National Trends in Treatment of Type 2 Diabetes Mellitus, 1994-2007

G. Caleb Alexander, MD, MS; Niraj L. Sehgal, MD, MPH; Rachael M. Moloney, BA; Randall S. Stafford, MD, PhD

Background: Diabetes mellitus is common, costly, and increasingly prevalent. Despite innovations in therapy, little is known about patterns and costs of drug treatment.

Methods: We used the National Disease and Therapeutic Index to analyze medications prescribed between 1994 and 2007 for all US office visits among patients 35 years and older with type 2 diabetes. We used the National Prescription Audit to assess medication costs between 2001 and 2007.

Results: The estimated number of patient visits for treated diabetes increased from 25 million (95% confidence interval [CI], 23 million to 27 million) in 1994 to 36 million (95% CI, 34 million to 38 million) by 2007. The mean number of diabetes medications per treated patient increased from 1.14 (95% CI, 1.06-1.22) in 1994 to 1.63 (1.54-1.72) in 2007. Monotherapy declined from 82% (95% CI, 75%-89%) of visits during which a treatment was used in 1994 to 47% (43%-51%) in 2007. Insulin use increased from 38% of treatment visits in 1994 to a nadir of 25% in 2000 and then increased to 28% in 2007. Sulfonylurea use decreased from 67% of treatment visits in 1994 to 34% in 2007. By 2007, biguanides (54% of treatment visits) and glitazones (thiazolidinediones) (28%) were leading therapeutic classes. Increasing use of glitazones, newer insulins, sitagliptin phosphate, and exenatide largely accounted for recent increases in the mean cost per prescription ($56 in 2001 to $76 in 2007) and aggregate drug expenditures ($6.7 billion in 2001 to $12.5 billion in 2007).

Conclusions: Increasingly complex and costly diabetes treatments are being applied to an increasing population. The magnitude of these rapid changes raises concerns about whether these more costly therapies will result in proportionately improved outcomes.

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Author Affiliations:
Department of Medicine, University of Chicago Hospitals (Dr Alexander and Ms Moloney), MacLean Center for Clinical Medical Ethics, University of Chicago (Dr Alexander), and Department of Pharmacy Practice, University of Illinois at Chicago School of Pharmacy (Dr Alexander), Chicago, Illinois; Division of Hospital Medicine, University of California, San Francisco (Dr Sehgal); and Program on Prevention Outcomes and Practices, Stanford Prevention Research Center, and Stanford University School of Medicine, Stanford, California (Dr Stafford).
We aimed to describe recent trends in the pharmacologic glycemic treatment of diabetes within and across different therapeutic classes using nationally representative data from 1994 to 2007. We examined how the availability of new oral treatment classes, plus new formulations of insulin, affects the use of older agents, such as sulfonylureas and biguanides. We also examined changes in complexity of care through the use of combination drug products and treatment from multiple therapeutic classes. Finally, we examined how changes in medication therapy have altered the costs of glycemic treatment in diabetes.

### METHODS

**DATA SOURCE**

We used data from the National Disease and Therapeutic Index (NDTI), an ongoing physician survey conducted by IMS Health (Plymouth Meeting, Pennsylvania). The NDTI provides nationally representative diagnostic and prescribing information on patients treated by office-based physicians in the continental United States. The physician sample consists of office-based physicians selected from the master lists of the American Medical Association and the American Osteopathic Association (both in Chicago, Illinois) through a random stratified sample by specialty and geographic region. Approximately 3300 physicians participate, with data collection on 2 randomly assigned consecutive workdays in each calendar quarter. The geographic and specialty distribution of the participants is designed to closely match national patterns.

Physicians provide information on each patient encounter during their data collection period. Each reported patient diagnosis generates a unique diagnosis record on which the physician records medication therapies provided for that condition. Diagnosis records also may list no medications if none were used. A single patient may generate multiple diagnosis records, each of which may list multiple medications. Patient encounters are converted to an estimate of the number of patients based on the number of annual visits made by the patient. The number of patients is the sum of the inverse of this figure. For much of our analysis, we relied on visits for patients diagnosed as having diabetes and treated with at least 1 medication (referred to as a treatment visit) as our unit of analysis. Medication reporting reflects the physician’s best knowledge of new or continuing medications; the NDTI does not capture information on patient adherence or unreported self-medication. We present annual data as the aggregate of the quarterly surveys conducted within each year. Using available sampling weights, we extrapolated national estimates from annual samples of diabetes visits ranging from 8000 to 12,000 visits. To maximize the inclusion of patients who had type 2 rather than type 1 diabetes, we limited our analyses to patients older than 35 years who had received a diagnosis of diabetes (International Classification of Diseases, Ninth Revision [ICD-9] codes 250.00 through 250.92) except for diagnoses associated with type 1 diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification codes 250.002, 250.004, 250.101, and 250.103). Given the limitations of ICD-9 coding, this definition provides a reasonable estimate of medication use for type 2 diabetes.

