Are diabetes medications really worth it?

Tuan Vo, PharmD.
PGY-1 Community Ambulatory Care Pharmacy Resident
Scott & White Residency Program

Objective:

1. Review epidemiology, etiology, and presentation of diabetes.
2. Describe insulin therapy
3. Identify barriers to therapy including barriers to adherence
4. Review clinical studies regarding adherence, compliance, and patient education
Introduction

- 23.6 million individuals in U.S.\textsuperscript{1,12,13}
- 25 million in Europe with Type 2\textsuperscript{2}
- Affects almost 200 million people (5% of the adult population)\textsuperscript{3}
- 1.8 million aged 18 years and older in Texas; about 460,040 undiagnosed in this age group; up to 2.2 million undiagnosed nation-wide\textsuperscript{4}
- In 2007, $174 billion in diabetes care accounting for 19% of total healthcare costs\textsuperscript{8}
- Diabetes costs state of Texas $12.5 billion annually in health care costs and lost productivity\textsuperscript{4}
- Sixth leading cause of death in Texas\textsuperscript{4}
- It projected that with the current overweight population and type 2 diabetes prevalence, that those born in the year 2000 will have one in three chance of developing diabetes in their lifetime\textsuperscript{4}

![FIGURE 5](image)

**Texas Diabetes Prevalence by Leisure Time Physical Activity Status, 2000–2005\textsuperscript{5}**

- Diabetes is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both\textsuperscript{5}
  - Symptoms of hyperglycemia may include polyuria, polydipsia, weight loss, possible polyphagia, and blurred vision
- Long-term complications may include\textsuperscript{4,5}
  - Retinopathy with potential loss of vision
  - Nephropathy that may lead to renal failure
  - Peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints
  - Autonomic neuropathy leading to GI, genitourinary, sexual dysfunction, and cardiovascular problems
  - Higher incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease
Concomitant conditions often include hypertension and dyslipidemia

Two patient groups

- **Type 1** – beta-cell destruction often leading to absolute insulin deficiency
  - Insulin deficiency caused by autoimmune destruction of the beta-cells of the pancreas
    - Genetic markers may be able to identify deficiency of insulin secretion
    - Markers may include islet cell autoantibodies, autoantibodies to insulin, autoantibodies **to GAD65, and to tyrosine phosphatases IA-2 and IA-2beta**
    - HLA association with linkage to DQA and DQB genes and may also be influenced by DRB genes
  - Accounts for only 5-10% of the diabetic population
  - First manifestation may occur as ketoacidosis as a child or adolescent
    - May present due to presence of infection or other stress
    - But may occur in later stages of life as well
  - Adults may retain residual beta cell function for years
  - Patients may be prone to other autoimmune disorders like grave’s disease, hasimotos’s thyroiditis, addison’s disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia
  - **Idiopathic** – unknown etiology with no evidence of autoimmunity
    - Most are African or Asian ancestry and inherited
    - Episodic ketoacidosis with varying degrees of insulin deficiency
    - Insulin requirement may come and go as well

