

The Economic Rationale for Adherence in the Treatment of Type 2 Diabetes Mellitus

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Patient adherence to prescribed therapies in type 2 diabetes mellitus (T2DM)—including lifestyle changes as well as medications—is an area of enormous importance because of the strong correlations between adherence, patient outcomes, and treatment costs.^{1,2} Because diabetes is a chronic condition, long-term adherence to therapy is a necessity, which differs from adherence to short-term therapy for an acute condition (eg, antibiotics, antacids). The topic of adherence to therapy in T2DM is of particular interest to managed care stakeholders because T2DM is a disease that affects a large number of patients and is associated with considerable costs. The relationship between treatment adherence and costs would appear to be intuitive; that is, the economic benefits of achieving better treatment adherence in terms of lower long-term costs would seem to justify the up-front costs of medications and therapeutic strategies that improve adherence. However, the high costs of specific medications, and the costs of implementing certain therapeutic strategies, mean that the use of a given medication or treatment strategy can only be justified from a cost perspective if the incremental improvement in adherence is associated with cost savings greater than the cost of therapy. This article focuses on key factors pertinent to the economic rationale for treatment adherence in T2DM.

The Cost of Diabetes in the United States

According to the American Diabetes Association (ADA), approximately 17.5 million people in the United States had a diabetes diagnosis (type 1 diabetes mellitus [T1DM] or T2DM) in 2007, a large increase from the ADA estimate of 12.1 million in 2002. In addition, approximately 6.6 million people in the United States had diabetes in 2007, and remained undiagnosed.³

The ADA estimates that the total costs related to diabetes in 2007 were \$174 billion, \$116 billion of which resulted from excess medical costs and \$58 billion from lost productivity.³ An analysis of diabetes-related costs, performed by Dall et al, separated out both epidemiological and cost data related to T2DM versus T1DM. They determined that in 2007, 16.5 million of the 17.5 million people in the United States with diabetes had T2DM. Furthermore, they established that T2DM accounted for \$159.5 billion of the \$174 billion total costs, including medical costs

Abstract

Among patients with type 2 diabetes mellitus, adherence to prescribed medications has been reported to be as low as 60%, meaning that many patients may not be following the treatment plan that has been prescribed for them. The importance of treatment adherence is intuitive: better adherence would promote better outcomes. Data show this to be the case: for every 25% increase in medication adherence, a patient's glycated hemoglobin (A1C) is reduced by 0.34%. Unfortunately, only a little more than half of patients with diabetes achieve an A1C target below 7%. Poor therapeutic adherence affects diabetes-related costs. Patients who are nonadherent are far more likely to require hospitalization and to incur significantly higher healthcare costs. The lesser costs of lower medication utilization in nonadherent patients are more than compensated for by the increased costs arising from poorer glycemic control, as multiple studies employing large managed care databases have demonstrated. Improvements in outcomes and reductions in costs related to the management of diabetes require focused efforts toward facilitating treatment adherence, efforts that should be undertaken by third-party payers in addition to physicians and patients.

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Reports

of \$105.7 billion and indirect costs of \$53.8 billion.⁴ With regard to healthcare expenditures, the ADA data show that approximately half of these costs are attributable to hospitalization and to longer length of stay (LOS) per admission as compared with patients without diabetes. In 2007, outpatient medication and supplies attributable to diabetes cost \$27.7 billion, including \$3.7 billion for insulin (2.3% of total costs related to T2DM) and \$8.6 billion for oral agents (5.4% of total costs related to T2DM).³

Rates of Adherence, Association With Achieving A1C Targets, and Consequences of Poor Glycemic Control

Given the large number of patients impacted by T2DM and the associated cost burden to payers, employers, and patients themselves, there exists a significant opportunity to improve outcomes and reduce costs. One potential target for improving outcomes is patient adherence to prescribed therapy. Improvements in adherence would improve glycemic control, and improvements in glycemic control would help reduce morbidity and mortality related to uncontrolled T2DM.^{2,5} Based on data from studies involving patients with diabetes in the United States, every percentage point reduction in glycated hemoglobin (A1C) is associated with a 40% reduction in the risk of microvascular complications such as kidney diseases, eye diseases, and neuropathies.⁶

The management of T2DM necessitates patient adherence to both drug and nondrug therapies. While lifestyle interventions remain an essential component of therapy, as recognized by professional guidelines for the management of T2DM,⁷ this article will focus on the health economic impact of improving adherence to drug therapy.