Our data on prescription expenditures were available for 2001 to 2007 and solely derived from the National Prescription Audit (NPA), which provides a national sample of approximately 20,000 retail, mass merchandise, and mail order pharmacies. Data reflect estimates of the total number of new or refilled medications provided to US consumers from these sources. These pharmacies account for more than half of the retail pharma-

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### Table. Leading Diabetes Medications by Treatment Class

<table>
<thead>
<tr>
<th>Diabetes Treatment Class</th>
<th>Total 2007 Drug Uses (95% CI), in Millions</th>
<th>Most Frequently Reported Medication in Each Treatment Class in 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral treatments</td>
<td></td>
<td>Generic Name</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>10.1 (9.03-11.2)</td>
<td>Glipizide</td>
</tr>
<tr>
<td>Biguanides</td>
<td>15.0 (13.6-16.4)</td>
<td>Metformin</td>
</tr>
<tr>
<td>Meglitazones</td>
<td>0.76 (0.56-0.96)</td>
<td>Nateglinide</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>0.08 (0.06-0.03)</td>
<td>Acarbose</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>2.30 (1.89-2.71)</td>
<td>Sitagliptin</td>
</tr>
<tr>
<td>Sulfonylurea and biguanide</td>
<td>1.88 (1.52-2.24)</td>
<td>Glyburide and metformin</td>
</tr>
<tr>
<td>Sulfonylurea and glitazone</td>
<td>0.35 (0.23-0.47)</td>
<td>Rosiglitazone maleate and glimepiride</td>
</tr>
<tr>
<td>Biguanide and glitazone</td>
<td>2.05 (1.67-2.43)</td>
<td>Rosiglitazone maleate and metformin hydrochloride</td>
</tr>
<tr>
<td>Biguanide and DPP-4</td>
<td>0.49 (0.34-0.64)</td>
<td>Sitagliptin and metformin hydrochloride</td>
</tr>
<tr>
<td>Injectable treatments</td>
<td></td>
<td>Lantus</td>
</tr>
<tr>
<td>Long-acting insulin analogues</td>
<td>4.23 (3.62-4.84)</td>
<td>Insulin glargine</td>
</tr>
<tr>
<td>Intermediate insulins</td>
<td>0.88 (0.66-1.10)</td>
<td>Human insulin (NPH insulin)</td>
</tr>
<tr>
<td>Regular insulins</td>
<td>0.95 (0.72-1.18)</td>
<td>Human insulin (regular)</td>
</tr>
<tr>
<td>Ultrashort-acting insulin analogues</td>
<td>1.65 (1.32-1.98)</td>
<td>Insulin lispro</td>
</tr>
<tr>
<td>Combinations including analogues</td>
<td>1.02 (0.78-1.26)</td>
<td>Insulin aspart protamine and insulin aspart</td>
</tr>
<tr>
<td>Human insulin combinations</td>
<td>0.99 (0.75-1.23)</td>
<td>Insulin regular and NPH insulin</td>
</tr>
<tr>
<td>Incretins</td>
<td>1.24 (0.96-1.52)</td>
<td>Exenatide</td>
</tr>
<tr>
<td>Amylin analogues</td>
<td>0.08 (0.03-0.13)</td>
<td>Pramlintide acetate</td>
</tr>
<tr>
<td>Inhaled treatments</td>
<td></td>
<td>Human insulin</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl-peptidase-IV; FDA, US Food and Drug Administration; NPH, isophane.

aName represents original brand name first approved by the FDA, which may differ from current most frequently reported drug name (generic or brand).
 reported (treatment visits) increased from 25 million (95% CI, 23 million to 27 million) in 1994 to 30 million (28 million to 32 million) in 2000 and to 36 million (34 million to 38 million) in 2007. The proportion of total diabetes visits for which no medication therapy was reported increased from 15% (95% CI, 13%-17%) in 1994 to 18% (16%-20%) in 2000 and to 20% (18%-22%) in 2007. The mean number of medications prescribed per treatment visit increased from 1.06 medications per visit in 1994 to 1.45 in 2007. When individual components of combination products were counted separately, an increase was seen from 1.14 components per visit in 1994 to 1.63 in 2007.