- **Type 2** – usually insulin resistance with relative deficiency to predominant insulin secretory defect with resistance
  - Resistance can be caused by abnormalities and diminished tissue response to insulin at one or more points in the pathways of hormone action
    - Pathological and functional changes in target tissues may progress with out clinical symptoms for a long period of time before detection
  - This accounts for 90-95% of diabetic population out there previously known as non-insulin dependent / adult-onset diabetes
- Etiology is unknown but autoimmune destruction of the beta-cells does not occur nor do they have any causes listed previously
- Patient demographics
  - Obesity (attributes to a degree of the insulin resistance)
  - May not be obese by weight but have increased body fat percentage in the abdominal region
  - Ketoacidosis normally is a result of a stressor like an infectious process
- Beta-cell function may have been normal but insulin secretion may not be able to compensate for the insulin resistance which is then considered to be defective
  - Resistance may improve with weight reduction and medication therapy but normal secretion is seldomly restored
- Risk of development increases with age, obesity, and lack of physical activity
  - Higher in women with prior diabetes during pregnancy and in those with hypertension or dyslipidemia
  - Varies with racial / ethnic subgroups
  - Has a strong genetic disposition but is complex and not clearly defined
- Other types
  - Genetic defects of beta-cell
    - Early age before 25 – maturity-onset diabetes of the young (MODY) with impaired secretion with minimal defects in insulin action – autosomal dominant pattern – impairment may be from inability to stimulate insulin secretion (glucokinase \(\rightarrow\) glucose to glucose-6-phosphate) / inability to convert proinsulin to insulin / mutant insulin molecules with resistant insulin receptor binding \(\rightarrow\) mild glucose intolerance or even normal
  - Genetic defects in insulin action
    - Mutations in insulin receptors – some may have acanthosis nigricans – enlarged cystic ovaries in women – Leprechaunism and Rabson-Mendenhall syndrome (abnormalities of teeth & nails)
  - Diseases of exocrine pancreas
    - Injuries to the pancreas – pancreatitis, trauma, infection, pancreatectomy, and carcinoma – damage usually has to be extensive – even small adenocarcinomas – extensive cystic fibrosis and hemochromatosis can cause
  - Endocrinopathies
    - Hormones can antagonize insulin action (growth hormone, cortisol, glucagon, epinephrine) – seen in acromegaly, Cushing’s syndrome, glucagonoma, pheochromocytoma – usually preexisting defects in secretion and hyperglycemia will resolve when hormone excess is removed – somatostatinoma & aldosterone-induced hypokalemia can inhibit secretion and resolves after removal of tumor
  - Drug or chemical-induced diabetes
    - Not a core cause of diabetes but may precipitate diabetes in those with insulin resistance – classification can become unclear – vacor rat poison (non-warfarin based), pentamidine can destroy beta-cells (rare) – nicotinic acid
and glucocorticoids can impair insulin action – also thyroid hormone, beta-agonists, dilantin

- Infections – viruses have been associated with beta-cell destruction
- Other genetic syndromes – down syndrome, Klinefelter syndrome, and turner syndrome – Wolfram’s syndrome – insulin deficient with absence of beta-cells – hypogonadism, optic atrophy...

- Gestational Diabetes mellitus (GDM) – 7% of pregnancies depending on the population – can result in 200,000 cases annually – onset or first recognition during pregnancy
  - Risk for gestational diabetes should be undertaken with those that have marked obesity, history of GDM, glycosuria, or strong family history of diabetes
  - Patients should be screened at initial prenatal visit and retested between 24 and 28 weeks of gestation if initial screening is negative.

<table>
<thead>
<tr>
<th>Table 2—Categories of increased risk for diabetes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l) [IFG]</td>
</tr>
<tr>
<td>2-h PG in the 75-g OGGT 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11.0 mmol/l) [IGT]</td>
</tr>
<tr>
<td>A1C 5.7–6.4%</td>
</tr>
</tbody>
</table>

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

<table>
<thead>
<tr>
<th>Table 3—Criteria for the diagnosis of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>2. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>3. 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGGT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).</td>
</tr>
</tbody>
</table>

*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.
Table 4—Criteria for testing for diabetes in asymptomatic adult individuals

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m²*) and have additional risk factors:
   - physical inactivity
   - first-degree relative with diabetes
   - members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - women who delivered a baby weighing >9 lb or were diagnosed with GDM
   - hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dl (0.90 mmol/l) and/or a triglyceride level >250 mg/dl (2.82 mmol/l)
   - women with polycystic ovary syndrome
   - A1C ≥5.7%, IGT, or IFG on previous testing
   - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - history of CVD

2. In the absence of the above criteria, testing diabetes should begin at age ≥45 years

3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

*At-risk BMI may be lower in some ethnic groups.