The ADA recommends an A1C target of less than 7%.⁷ However, a substantial proportion of individuals with diabetes do not achieve this goal. An analysis published in 2009 of data from the National Health and Nutrition Examination Survey (2003-2006) showed that only 57% of adults with diabetes achieved the ADA A1C target of less than 7%.⁸

In the case of drug therapy, adherence is the degree to which a patient takes a medication as prescribed. Methods of measuring adherence include direct methods (eg, observing the patient taking their medication) and indirect methods (eg, asking the patient whether they took their medication; counting pills; reviewing data regarding prescription refills).⁹

The importance of adherence to glycemic control may be seen in the results of a 1-year study of 1560 patients with T2DM which found that A1C was reduced by 0.34% for every 25% increase in medication adherence ($P = .0009$).⁵ In this study, adherence was assessed during clinic visits;

patient-reported medication use was compared with the clinician-recommended medications from the previous visit.⁵ Despite the importance of adherence to glycemic control, there is room for improvement with regard to current levels of adherence. The rate of adherence to oral medications for glycemic control ranges from approximately 65% to 85%, and the rate of adherence to insulin ranges from approximately 60% to 80%. Regimens requiring more frequent dosing tend to have lower adherence rates.¹⁰ The impact of dosing schedule on adherence will be discussed in the other articles in this supplement.^{11,12}

The potential consequences of poor adherence in terms of healthcare utilization and mortality were demonstrated in a study at Kaiser Permanente of Colorado, which included 11,532 patients with diabetes.⁵ This study found a 21.3% rate of nonadherence to treatment, where nonadherence was defined as filled prescriptions covering less than 80% of the total days during which medication should have been taken. Patients who were nonadherent to treatment had a higher risk of hospitalization and all-cause mortality compared with patients who were adherent (both $P < .001$).⁵

Cost Implications of Poor Adherence

There are multiple ways to evaluate the impact of treatment adherence on costs in diabetes. Broadly speaking, the available studies fall into 2 categories: a) those that compare levels of treatment adherence with measurable treatment costs and/or healthcare utilization, and b) those that do not necessarily evaluate adherence per se but examine the impact of poor glycemic control on treatment costs and/or healthcare utilization.

Relationship of Treatment Adherence to Costs and Healthcare Utilization

A recent literature review identified studies examining the association between treatment adherence and costs in T2DM, and found 12 out of 449 studies that met the authors' inclusion criteria, all of them US studies involving inpatients, outpatients, and pharmacy claims.¹ Seven of the 12 studies observed an inverse relationship between adherence and total healthcare costs, 4 observed an inverse relationship between adherence and hospitalization costs, and 1 study found no significant association between adherence and healthcare costs.¹

A separate literature review, published in 2011, identified 37 studies that evaluated medication adherence in patients with diabetes and the corresponding use of healthcare resources among those patients as well as their success in glycemic control.¹³ A majority of the 23 studies that reported

on correlations between adherence and glycemic control found a notable association. Of 8 studies that evaluated a link with healthcare utilization, 7 found that greater adherence was correlated with fewer hospitalizations. Patients with adherence ratios less than 80% had 2½ times the risk of hospitalization for reasons either directly related to diabetes or to cardiovascular disease (odds ratio = 2.53; 95% confidence interval, 1.38-4.64).¹³ These results are consistent with a large Medicare study that found that greater medication adherence was significantly associated with lower rates of hospitalization as well as lower healthcare costs.¹⁴

Finally, a systematic literature review, published in 2009, analyzed studies of healthcare costs related to rates of adherence in patients with diabetes. Out of 209 studies identified, 10 studies fulfilling the inclusion criteria were selected for analysis; included studies were based on claims data, 70% of which came from non-Medicare or Medicaid databases.¹⁵ The authors found a high degree of variability between studies regarding the reporting of additional costs arising from nonadherence. That said, higher levels of medication adherence were largely correlated with lower costs. One study observed an 8.6% decrease in annual total healthcare costs for every 10% increase in medication possession ratio for an antidiabetic medication.¹⁵

