Rapid Increase in the Use of Oral Antidiabetic Drugs in the United States, 1990–2001

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OBJECTIVE — To describe the use of oral antidiabetic drugs for management of type 2 diabetes in the U.S. from 1990 through 2001.

RESEARCH DESIGN AND METHODS — Data on oral antidiabetic drugs were derived from two pharmaceutical marketing databases from IMS Health, the National Prescription Audit *Plus* and the National Disease and Therapeutic Index.

RESULTS — In 1990, 23.4 million outpatient prescriptions of oral antidiabetic agents were dispensed. By 2001, this number had increased 3.9-fold, to 91.8 million prescriptions. Glipizide and glyburide, two sulfonylurea medications, accounted for ~77% of prescriptions of oral antidiabetic drugs in 1990 and 35.5% of prescriptions in 2001. By 2001, the biguanide metformin (approved in 1995) had captured ~33% of prescriptions, and the thiazolidinedione insulin sensitizers (rosiglitazone and pioglitazone marketed beginning in 1999) accounted for ~17% of market share. Compared with patients treated in 1990, those in 2001 were proportionately younger and they more often used oral antidiabetic drugs and insulin in combination. Internists and general and family practitioners were the primary prescribers of this class of drugs.

CONCLUSIONS — Consistent with the reported increase in the prevalence of type 2 diabetes, the number of dispensed outpatient prescriptions of oral antidiabetic drugs increased rapidly between 1990 and 2001. This period was marked by an increase in the treatment of younger people and the use of oral antidiabetic drugs in combination. With the approval in the last decade of several new types of oral antidiabetic medications with different mechanisms of action, options for management of type 2 diabetes have expanded.

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Oral medications for the management of type 2 diabetes have been available in the U.S. since 1957, when the sulfonylurea drug tolbutamide was approved by the Food and Drug Administration (FDA). This was followed in the 1950s and 1960s by the approval of other first-generation sulfonylureas—chlorpropamide, acetohexamide, and tolazamide. A biguanide, phenformin, was approved in 1959 for use in the management of type 2 diabetes, but its association with fatal lactic acidosis resulted in its recall as an "imminent hazard" in 1977 (1,2).

Two second-generation sulfonylureas, glipizide and glyburide, were introduced in the U.S. in 1984. More than a decade later in 1995, the second biguanide, metformin, was approved by FDA, followed in 1996 by glimepiride, a sulfonylurea; acarbose, the first α-glucosidase inhibitor; and repaglinide, a nonsulfonylurea insulin secretagogue. In 1997, troglitazone, the first thiazolidinedione insulin sensitizer, was approved, but it was withdrawn in 2000 due to liver toxicity. The thiazolidinedione insulin sensitizers rosiglitazone and pioglitazone and the second glucosidase inhibitor miglitol were marketed beginning in 1999.

This article describes the use of oral antidiabetic drugs in the U.S. from 1990 through 2001. A previous article on this topic that used the same databases (1) covered trends from 1964 through 1986.

RESEARCH DESIGN AND METHODS

— National data on drug products approved for treatment of type 2 diabetes were derived from two pharmaceutical marketing research databases purchased from IMS Health (National Prescription Audit *Plus* [NPA *Plus*] and National Disease and Therapeutic Index [NDTI]). NPA *Plus* provides national estimates of prescriptions dispensed by chain, independent, food store, mail order, and long-term care pharmacies (3). For the period 1996–2001, IMS Health's pharmacy database consisted of ~34,000 reporting pharmacy stores. The number of dispensed prescriptions was obtained from a sample of ~22,000 randomly selected stores and projected nationally. The pharmacies in the database account for 40% of pharmacy stores and represent 45% of prescription coverage, according to estimates by IMS Health.

The design features and sampling frame of the NPA *Plus* have changed over time in the direction of greater representation and statistical accuracy. For the period of this report, the most significant changes occurred in 1992 with the addition to the sampling frame of food stores and the states of Alaska and Hawaii and the increase from 2,500 to 20,000 in the number of computerized pharmacies in the sample. The database accessed by FDA was also expanded in 1997 to include prescriptions from mail order houses and in 2001 from long-term care facilities. Although NPA sampling meth-

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Abbreviations: FDA, Food and Drug Administration; NDTI, National Disease and Therapeutic Index; NPA *Plus*, National Prescription Audit *Plus*; UKPDS, U.K. Prospective Diabetes Study.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Estimated number of dispensed outpatient prescriptions (in millions) for oral antidiabetic drugs in the U.S. in 1990, 1996, and 2001*