- Prevention / Delay in populations at risk:¹¹
  - A1c 5.7 – 6.4
  - Family history
  - Obesity
  - Under 60 years of age
  - Low HDL
  - High TGs

Summary of Therapy¹¹
- Glucose monitoring – 3 or more times daily as needed with insulin injections
- A1c – twice a year or quarterly if therapy changing or glycemic goals not being met
- Therapeutic Life Style changes
  - 7% Weight loss
  - Medication nutritional therapy
  - Physical activity
    - 0.66% A1C reduction with physical activity
    - Moderate – 150 min / wk or vigorous – 75 min / wk
  - Reduction in calories
  - Reduction in fat intake
  - Whole grains and 14 g fiber/1000 kcal
  - <7% sat fat in total calories
  - Monitor carb intake and adequate sugar alcohol or non-nutritional sweetener intake
  - Limit alcohol (1 / women, 2 / men)

- Target BP 130/80 mmHg
- LDL < 100 mg/dL
- A1C < 7.0%
- Aspirin 75-162 mg/day for men > 50 or women > 60 who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria)
- Nephropathy, retinopathy, neuropathy – pin prick testing / vibration

### Table 9 — Correlation of A1C with average glucose

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Mean plasma glucose (mg/dl)</th>
<th>Mean plasma glucose (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>126</td>
<td>7.0</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
<td>8.6</td>
</tr>
<tr>
<td>8</td>
<td>183</td>
<td>10.2</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
<td>11.8</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
<td>13.4</td>
</tr>
<tr>
<td>11</td>
<td>269</td>
<td>14.9</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
<td>16.5</td>
</tr>
</tbody>
</table>

### Table 17 — Plasma blood glucose and A1C goals for type 1 diabetes by age group

<table>
<thead>
<tr>
<th>Values by age (years)</th>
<th>Before meals</th>
<th>Bedtime/overnight</th>
<th>A1C</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toddlers and preschoolers (0–6)</td>
<td>100–180</td>
<td>110–200</td>
<td>&lt;8.5% (but &gt;7.5%)</td>
<td>High risk and vulnerability to hypoglycemia</td>
</tr>
<tr>
<td>School age (6–12)</td>
<td>90–180</td>
<td>100–180</td>
<td>&lt;8%</td>
<td>Risks of hypoglycemia and relatively low risk of complications prior to puberty</td>
</tr>
<tr>
<td>Adolescents and young adults (13–19)</td>
<td>90–130</td>
<td>90–150</td>
<td>&lt;7.5%</td>
<td>Risk of severe hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Developmental and psychological issues</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A lower goal (&lt;7.0%) is reasonable if it can be achieved without excessive hypoglycemia</td>
</tr>
</tbody>
</table>
Insulin Therapy

Average prescription costs for diabetes went from $56 in 2001 to $76 in 2007.

Insulin Algorithms

- Type 1 UCSF
  - Once or twice daily long acting insulin with rapid acting before meals
  - Rapid acting insulin delivered by an insulin pump

---

**RELATIVE EFFECTS OF INSULIN ANALOGS**

*Figure 1. Representative time action profiles of selected exogenous insulins. Source: References 25, 26.*

---

**Intensive Insulin Therapy: Multiple Daily Injections/CSII Insulin Regimens for Type 1 Diabetes**

- Aspart or Lyspro or Glulisine
- Glargine
- Detemir
- Rapid Acting insulin
- Type 2
  - Once daily
    - At bedtime with NPH or long-acting (lantus / levemir)
    - Before supper: NPH with short acting or premix 70/30 or 75/25
  - Multi-dose (2 – 3 shots)
    - NPH and short acting insulin – 2:1 AM + 1:1 PM or sliding scale SAI
    - SAI at breakfast and supper as sliding scale and NPH at breakfast and bedtime or long-acting once daily
  - Intensive insulin management
    - Basal: NPH breakfast and supper or bedtime, or 4 times daily
      - Or a long acting insulin
    - Bolus: SAI at each meal – lispro or aspart preferred
      - This should cover carbs ingested and additional for high self-monitored-blood glucose (SMBG)

- Combinations of metformin and insulin also help improve body weight, glycemic control, and improve the risk of macrovascular disease.

