prescription refills. The observation period began with the first date of dispensing within each year and ended as the dispensing date of the last prescription	Administrative claims data of the HMO	Total costs not specified	Sequential mixed-model and regression analysis	Yes	Charlson index was used to adjust by severity	Number of days during hospitalization was subtracted from the denominator	MPR for 1 to 5 years of follow up were 0.70, 0.71, 0.75, 0.77, and 0.78; and mean health care costs were $8,306, $5,947, $5,821, $5,043, $5,118. 10% increase in antidiabetic MPR was associated with an 8.6% decrease in total annual health care costs ($P < 0.001$). After 5 years, high adherence = $4,000 while low adherence = $10,500	14/30
Cobden D, 2007 [29]	486	MPR: sum of the days' supply of drug divided by the number of days between the first fill and the last refill plus the days' supply of the last refill	Physician visits, hospitalization, emergency department visits, pharmacy data	Total health care costs, annual adjusted mean all-cause health care costs/adjustment for inflation to 2005 dollars	Person-time and event-time analysis adjusted by length of follow-up. Poisson regression model and gamma regression model	Yes	Hypoglycemia/ adjustment for Comorbidities	Not reported	MPR of 80% or greater was associated with significant reduction in all-cause health care costs (OR 0.55, 95% CI 0.31–0.80, $P < 0.05$). MPR of 68% was associated with total mean costs of $8,056 ± 8,559, while an MPR of 59% had total mean costs of $8,699 ± 9,268.	14/30
Balkrishnan R, 2004 [30]	3,483	MPR	Claims data	Total annual health care costs	Multivariate techniques	NR	NR	NR	13% increase in MPR was associated with 16.1% lower total annual health care costs ($P < 0.001$).	12/30
Hepke KL, 2004 [31]	57,687	Medication adherence rate calculated as percentage of days that the patient possessed any available diabetic drug during the year	Inpatient hospitalization, outpatient care, emergency care, clinic visits, laboratory tests, professional services and pharmaceuticals	Overall cost of healthcare and cost related with diabetes care	Least squares regression model and multivariate logistic regression	Yes	Illness severity using diagnosis cost group.	NR	20% to 39% adherence level was needed before medical care costs were reduced. For diabetes related costs, the threshold was seen until 40% to 59% adherence level. Adherence-total average expenditures 0% = $6,500, 1–19% = $7,250, 20–39% = $7,750, 40%–59% = $7,500, 60%–79% = $7,700, 80%–99% = $7,300, 100% = $7,900.	11/30
Lee WC, 2006 [17]	1,156	MPR: sum of the days' supply of medication divided by the number of days between the first fill and the last refill plus the days' supply of the last refill.	Physician visits, hospitalizations, ER visits	Total health care costs/ Costs adjusted to 2005 dollars using the consumer price index	Person-time and time-event analysis. Poisson regression models and incident rate ratios.	Enrollment for at least 6 months before the index date and at least 2 years of continuous enrollment after the index date	Hypoglycemic events	NR	62% MPR to insulin pen therapy = mean annual all-cause health care costs $14,769	11/30

Shenolikar RA, 2006 [32]	1,073	MPR: Number of days of antidiabetic prescription supply dispensed (e.g., a 30-day supply) divided by the number of days between the first and last dispensation. Med-Total approach: ratio of total number of days the drug was supplied to the difference in the number of days between the first and last prescription dates.	Medical and dental care, in patient and outpatient care, regular checkups, office visits, home health care, long-term facility care and prescription drugs.	Annual total and diabetes-related health care costs/No discounted rate reported	Multivariate regression analysis adjusted by covariates. Costs were transformed using logarithm and they were transformed back using antilogarithms of the parameter estimate	Yes	Adjusted by comorbidities	No	Mean rate of adherence to new medication of 59% = $9,546 ± $14,861 mean total health care costs for year 2 and mean diabetes-related costs for year 2 of $4,576 ± $8,208; The estimated coefficients and standard errors for total annual health care cots as a function of covariates were: male sex 1,117.35 ± 1,001.69, high total number of prescriptions 8,223.48 ± 1,002.38; African American race 1,125.49 ± 914.39; rate of adherence—2,721.68 (932.50), constant 728.82 (1,180.29) and adjusted r2 = 0.06.	13/30
Sokol MC, 2005 [33]	137,277	Percentage of days during the analysis period that patients had a supply of 1 or more maintenance medications for the condition	Medical and drug claims: hospitalization, ER service, outpatient services including physician office visits and outpatient visits. Nursing home and home care services were not included	Total health care costs (Sum of medical—outpatient services, ER services, hospitalization- and drug costs), and disease-related costs. Net cost to the plan sponsor, patient copayments and deductibles were not included. Costs were adjusted for age, sex, comorbidity, disease subtype, employment group and medical plan type.	Logistic regression model. No detail for costs transformation was provided.	Yes	Comorbidities were included in the analysis.	NR	Adherence level and total costs: 1–19% = $8,867; 20–39% = $7,124; 40–59% = $6,522; 60–79% = $6,291; 80–100% = $4,570. Differences were statistically significant for most adherence levels when compared with the highest level of adherence ($P < 0.05$).	8/30
Wagner EH, 2001 [34]	4,744	Not included a measure of adherence and HbA1c was used as a proxy of medication adherence	Annual utilization rates	Total health care costs and mean costs per person	Cost data logarithmically transformed. Regression analysis.	Yes	No	NR	Baseline HbA1c, Level, % and mean annual costs$, (p values were calculated for the difference in log costs) <8 = $4,475 ($P = 0.18$); 8–10 = $5,898 ($P = 0.32$); >10 = $8,088 ($P = 0.53$)	11/30
White TJ, 2004 [35]	NR	Percentage of adherence	Hospitalization and ER	Adjusted total healthcare costs	Regression model	Yes	NR	NR	Patients with ≤75, >75 to ≤95 and 95% adherence, adjusted total healthcare costs were $US 5,706, $5,314 and $4,835 ($P < 0.001$).	9/30
Shetty S, 2005 [36]	3,121	Not included but HbA1c was used as a proxy of medication adherence.	Claims data	Costs of 6 months period	Multiple linear regression analysis. Logarithmic transformation of cost data was done prior analysis.	Yes	Adjustment by age, gender, specialty of the physician, comorbidity and total baseline costs.	NR	Predicted total diabetes-related cost for target HbA1c level group during the first year of follow up was $1,540 per patient, 32% higher than the total diabetes related cost ($1,171) for the same target group ($P < 0.001$).	11/30