One potentially confounding factor in determining the relationship between drug adherence and hospitalization is the fact that patients' disease severity is likely to affect both their adherence to therapy and their risk of hospitalization. A 2010 study of hospitalization in patients with diabetes sought to account for the influence of disease severity as well as other potentially influential factors including level of coinsurance.¹⁶ The authors found that patients with greater disease severity had higher levels of treatment adherence. The authors speculate that patients with less severe disease may be less adherent because they may not be experiencing recognizable symptoms. They further observed that an increase in treatment adherence from 50% to 100% was associated with a 23.3% reduction in the rate of hospitalization (from 15% to 11.5%), while emergency department (ED) visits were reduced by 46.2% (from 17.3% to 9.3%). The impact of such an increase in adherence on drug costs was found to be \$766 per patient annually, while the savings in costs from reduced hospitalizations and ED visits was \$886 per patient, which amounts to \$1.14 gained in cost reductions for every \$1.00 spent in additional drugs annually.¹⁶

A novel approach toward analyzing the influence of adherence on cost effectiveness in diabetes treatment was undertaken in a study by Cobden et al which applied a cost-effectiveness analysis (using a Markov model) comparing

insulin and oral therapies in 2 models: 1 model included adherence in the analysis and the other model did not.¹⁷ In the first model, which did not incorporate adherence, insulin therapy generated an incremental cost-effectiveness of \$12,097 per quality-adjusted life-year (QALY) gained versus oral therapies. Whereas life expectancy and quality-adjusted life expectancy strongly favored insulin therapy in the first analysis, the impact of adherence reflected in the second analysis involved a narrowing of the gap for both life expectancy and quality-adjusted life expectancy. Moreover, differences in complication rates (including amputation as well as cardiovascular, nephropathy, stroke, neuropathy, and retinopathy), which all favored insulin therapy in the first model, became notably smaller when adherence was taken into account. The rate of major hypoglycemia increased by 3.1% with insulin therapy, which resulted in increased medical costs for the treatment of hypoglycemia. Overall, in the second model, which included adherence, rates of complications decreased, while direct medical costs increased, and the incremental cost-effectiveness increased to \$16,241 per QALY.¹⁷

Impact of Poor Glycemic Control on Costs and Outcomes

In general, poor glycemic control is associated with worse patient outcomes and increased treatment costs.¹⁸⁻²⁰ The relationship between glycemic control and medical costs was the subject of a retrospective analysis of the Health Core Managed Care Database by Oglesby et al, a database which included information about 2.1 million people, covering the period from October 1998 through April 2003.¹⁹ A1C and cost data were available for 10,780 patients with diabetes, including 6069 who had good A1C control (≤ 7), 3586 with fair control (>7 and ≤ 9), and 1125 with poor control (>9). The authors determined that direct medical costs related to T2DM (reported in 2003 dollars) were 16% lower for good versus fair control (\$1505 vs \$1801; $P < .05$) and 20% lower for good versus poor control (\$1505 vs \$1871, $P < .05$). Prescription drug expenditures were \$377 for those with good control compared with \$465 for fair control and \$423 for poor control ($P < .05$ for good vs fair and poor, [Table](#)).¹⁹

A somewhat similar study was conducted by Shetty et al using 2002 data from a nationwide managed care organization (MCO) comprising a number of commercial preferred provider regional health plans with a total of 5.4 million members.²⁰ The purpose of the study was to determine diabetes-related 1-year medical and pharmacy costs for patients with good control (A1C < 7) versus patients with suboptimal control (A1C ≥ 7). The prevalence of T2DM among those enrolled in this MCO was 3.1%, and after exclusion criteria

Table. Annual Costs for Patients With Diabetes in a Managed Care Organization Stratified by Glycemic Control (in 2003 Dollars)¹⁹

Cost	Good A1C (≤ 7) (n = 6069)	Fair A1C (>7 and ≤ 9) (n = 3586)	Poor A1C (>9) (n = 1125)
Antidiabetic prescription drugs	\$377 (\$366-\$390)	\$465 ^a (\$450-\$480)	\$423 ^a (\$400-\$449)
Total diabetes-attributable costs	\$1505 (\$1441-\$1571)	\$1801 ^a (\$1674-\$1937)	\$1871 ^a (\$1684-\$2078)

A1C indicates glycated hemoglobin.