**Importance of Medication Adherence and Barriers**
- Combinations of medication, diet, and exercise should be adequate to achieve control so suboptimal control may be due to medication adherence and self-management
- Studies have shown...
  - When 35.4% of type 2 adherent to their medications and only 50% of these patients were adherent to their OGLA (oral glucose lowering agents)
  - But 38% of patients that were 90% adherent to their initial therapy received a dose escalation after a year compared with only 21% of those that were less than 50% adherent
  - Patients with less adherence resulted in worsening outcomes and increased total healthcare costs per patient per year – almost double of the adherent patients
- Reductions in A1Cs have shown 80% reduction in blindness and end-stage renal disease when targeting less than 20% of patients with worst A1C control.
- Rates of non adherence in diabetes can vary from 36% to 93% in retrospective and prospective studies.
- Cost-sharing can decrease medication adherence, for every 10% increase there is a 2-6% decrease in prescription drug use
- Potential barriers
  - Fear of hypoglycemia
  - Fear of giving self-injection
  - Failure of diabetes therapy
  - Fear of needles
  - Weight gain
  - Inconvenience of scheduled injections
  - Complexity of regimen
  - Low health literacy
  - Cost of insulin
- Strategies to improve Medication adherence
  - Patient education
  - Primary care clinics or pharmacist managed clinics
  - Pharmacy benefit designs – reduction in co-pays, out of pocket expenses
    - Value benefit design – lower co-pays – after implementation at Pitney Bowes there was a 10% improvement in med adherence⁶
Review of Clinical Literature
Trial 1: Gibson et al -

<table>
<thead>
<tr>
<th>Study Design</th>
<th>A retrospective, cross-sectional study conducted over a 2 year period following patients with type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To assess relationship between cost sharing and adherence to antidiabetic medications in patients with type 2 diabetes and to examine relationship between medication adherence and outcomes (complication rates, medical service utilization, and workplace productivity measures)</td>
</tr>
<tr>
<td>Population</td>
<td>Patients within the Thomson Reuters MarketScan Database from 2002-2006 Adults &gt;= 18 years old with diabetes on an oral antidiabetic medication (OAD) continuously enrolled from January 1, 2002 through June 30, 2006 Needed to fill at least 2 antidiabetic agents within first study year period</td>
</tr>
<tr>
<td>End Points</td>
<td>1st stage – assess effects of cost sharing on medication adherence over 18 months 2nd stage – assess cost sharing, adherence and complication, medical utilization rates, and measures of productivity</td>
</tr>
</tbody>
</table>
| Methods     | Patients in the database had in-/outpatient medical, pharmacy claims, absenteeism data, and short-term disability benefits linked to enrollment  
Explanatory variables  
  o Charleston Comorbidity Index – cost and utilization measures for differences in health statuses  
  o Patient cost sharing measures  
  o Patient social demographic characteristics  
Adherence was measured as percentage of days covered (PDC) or percent of days with antidiabetic medication on hand during an 18 month period (Jan 2003 – June 2004)  
  o Hospitalization days were counted as adherent  
  o Insulin utilization and adherence was based on 1.5 times the day supply to account for the extent of coverage per fill  
  o Defined adherence as PDC >= 80% |
| Results     | $10 increase in patient cost-sharing resulted in 5.4% reduction in adherence to OAD only and 6.8% reduction in patients on OAD with or without insulin  
Shot-term disability – 40 days for non and 22 for adherent patients; p<0.01  
ED visits significantly lower in adherent patients (incidence rate ratio 0.8; p<0.018)  
Refer to Appendix A for more results |
| Conclusion  | Implementing interventions that are targeted to improve diabetes may translate to better outcomes for health plans, employers, and policy makers. |
| Limitations | Indirectly assessed the adherence of insulin – focused on OADs – insulin was supplemental to OAD  
Claims data – antidiabetic medication consumption patterns cannot be determined – regimens unknown |
Trial 2: Cohen et al – Measurements of medication adherence in diabetes patients