CHANGES IN MEDICATION CLASSES USED AS DIABETES THERAPY

Significant shifts occurred in the medications used for diabetes therapy (Table and Figure 1). In 1994, pharmacotherapy for diabetes was divided between insulin preparations (38%; 95% CI, 34%-42% of treatment visits) and sulfonylureas (67%; 67%-73%). By 2007, a variety of newer drug classes also were used to treat diabetes. In 2007, the most frequent therapies were metformin (the only available biguanide; 54%; 95% CI, 49%-59% of treatment visits), sulfonylureas (34%; 31%-37%), glitazones (28%; 25%-31%), insulin (28%; 25%-31%), sitagliptin phosphate (only available DPP-4 inhibitor; 8%; 7%-9%), and exenatide (only available incretin; 4%; 3%-4%).

INSULIN USE

Insulin use decreased from 38% (95% CI, 34%-42%) of treatment visits in 1994 to a nadir of 25% (22%-27%) in 2000, only to increase to 28% (25%-31%) by 2007. Nearly all insulin use in 1994 was in the form of regular and intermediate-acting (eg, NPH) preparations. In 1994, 25% of treatment visits involved patients receiving a prescription for regular insulin and 21% involved patients receiving a prescription for intermediate-acting insulin, with approximately one-third of regular insulin use in combination with other therapies.
combination products (Figure 2). By 2000, use of each of these preparations had decreased, particularly for regular insulin (14% of treatment visits) compared with NPH (18%).

Since 2001, the use of newer insulin preparations has been rapidly increasing. Ultrashort-acting insulin analogues (available in 1996) and combinations that include them have increased from 2% of treatment visits in 2001 to 7% in 2007, with approximately half in the form of combination products. Likewise, long-acting insulin analogues (available in 2000) increased from 2% in 2001 to 12% in 2007. With the increase of these newer insulins, use of older insulin preparations has continued to decrease. In 2007, the use of regular insulin (5% of treatment visits) and NPH (5%), including their combinations, together constituted only 30% of all treatment visits with insulin. The use of single-component insulin monotherapy (eg, NPH alone) decreased from 48% of all insulin treatment visits in 1994 to 22% in 2007. Inhaled insulin was introduced in January 2006 but, because of its limited adoption (less than 1% of treatment visits in 2007), this product was removed from the market in November 2007. The most common individual insulin therapies in 2007 were insulin glargine and insulin lispro.

SULFONYLUREAS

Once the mainstay of diabetes therapy (67%; 95% CI, 61%-73%), sulfonylureas were used in only 34% (31%-37%) of treatment visits in 2007. This change was notably slower between 1994 and 1999 (60%) and more rapid recently. Combination drugs, including sulfonylureas, were first available in 2000. These drugs increased to 11% of treatment visits by 2003 but decreased to 6% in 2007. Most combination therapy in 2007 was a sulfonylurea combined with metformin (5% of treatment visits). Combination therapy accounted for 18% of all sulfonylurea use in 2007. Sulfonylurea monotherapy declined from 94% of all sulfonylurea use in 1994 to 30% in 2007. In 1994, the most common individual sulfonylurea was glyburide. In 2007, the most common individual noncombination sulfonylurea was glipizide, whereas those most common in combination products were glyburide and glimepiride (with metformin) and glimepiride (with glitazones).

BIGUANIDES

As a safer biguanide than phenformin (removed from the market in 1977), metformin was released in the United States in 1995. This drug was rapidly adopted (18% of treatment visits in 1996 and 38% in 2000). After surpasing sulfonylureas as the leading class of diabetes treatment in 2004 (48%; 95% CI, 44%-52%), metformin use has continued to increase (2007: 54%; 49%-59%). Metformin-containing combination products were introduced in 2000 (with sulfonylureas), 2002 (with glitazones), and 2007 (with sitagliptin). In 2007, these combinations accounted for 12% of treatment visits or 23% of all metformin use, including metformin and sulfonylurea (5% of treatment visits), metformin and glitazone (6%), and metformin and sitagliptin (1%).