^a $P < 0.05$ compared with “Good” group; there were no statistically significant differences between the “Fair” and “Poor” groups.

Confidence intervals are shown in parentheses.

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were imposed, 8991 patients were identified for the study. The adjusted costs were found to be significantly lower for patients at A1C target compared with patients above target. For the above-target patients, costs were \$1540 versus \$1171 for the at-target group, a difference of 32% ($P < .001$).²⁰

A recent study of the effect of glycemic control on hospital costs in patients with diabetes analyzed data from the Fallon Clinic, comprising a mainly managed care patient population of 200,000 people.¹⁸ The study population included 9887 adult patients with either T1DM or T2DM and covered the period from the beginning of 2002 through the end of 2006. Hospitalizations evaluated in the study were designated diabetes-related, although the immediate causes for hospitalization were most commonly ischemic heart disease, electrolyte imbalance, and pneumonia. In patients with very poor glycemic control, the most common causes for hospitalization were ischemic heart disease, hyperglycemia, and hypoglycemia. The study authors found that 28.7% (2841) of patients were hospitalized for diabetes-related causes, accounting for 5874 total hospital stays. They further observed that, after adjustment for confounding variables, the proportion of patients hospitalized was significantly lower among patients with an A1C less than 7% (19.5%) compared with patients with an A1C of 10% or greater (33.9%). The increased risk did not reach significance for those with an A1C between 7% and 10%. However, patients with an A1C between 7% and 10% were between 1.18 and 1.72 times more likely to be hospitalized for diabetes-related causes versus those with an A1C less than 7% (all $P < .001$). Hospitalization costs increased in a roughly linear fashion relative to glycemic control. Patients with an A1C less than 7% had mean hospital costs of \$2792 compared with \$6759 for patients with an A1C of 10% or more. The **Figure** shows a full breakdown by A1C values.¹⁸

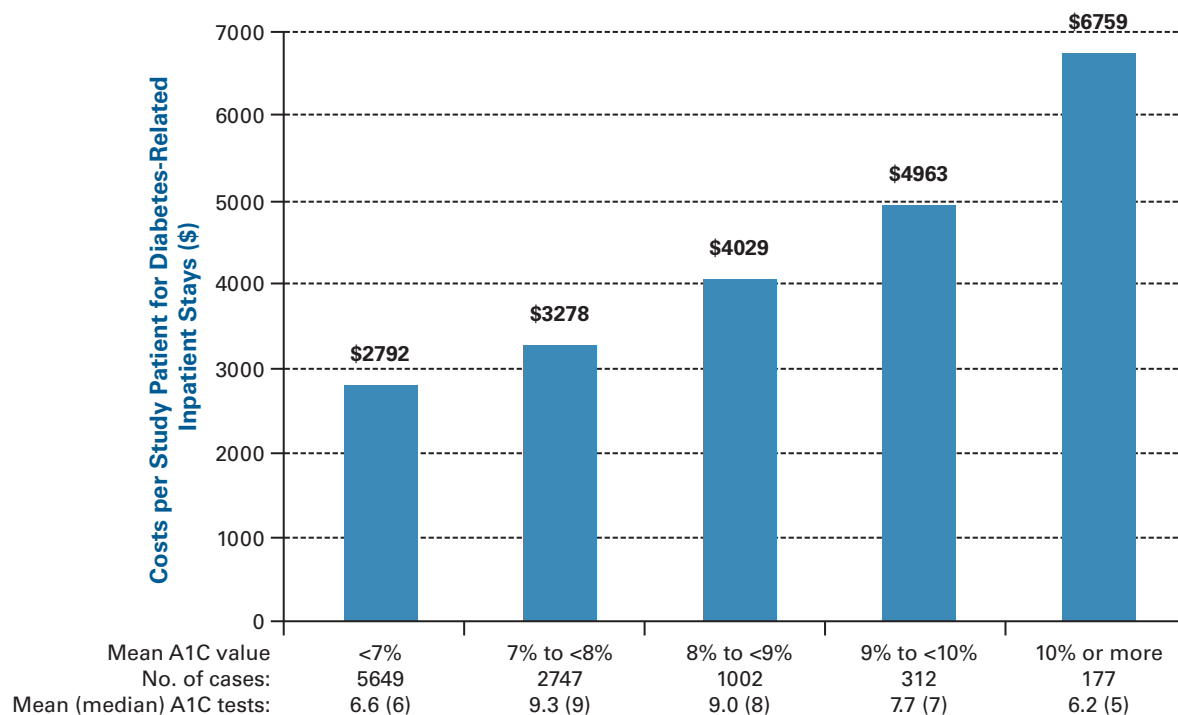
Other Contributors to Costs Associated With Nonadherence