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Randomized, controlled, behavioral intervention study delivered via telephone to patients who might not have participated in conventional face-to-face diabetes education programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To assess pharmacy claims and self-report data as measures of medication adherence and to describe baseline characteristics of subjects in the Improving Diabetes Outcomes Study</td>
</tr>
</tbody>
</table>
| Population  | • Multi-ethnic, lower-income, insured adults in New York City with type 2 diabetes  
• Adults >= 30 years old that are members of the Benefit and Pension Funds  
• Eligibility: ability to read / speak English or Spanish, being in New York area for protocol duration, and no evidence of cognitive impairment  
  o Prescribed oral glucose-lowering agent (OGLA) a year prior to enrollment and HbA1c >= 7.5%; exclude current study or programs |
| End Points  | HbA1c change from baseline and medication adherence |
| Methods     | • Measures – HbA1c mail-in kits were sent out to patients  
  o Patient uses lancet to draw blood from fingertips and fill in circles on filter card – health educators were used to guide them  
• Medication adherence – assessed by using pharmacy claims data indicating date and number of pills dispensed to participants used to calculate medication possession ratio (MPR)  
  o Terminal gaps were defined by >= 120 and 270 continuous days without medication  
  o Summary of Diabetes Self Care Activities (SDSCA) scale – how many days in most recent week medication taken as prescribed  
    ▪ 0 – 7 adherent days  
  o Morisky Self-Reported Medication-Taking Scale where scores <= 2 were considered poor adherence  
• Other data: sex, age, race/ethnicity, work status, marital status, income, education, birth place, height, weight, years with diabetes, and insulin use in the previous year |
| Results     | • 526 enrolled participants with a mean age 55.5 +/- 7.3 years  
• Adherence classification  
  o MPR low, Morisky low / not low – 174 (33.1%) – 8.9% HbA1c  
  o MPR not low, Morisky not low – 239 (45.4%) – 8.4% HbA1c  
• Association of MPR with HbA1c was strong in the upper HbA1c (P = 0.007) but not in the lower stratum (P = 0.6)  
  Refer to Appendix B / C |
| Conclusion  | Supports the validity of MPR as an adherence measure for OGLA among insured diabetes patients with poorly controlled HbA1c, especially with multiple OGLA. |
| Limitations | • Reliance on self-administered dry-dot HbA1c capillary measure  
• Low HbA1c entry requirement of >= 7.5% - limits generalizability  
• Measure of medication possession but not taking the actual medication |
### Trial 3: Nair et al – Prescription Co-Pay Reduction Program

<table>
<thead>
<tr>
<th><strong>Study Design</strong></th>
<th>Cohort of members with diabetes continuously enrolled in the 12-month pre-period and 2 years following co-pay reduction on all diabetic drugs and testing supplies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>Examine the impact of reducing prescription co-pay for diabetes medications on pharmacy utilization, medication adherence, medication utilization, and expenditures</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>27,881 state employees enrolled with health benefits</td>
</tr>
<tr>
<td><strong>End Points</strong></td>
<td>Measured diabetic prescription utilization, medication adherence, medical utilization, and expenditures with adjustments for age, sex, and comorbidity risk</td>
</tr>
</tbody>
</table>
| **Methods**      | - Program placed all diabetic medications and testing supplies at tier 1 regardless of brand or generic status with $10 retail co-pay and $20 mail-order co-pay after $100 annual prescription deductible  
- Annualized measurements per member per year (3 times)  
  - Number of diabetes medications  
  - Number of diabetes testing supplies  
  - Medication adherence – defined as proportion of days covered (PDC) for diabetes medications  
    - Adherence if PDC >= 80%  
- Medical utilization measures – number of diabetes-related health care visits and hospitalizations / emergency room visits  
- Expenditure-based measures – expenditures for diabetes medications, testing supplies, and medical services related to diabetes |
| **Results**      | - 589 individuals were continuously enrolled for 3 years meeting for all inclusion criteria with mean age of 51 years, 43.3% female, and mean risk score of 1.09  
- Pharmacy utilization – Appendix D  
- Medication adherence – adherence increased by 3.2% in year 1 but only by 1.3% in year 2  
  - Insulin adherence was lower – 56.1% preperiod, 61.4% year 1, and 62.5% in year 2  
  - Increase of 9.4% in year 1 and slight in year 2 compared to year 1  
- Medical utilization – decrease in specific office visits in year 1 (-11.9%) and year 2 (-5.0%); ER visits in year 1 (-30.7%) and year 2 (-36.0%)  
- Expenditures – 61% increase in payer paid pharmacy expenditures in year 1 and 85% in year 2  
Refer Appendix D, E, F |
| **Conclusion**   | Modest increase in adherence and use of diabetes medications observed. |
| **Limitations**  | - No control group – couldn’t get appropriate matches  
- Regression to mean – without the program may have led to lower expenditures in non program patients  
- Insulin adherence measured with individual vials and pens as multiple doses |
Conclusion and Research