ER, emergency room; HMO, health maintenance organization; MPR, medication possession ratio; NR, not reported. HbA1c, glycosylated hemoglobin.

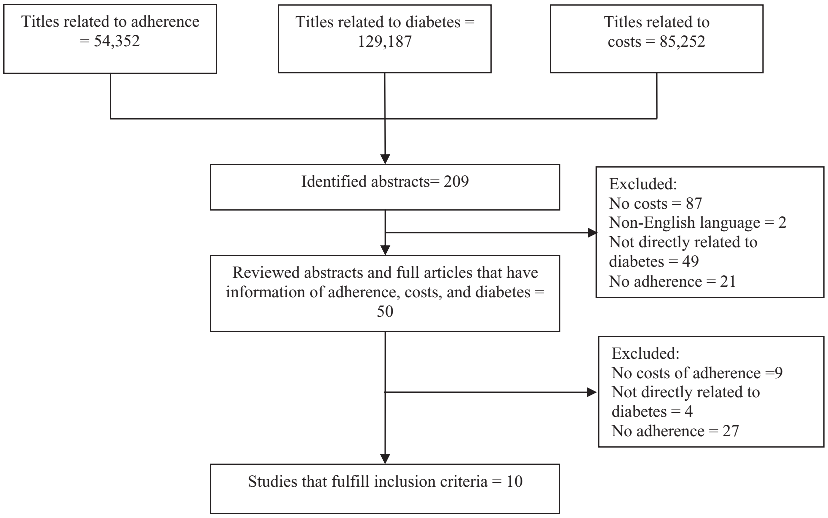

Figure 1 Flow diagram showing the number of references identified, retrieved and included in the review.

date of the last prescription [28,32]. Others added the days' supply of the last refill to the denominator [17,29], or they used the percentage of days that the patient possessed any available diabetic drug during the year [31]. None of the studies considered the effects of censoring, which is important, because six filled prescriptions evaluated over 12 months equals an MPR of 50%, but if they are evaluated over 6 months, the six filled prescriptions equals an MPR of 100%.

The non-MPR measures included were: Med-total approach defined as the ratio of total number of days the drug was supplied to the difference in the number of days between the first and last prescription dates [32]; the percentage of days during the analysis period that patients had a supply of one or more maintenance medications for the condition [33], and the percentage of adherence [35]. The problem is that these measures are not comparable. Hess [48] analyzed various adherence measures and found that only 4—Continuous Measure of Medication Acquisition; Continuous Multiple Interval Measure of Oversupply; MPR; and Medication Refill Adherence—out of 11 measures were identical for measuring adherence to prescription refills throughout the study period.

With regard to confounders, 6 out of 10 studies made some effort to adjust their estimates by disease severity, but most did not adjust by comorbidities, thereby potentially underestimating the real costs. None of the databases used by analysts contain information of behavioral variables such as smoking and alcohol that are closely related to adherence [49–53]. There was also lack of information on adverse drug events, such as hypoglycemia, which has been shown to be a costly component of diabetes-related treatment [54]. None of the studies were able to measure the direct consequences of either nonadherence (e.g., hyperosmolar coma) or associated utilization-based outcomes. Costs were, therefore, not disaggregated according to the main drivers that are a consequence of loss of therapeutic effect through nonadherence.

All studies used charges as proxy for costs. However, charges have been criticized because they do not reflect real costs [55], and they do not take into account the various levels of copayment, deductibles, and coinsurance for prescriptions and other medical services, including physician office care, medical emergency care, and inpatient hospitalization.

Only one study tried to deal with skewed distribution of health-care costs and MPR [22]. This is important, because inappropriate analysis of costs will produce biased estimates for the mean. For costs, nonparametric bootstrap techniques or GLM regression analyses are recommended [56,57].

Conclusion

The research assessing the association between medication adherence/nonadherence and health-care costs is limited and of poor quality. There are important methodological differences among studies of costs of adherence/nonadherence in patients with diabetes, making robust comparisons difficult; and those differences might explain the inconsistency in the reported associations between medication adherence and costs. Readers should be cautious when interpreting or comparing the results of such studies. More research is needed to validate measures of medication adherence using claims data and to determine the impact of nonadherence on health-care costs.

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