A number of more indirect factors can be seen to exert an influence on adherence, including the burden of out-of-

pocket expenses borne by patients, levels of patient education and awareness regarding the importance of medication adherence, and third-party barriers to treatment access. The TRIAD study—conducted under the auspices of the Centers for Disease Control and Prevention (CDC) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)—was a multicenter, prospective observational study involving one of the largest cohorts of patients with diabetes to be studied.²¹ The study involved 3 surveys; the numbers of participants (and response rates) were 11,927 (69%), 8781 (83%), and 5751 (75%), respectively. Among the insights that emerged from TRIAD was that strategies that increased the cost burden to patients were associated with adverse patient behaviors; for example, reduced rates of blood glucose self-monitoring, less frequent retinal exams, and poorer likelihood of engaging in diabetes education. An initial survey of patients found that monthly out-of-pocket costs of \$150 or more were associated with medication underuse by 24% of subjects compared with 7% underuse when monthly out-of-pocket costs were less than \$50. A subsequent survey of those patients who had reported out-of-pocket expenses to be a barrier to adherence found these patients to have poorer control than other patients for 3 out of 3 cardiometabolic risk factors: A1C, blood pressure, and LDL cholesterol.²¹

Another factor influencing adherence is the fact that many patients with diabetes fail to understand the critical importance of adherence and the consequences of nonadherence. A recently published systematic review of the medical literature regarding patient knowledge of diabetes management found that a variety of inaccurate beliefs and assumptions on the part of patients, and a generally poor level of health literacy, contribute to an imbalanced view of diabetes therapy that significantly underestimates the consequences of being nonadherent.²² For example, the widespread belief that the need for insulin therapy is a mark of personal failure, and even punishment for poor self-care, causes approximately one-third of insulin-naïve patients to express an unwilling-

■ **Figure.** Diabetes-Related Hospitalization Costs per Patient Stratified by Degree of Glycemic Control¹⁸



A1C indicates glycated hemoglobin.

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ingness to use insulin if prescribed.²² Investing in patient education pertaining to the importance of adherence to both lifestyle changes and medications would likely have an important beneficial effect on treatment outcomes and costs.

With regard to barriers to adherence associated with third-party payers, a 2010 position statement by the ADA on third-party payers recognizes the importance of formularies and other cost-controlling mechanisms so long as they do not impede access to necessary treatments.²³ The ADA statement, however, makes the point that limitations on access to therapies imposed by third-party payers must be seen in the context of a patient population that lives with a high disease burden comprising both the effects of the disease itself and the need to manage the disease through conscientious adherence to medications as well as lifestyle and dietary behavior. Consequently, seemingly well-justified limitations to access may impose an unexpectedly outsized barrier to treatment adherence in a patient population already experiencing stresses arising from their disease and disease management program.²³

Conclusion

As a disease, diabetes combines several unique and challenging characteristics. It is a chronic disease with high rates

of morbidity and comorbidities while being, at the same time, extremely prevalent, and increasingly more so. Diabetes is also a disease that requires constant vigilance and discipline on the part of its patients to maintain appropriate dietary and lifestyle behaviors while adhering to a potentially complex medication regimen. Optimal outcomes can only be achieved with effective and consistent treatment. Due to the nature of T2DM as well as available treatments, a multitude of factors may influence treatment efficacy. Adherence is one of the factors that influences treatment efficacy, and a number of potential barriers may prevent patients from adhering to therapy, as will be discussed in the other articles in this supplement. Adherence rates in diabetes are currently suboptimal, and the consequences of poor adherence are very serious in terms of both patient outcomes and increases in treatment costs. The available data show benefits in terms of outcomes and costs when medication adherence is improved. Multiple strategies are necessary to improve medication adherence in patients with diabetes and should ideally include the efforts and contributions of patients, providers, and third-party payers alike.

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