Patient adherence and compliance is often the key to managing every disease state successfully. Recent studies show that pharmacist managed clinics often help increase patient awareness of their disease state\(^8\). Awareness and education can only go so far as patient compliance is an issue on its own. Compliance is a behavior that has to be acquired and learned over time. For some people it requires repetition and others it may require integration into their daily habits. It also takes an open mind to make the necessary changes to be successful. Clinical evidence has shown that reduction in costs has helped somewhat with medication compliance. As well as education and awareness can help patients understand their disease state. Increasing visits to a health care provider also helps strengthen disease state management. However, as healthcare providers we can only provide awareness, counseling, and education to a certain extent. The rest really is up to the patient.

These studies provided good evidence that adherence can be an issue of cost, the need for more education on disease state management, and the support for certain measures for patient adherence to medications. However, these studies did not address whether adherence to insulin, would affect the outcome of the disease state. The goal of this current research will focus on two factors to determine medication adherence and the impact it has HbA1c levels. The medication possession or a persistence rate will be based on a refill pattern by both control and study patients within the Scott & White diabetes outcome program. Patients enrolled at the Scott & White diabetes outcomes program are limited to a 30-day supply of their medication with a mandatory monthly visit with a clinical pharmacist and in turn receive a co-pay waiver on their medications. Medication adherence is assessed via a six-item questionnaire, called the modified-Morisky score (MMS)\(^{\text{See appendix G}}\), administered periodically to patients participating in the study. By analyzing both health plan claims data and the MMS, the degree of adherence to insulin will then be used to assess change in baseline HbA1c %.
Appendix A

Figure 1. Predicted Effects of Prescription Drug Cost Sharing on Adherence to Antidiabetes Medications

72.4%  69.2%  64.7%  71.2%  66.3%  61.5%

0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1

$10  $20  $30  $10  $20  $30

Patients With Type 2 Diabetes on OAD Only
Patients With Type 2 Diabetes on OAD With or Without Insulin

PDC indicates percentage of days covered.
*Adherence was measured from January 2003 through June 2004.
Source: 2002-2004 Thomson Reuters MarketScan Database.

Appendix B

Table 2 Classification of adherence by MFR and Morisky score with HbA1c

<table>
<thead>
<tr>
<th>Adherence classification</th>
<th>Number (%)</th>
<th>Median HbA1c (%)</th>
<th>Interquartile range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFR low, Morisky low*</td>
<td>81 (15.4)</td>
<td>8.9</td>
<td>8.1-10.5</td>
</tr>
<tr>
<td>MFR low, Morisky not low</td>
<td>93 (17.7)</td>
<td>8.9</td>
<td>8.0-10.9</td>
</tr>
<tr>
<td>Morisky low, MFR not low</td>
<td>113 (21.5)</td>
<td>8.7</td>
<td>8.2-9.9</td>
</tr>
<tr>
<td>MFR not low, Morisky not low</td>
<td>239 (45.4)</td>
<td>8.41</td>
<td>7.9-9.5</td>
</tr>
<tr>
<td>Total</td>
<td>526 (100)</td>
<td>8.6</td>
<td>8.0-10</td>
</tr>
</tbody>
</table>