GLITAZONES (THIAZOLIDINEDIONES)

The first glitazone, troglitazone, was approved in 1997. This drug was adopted rapidly so that by 1998 it accounted for 10% (95% CI, 8%-12%) of treatment visits. Because of hepatotoxicity, however, troglitazone was removed from the market in 2000. With the addition of rosiglitazone maleate (1999) and pioglitazone hydrochloride (1999), this class continued to increase until peaking at 34% (95% CI, 31%-37%) of treatment visits by 2005, then decreased to 28% (25%-31%) by 2007. A significant reduction in use was evident during 2007. The use of glitazone combinations (introduced in 2002) has increased to constitute 24% of all glitazone uses in 2007. Glitazone use as monotherapy increased from 1997 (2% of treatment visits) to 2004 (9%), then decreased to 7% of treatment visits during 2007 (25% of all glitazone use). The most commonly used individual glitazone has shifted from troglitazone in 1999 to rosiglitazone (59% of...
glitazone uses by 2004) to pioglitazone (64%) in 2007. In 2007, a further shift was seen toward pioglitazone, with an associated 63% decrease in rosiglitazone use.

**NEWLY AVAILABLE MEDICATIONS**

Several recently released medications have shown rapid early adoption into practice, although several more years of data will provide a more accurate assessment of their places in therapy. Sitagliptin, a DPP-4 inhibitor released in October 2006, increased to 10% of treatment visits by the fourth quarter of 2007 (8%; 95% CI, 7%-9%; for all of 2007). Exenatide, an injectable incretin initially derived from Gila monster saliva, was released in June 2005. By 2006, exenatide accounted for 3% (95% CI, 2%-4%) of treatment visits but with only modest increase to 4% by the fourth quarter of 2007.

Three other new classes of diabetes medications have not been widely adopted. α-Glucosidase inhibitors were noted at less than 1% of treatment visits since their first approval in 1996 and decreased to less than one-half percent by 2007. Use of the short-acting meglitinide secretagogues, available since 2000, peaked in 2002 at 3% of visits but were used in only 2% of treatment visits in 2007. Released in 2005, the injectable amylin analogue, pramlintide acetate, accounted for less than one-half percent of treatment visits in 2007.

**COMBINATION PRODUCTS**

In aggregate, combination products with 2 constituent medications have increased substantially from 9% (95% CI, 9%-9%) of treatment visits in 1994 to a peak of 21% (19%-24%) in 2004 before decreasing to 19% (17%-21%) in 2007. As a proportion of treatment visits, insulin combinations peaked in 1995 at 10% and have since decreased to 6% in 2007. Oral combinations increased rapidly after being introduced in 2000 to 15% of treatment visits in 2004 but have failed to increase further (13% in 2007). At the peak of oral and insulin combination therapy use in 2004, these combinations were the only therapy provided in 14% of treatment visits or 66% of all combination product use. By 2007, these products were less likely to be used as sole therapy (11% of treatment visits or 59% of all combination product use).

**PRESCRIPTION DRUG EXPENDITURES**

Drug expenditures and prescription prices increased rapidly between 2001 and 2007 according to our analysis of the IMS Health NPA data (Figure 3 and Figure 4). Aggregate drug expenditures for diabetes increased by 87% from $6.7 billion in 2001 to $12.5 billion in 2007. Major contributors to this increase were glitazones and combination products, including glitazones ($1.9 billion to $4.2 billion), ultrashort-acting insulins and their combinations ($0.4 billion to $1.9 billion), and long-acting insulins ($0.1 billion to $2.0 billion). During this same period, decreases were seen in metformin and sulfonylurea expenditures. The mean price of a diabetes drug prescription increased from $56 in 2001 to $76 in 2007. This increase was due to increasing use and increasing prescription prices of glitazones ($119 in 2001 to $160 in 2007) and increased use of more costly newer drugs, including ultrashort-acting insulins ($156 in 2007), long-acting insulins ($123 in 2007), exenatide ($202 in 2007), and sitagliptin ($160 in 2007). The cost of metformin ($63 to $29) and sulfonylurea ($27 to $20) prescriptions decreased during this same period.

**COMMENT**

Our study, which used a large and nationally representative survey of physician office visits, indicates the increasing complexity and cost of diabetes pharmacotherapy. The increased complexity we describe is due to several factors, including more combined products, more medications per patient, and greater numbers of drugs and drug classes available. The rapid diffusion of several of these new therapeutic classes demonstrates the success of translational research in bringing innovative
medications to market and into widespread use. Exenatide and sitagliptin both act on new metabolic pathways that were not exploited by preexisting drugs. Although less innovative than some new drugs, the introduction of insulin analogues with short and long effective half-lives has prompted renewed interest in insulin therapy. New insulin analogue costs have increased from $0.5 billion (2001) to $3.9 billion (2007) because of increasing drug prices, the expanding population of individuals with diabetes, and increased selection of these preparations. In contrast, glitzone costs have more than doubled from $1.9 billion to $4.2 billion because of more patients and increased drug prices, despite the relatively constant likelihood of physicians selecting glitzones. Potential negative effects of increased financial burden on patients with diabetes because of therapy costs have been examined and include reduced medication adherence and disease control. Although increasing costs of therapy are partly attributable to more patients with diabetes and more medications per patient, the greatest contributor to increasing costs is the substantially greater use of newer, more costly medications.