Generic name	Trade name	Date marketed	1990	1996	2001
Sulfonylureas					
Tolbutamide	Orinase	1957	0.8 (3)	0.2 (<1)	0.08 (<1)
Chlorpropamide	Diabinese, glucamide	1958	3.2 (14)	1.1 (3)	0.3 (<1)
Acetohexamide	Dymelor	1964	0.2 (1)	0.02 (<1)	0.006 (<1)
Tolazamide	Tolinase	1966	1.1 (5)	0.3 (1)	0.1 (<1)
Glipizide	Glucotrol, glucotrol XL	1984	5.1 (22)	11.6 (28)	17.9 (19.5)
Glyburide	Diabeta, micronase, glynase	1984	13.0 (55)	19.3 (47)	14.7 (16.0)
Glimepiride	Amaryl	1996	—	0.2 (<1)	6.1 (6.7)
Biguanide					
Metformin	Glucophage	1995	—	7.8 (19)	30.0 (32.7)
Combination*					
Glyburide-metformin	Glucovance	2000	—	—	4.5 (4.9)
Glucosidase inhibitors					
Acarbose	Precose	1995	—	0.5 (1)	0.5 (0.5)
Miglitol	Glyset	1999	—	—	0.2 (0.2)
Nonsulfonylurea insulin secretagogues					
Repaglinide	Prandin	1998	—	—	1.4 (1.5)
Nateglinide	Starlix	2001	—	—	0.5 (0.5)
Thiazolidinedione insulin sensitizers					
Troglitazone†	Rezulin	1997	—	—	—
Rosiglitazone	Avandia	1999	—	—	8.2 (8.9)
Pioglitazone	Actos	1999	—	—	7.2 (7.9)
Total			23.4	41.0	91.7

Data are *n* (%). Source: IMS Health, National Prescription Audit *Plus*, Plymouth Meeting, PA, extracted June 2002. *Combination sulfonylurea and biguanide; †14 million dispensed outpatient prescriptions from the start of marketing in 1997 until withdrawal due to hepatotoxicity in 2000.

odologies have changed over time, the data have always been projected to obtain national prescription estimates. The NPA *Plus* database was used to obtain the estimated annual number of dispensed outpatient prescriptions for each oral antidiabetic drug included in the Uniform System of Classification class 39200, oral agents for diabetes.

The second database, the NDTI, provides descriptive information on the patterns and treatments of diseases encountered in office-based medical practices in the U.S. (4). Data are obtained from a panel of 2,000–3,000 participating physicians who report on each patient-physician contact in the office, in the hospital, on the telephone, or elsewhere for 2 consecutive working days per calendar quarter. These data are also projected nationally. The sampling methodologies of the two databases are described elsewhere in more detail (5).

By convention, NDTI uses the term "mentions" for drug reports. A mention refers to a drug in association with a diagnosis during a patient-physician contact. Mentions are not directly equivalent to prescriptions because access to a drug product can be gained in a number of ways, including written prescriptions, authorized refills, office samples, etc. However, we have observed that for most drugs, mentions are primarily associated with written prescriptions. For instance, in 2001, 53% of mentions for Glucophage (metformin) were for issuance of a prescription or a prescription and a sample, 1% were for issuance of a sample, 2.5% involved a hospital order, 26% had no prescription (or sample) that visit (probably with discussion of continued therapy), and 16% were unspecified as to disposition (3). The category "recommended," which is a small proportion of mentions for most drugs, was 1% for metformin.

RESULTS — In 1990, 23.4 million outpatient prescriptions for oral antidiabetic medications were dispensed in the U.S. By 2001, this number had increased 3.9-fold to 91.8 million prescriptions (Table 1). Through 1996, the market was dominated by the use of the second-generation sulfonylurea medications glipizide and glyburide. These two medications together accounted for ~77% of prescriptions in 1990 and 75% in 1996. With the introduction of the biguanide metformin in 1995 and the thiazolidinedione insulin sensitizers in 1997, the proportion of prescriptions dispensed for sulfonylureas decreased, despite the marketing of a new sulfonylurea, glimepiride. By 2001, prescriptions for glipizide and glyburide accounted for 35.5% of market share, whereas metformin captured nearly 33%, and the thiazolidinedione insulin sensitizers rosiglitazone and pioglitazone together accounted for ~17% (Table 1). Several new types of antidiabetic drugs, the glucosidase inhibitors (consisting of acarbose and miglitol) and the nonsulfonylurea insulin secretagogues (consisting of repaglinide and nateglinide), together accounted for only ~3% of market share in 2001.