* MFR low: lowest MFR tertile; not low: mid and upper tertile; Morisky low: Morisky score ≤ 2 (low adherence); not low: > 2.
†P for trend of HbA1c with categories of adherence = 0.005.
MFR, medication possession ratio; HbA1c, glycated haemoglobin.
### Table 3 HbA1c by medication adherence categories in whole sample and stratified by number of oral glucose-lowering agent classes

<table>
<thead>
<tr>
<th>Medication adherence measure</th>
<th>Median HbA1c</th>
<th>Interquartile range</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total sample</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR low tertile (n = 174)</td>
<td>8.9</td>
<td>8.0–10.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Mid and upper tertile</td>
<td>8.6</td>
<td>8.0–9.6</td>
<td></td>
</tr>
<tr>
<td>(n = 352)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morisky score ≤ 2 (n = 194)</td>
<td>8.8</td>
<td>8.1–10.2</td>
<td>0.10</td>
</tr>
<tr>
<td>&gt; 2 (n = 332)</td>
<td>8.5</td>
<td>7.9–9.9</td>
<td></td>
</tr>
<tr>
<td>SDSCA: &lt; 7 days (n = 140)</td>
<td>8.6</td>
<td>7.9–10.2</td>
<td>0.52</td>
</tr>
<tr>
<td>7 days (n = 386)</td>
<td>8.7</td>
<td>8.0–9.9</td>
<td></td>
</tr>
<tr>
<td><strong>One oral glucose-lowering agent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR low tertile (n = 96)</td>
<td>8.6</td>
<td>7.8–10.5</td>
<td>0.73</td>
</tr>
<tr>
<td>Mid and upper tertile</td>
<td>8.5</td>
<td>8.0–9.6</td>
<td></td>
</tr>
<tr>
<td>(n = 178)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morisky score ≤ 2 (n = 111)</td>
<td>8.8</td>
<td>8.1–10.2</td>
<td>0.29</td>
</tr>
<tr>
<td>&gt; 2 (n = 163)</td>
<td>8.5</td>
<td>7.9–9.9</td>
<td></td>
</tr>
<tr>
<td>SDSCA: &lt; 7 days (n = 80)</td>
<td>8.5</td>
<td>7.9–9.9</td>
<td>0.64</td>
</tr>
<tr>
<td>7 days (n = 194)</td>
<td>8.6</td>
<td>8.0–10.2</td>
<td></td>
</tr>
<tr>
<td><strong>≥ 2 oral glucose-lowering agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR low tertile (n = 78)</td>
<td>9.3</td>
<td>8.2–11.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Mid and upper tertile</td>
<td>8.6</td>
<td>8.0–9.6</td>
<td></td>
</tr>
<tr>
<td>(n = 174)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morisky score ≤ 2 (n = 83)</td>
<td>8.9</td>
<td>8.1–10.1</td>
<td>0.23</td>
</tr>
<tr>
<td>&gt; 2 (n = 169)</td>
<td>8.6</td>
<td>8.0–9.9</td>
<td></td>
</tr>
<tr>
<td>SDSCA: &lt; 7 days (n = 60)</td>
<td>8.5</td>
<td>7.8–10.1</td>
<td>0.18</td>
</tr>
<tr>
<td>7 days (n = 192)</td>
<td>8.7</td>
<td>8.1–10.0</td>
<td></td>
</tr>
</tbody>
</table>

*P*-values by Mann–Whitney U-test.

HbA1c, glycated haemoglobin; MPR, medication possession ratio; SDSCA, Summary of Diabetes Self Care Activities question: how many days per week taking diabetes pills as prescribed.
Appendix D

![Histogram of mean number of prescriptions](image)

**FIG. 1.** Per member per year pharmacy utilization for diabetes medications in all three observation periods for different categories of adherence.