Although many of these newer therapies have made therapy more convenient and may have potentially lowered the risk of treatment-associated complications, further research of their long-term benefits is needed. Mean hemoglobin A1c levels among patients with diabetes have decreased between 1999 to 2000 (7.6%) and 2003 to 2004 (7.1%). Changes in drug selection are a potential explanation, as are a reduced diagnostic threshold, better patient medication adherence, increased self-management of the disease by patients, and increased use of dietary and physical activity strategies. Cost-effectiveness analyses are lacking to demonstrate that these higher treatment costs yield proportionate improvements in outcomes. Substantial outcome differences would be needed to overcome the high cost of the newer drugs, with prescription costs for glitzones, exenatide, and sitagliptin 8 to 10 times those of sulfonylureas and 5 to 7 times those of metformin. Also, to the extent that increasing drug costs have been associated with more intensive goals for glycemic control, the potential harms associated with such goals raise further concerns about the cost-effectiveness of recent trends.

The diffusion of glitzones and exenatide into widespread use also has resulted in off-label use of these drugs. For example, although these drugs are approved by the US Food and Drug Administration as adjuncts to other diabetes medications, they are commonly used as monotherapy. Rapid diffusion of these drugs creates the potential for substantial exposure to these medications before definitive assessment of their safety. For example, we estimate that 7 million monthly prescriptions for exenatide were dispensed before the US Food and Drug Administration's recent warning about the potential risk of pancreatitis associated with this medication.

The rapid adoption of glitzones since their market release in 1997 is important to consider given the earlier removal of troglitazone because of its hepatotoxicity and the recent concern regarding the potential cardiovascular risks of at least 1 member of this drug class. Although further research is needed to clarify these cardiovascular risks, the lack of data regarding the comparative benefit of glitzones over other drug classes is noteworthy. Such a pattern of early diffusion and rapid adoption of new drugs followed by the emergence of concerns for potential harms is a recurrent pattern and one that might be addressed at least in part by changes to the system of drug regulation in the United States.

Despite the rapid diffusion of some new classes of diabetes medications, other classes have not been adopted. The limited use of α-glucosidase inhibitors, pramlintide, inhaled insulin, and the metaglinide secretagogues may reflect specific disadvantages of each of these medications. Nonetheless, it is not clear which factors are associated with rapid adoption vs lack of adoption. For example, it does not appear that characteristics such as drug cost, adverse effect profile, safety concerns, biological innovativeness, or dosing convenience are consistently associated with a greater likelihood of successful diffusion.

Our study has 3 important limitations. First, our data do not allow us to examine questions related to processes and outcomes of care, such as how the diagnosis of diabetes was made, prior treatment failures, adequacy of glycemic control, and impact of treatment on diabetes-related morbidity and mortality. Second, physicians report their best knowledge of what drugs the patient is taking; therefore, our data do not account for medication nonadherence. Third, we are unable to evaluate the appropriateness of therapy. Both overuse and underuse are likely to remain important challenges in diabetes pharmacotherapy.

In conclusion, significant increases in diabetes prevalence, the number of diabetic patient visits, complexity of diabetes pharmacotherapy, the availability of new, innovative therapies, and the cost of diabetes therapy have occurred in the past 15 years. We document large shifts in patterns of diabetes treatment and pharmaceutical expenditures across treatment classes. Whether increased treatment costs are balanced by improved outcomes associated with these changes cannot be evaluated in the absence of data comparing effectiveness and cost-effectiveness across treatment classes. Our findings suggest the importance of generating new comparative data and coupling this information with clinical and formulary guidelines that contribute to constraining costs, maximizing glycemic control, and minimizing diabetes-related morbidity and mortality.

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Correspondence: G. Caleb Alexander, MD, MS, Department of Medicine, Section of General Internal Medicine, The University of Chicago, 5841 S Maryland, MC 2007, Chicago, IL 60637 (galexand@uchicago.edu).

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