Appendix E

**TABLE 5. Adjusted Percent Differences in Per Member Per Year Medical Utilization for Diabetic Services in All Three Observation Periods**

<table>
<thead>
<tr>
<th>Sample (n = 589)</th>
<th>Pre period</th>
<th>Year 1</th>
<th>Year 2</th>
<th>% Difference (pre period vs. year 1)</th>
<th>% Difference (pre period vs. year 2)</th>
<th>% Difference (year 2 vs. year 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office visits(^1)</td>
<td>2.14</td>
<td>1.91</td>
<td>2.04</td>
<td>-11.9*</td>
<td>-5.0</td>
<td>6.1</td>
</tr>
<tr>
<td>Emergency room visits(^2)</td>
<td>0.11</td>
<td>0.07</td>
<td>0.07</td>
<td>-30.7*</td>
<td>-36.0*</td>
<td>-7.7</td>
</tr>
<tr>
<td>Hospitalizations(^2)</td>
<td>0.02</td>
<td>0.01</td>
<td>0.02</td>
<td>-52.8*</td>
<td>-12.8*</td>
<td>85.0</td>
</tr>
<tr>
<td>Laboratory/diagnostic visits(^1)</td>
<td>2.01</td>
<td>2.05</td>
<td>1.98</td>
<td>2.1</td>
<td>-1.4</td>
<td>-3.6</td>
</tr>
</tbody>
</table>

\(^1\)Estimates based on a Poisson model.

\(^2\)Estimates based on a zero-inflated Poisson model.

\(^*\)P < 0.01; Estimates are rounded up to 2 decimal points. Percent differences reflect differences that include all the decimal values.
Table 7. Difference in the Utilization of Key Medical Services for Adherent Individuals Versus Nonadherent Individuals in All Three Observation Periods

<table>
<thead>
<tr>
<th></th>
<th>Nonadherent Members PMPY</th>
<th>Adherent members PMPY</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre period</td>
<td>2.29</td>
<td>2.30</td>
<td>0.40%</td>
</tr>
<tr>
<td>Year 1</td>
<td>2.03</td>
<td>2.18</td>
<td>7.00%</td>
</tr>
<tr>
<td>Year 2</td>
<td>2.10</td>
<td>2.49</td>
<td>15.6%*</td>
</tr>
<tr>
<td>Emergency room visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre period</td>
<td>0.06</td>
<td>0.05</td>
<td>-26.20%</td>
</tr>
<tr>
<td>Year 1</td>
<td>0.12</td>
<td>0.08</td>
<td>-30.70%</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.06</td>
<td>0.04</td>
<td>-36.70%*</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre period</td>
<td>0.05</td>
<td>0.01</td>
<td>-72.80%</td>
</tr>
<tr>
<td>Year 1</td>
<td>0.02</td>
<td>0.02</td>
<td>0.00%</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.05</td>
<td>0.03</td>
<td>-29.60%*</td>
</tr>
<tr>
<td>Laboratory/diagnostic services</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre period</td>
<td>2.11</td>
<td>2.10</td>
<td>-0.50%</td>
</tr>
<tr>
<td>Year 1</td>
<td>2.08</td>
<td>2.29</td>
<td>10.50%</td>
</tr>
<tr>
<td>Year 2</td>
<td>1.95</td>
<td>2.45</td>
<td>26.00%*</td>
</tr>
</tbody>
</table>

*P < 0.05; PMPY, per member per year.
<table>
<thead>
<tr>
<th>Question</th>
<th>Motivation</th>
<th>Knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you ever forget to take your medicine?</td>
<td>Yes(0)</td>
<td>No(1)</td>
</tr>
<tr>
<td>2. Are you careless at times about taking your medicine?</td>
<td>Yes(0)</td>
<td>No(1)</td>
</tr>
<tr>
<td>3. When you feel better do you sometimes stop taking your medicine?</td>
<td>Yes(0)</td>
<td>No(1)</td>
</tr>
<tr>
<td>4. Sometimes if you feel worse when you take your medicine, do you stop taking it?</td>
<td>Yes(0)</td>
<td>No(1)</td>
</tr>
<tr>
<td>5. Do you know the long-term benefit of taking your medicine as told to you by your doctor or pharmacist?</td>
<td>Yes(1)</td>
<td>No(0)</td>
</tr>
<tr>
<td>6. Sometimes do you forget to refill your prescription medicine on time?</td>
<td>Yes(0)</td>
<td>No(1)</td>
</tr>
</tbody>
</table>
Sources