Compared with 1990, in 2001 a larger proportion of patients who were prescribed oral antidiabetic drugs were in the 40- to 59-year-old age group (Table 2). However, rates of diabetes increase with age, and older individuals remain the largest group of consumers of these

Table 2—*Characteristics of patients and physicians (%) based on U.S. patient-physician encounters* for oral antidiabetic drugs, 1990, 1996, and 2001*

	1990		1996		2001	
	Male	Female	Male	Female	Male	Female
Patient age (years)						
<20	0	0	0	0	0	0
20–29	0	1	1	1	1	1
30–39	3	2	3	4	5	5
40–40	10	9	12	12	15	14
50–59	18	15	22	20	25	22
60–69	34	31	27	27	26	26
70–79	25	28	26	26	21	22
≥80	8	14	8	11	7	9
% M/F	43	57	48	52	49	51
Therapy						
New	8		15		17	
Continued	92		85		83	
Concomitant drugs†						
Used alone	92		78		61	
Used with:	8		22		39	
Insulin‡	4		5		9	
Oral hypoglycemic‡	<1		15		29	
Physician specialty						
Internal medicine	41		41		39	
General family practice	36		31		33	
Osteopathic medicine	8		10		11	
Cardiology	5		6		4	
Endocrinology	4		5		6	
All others	6		7		7	

Data are %. *For the age/sex distributions, there were 16.7 million antidiabetic drug appearances in 1990, 20.2 million in 1996, and 31.9 million in 2001; †concomitant drugs are for the primary indication mentioned; ‡numbers do not add due to rounding and lack of mention of other therapies. Source: IMS Health, National Disease and Therapeutic Index, Plymouth Meeting, PA, extracted June–August, 2002.

drugs. Also, compared with 1990 levels, in 2001 an increasing proportion of patients began rather than continued therapy, which reflects the number of new drugs and is also consistent with the observed increase in incidence of type 2 diabetes in the U.S. For 1990, 1996, and 2001, the proportion of prescriptions that were refills was similar, ranging from 66 to 69%. Associated with the introduction of metformin in 1995, there has been a substantial increase in the co-prescribing of oral antidiabetic drugs. Consistently throughout the period of 1990 through 2001, mentions for these drugs were made most often in visits to internists and family and general practitioners.

CONCLUSIONS — The period of 1990 through 2001 saw the approval and marketing of many new oral antidiabetic medications for the management of type 2 diabetes in the U.S. In the early 1990s, the sulfonylurea drugs glyburide and glipizide were the primary medications prescribed for this condition. The introduction of metformin in 1995 and of the thiazolidinedione insulin sensitizers rosiglitazone and pioglitazone in 1999 contributed to a percent decline in prescriptions for glyburide and glipizide in 2001. Nevertheless, these two medications continued to capture more than one-third of the market of oral antidiabetic drugs in 2001, whereas metformin captured nearly one-third, and the thiazolidinedione insulin sensitizers accounted for 17%. All the other drugs combined accounted for only 15% of the market share.

During the 11-year period from 1990 to 2001, a 3.9-fold increase (from 23.4 million to nearly 92 million) occurred in dispensings of outpatient prescriptions for oral antidiabetic drugs. Only 21.5 million prescriptions were dispensed in 1986 (1). This rapid increase in prescriptions coexists with the increase in the incidence of type 2 diabetes in the U.S. In the data presented here, the largest proportionate increase in prescriptions between 1990 and 2001 was for 40- to 59-year-old individuals.

The prevalence of diagnosed diabetes in U.S. adults increased from 4.9% in 1990 to 6.9% in 1999 (6). Because obesity and duration of obesity are major risk factors of type 2 diabetes (7–9), the increase in prevalence of this disease and consequent use of oral antidiabetic drugs correspond to the increase in the prevalence of obesity. The age-adjusted prevalence of obesity (BMI >30 kg/m^2) in the U.S. increased from nearly 23% in the period 1988–1994 to 30.5% in 1999–2000 (10). Other factors that have contributed to the increase in the prevalence of diabetes include a change in the definition of diabetes to lower blood glucose levels (11) and the aging and ethnic composition of the population (12).

Besides the increasing prevalence of type 2 diabetes, the increase in prescriptions for oral antidiabetic drugs is also attributable to an increase in the frequency of co-prescribing drugs in this class. Such co-prescribing of these drugs and insulin was shown by the U.K. Prospective Diabetes Study (UKPDS) to increase the probability of achieving glycemic control (13), which delays the onset and slows the progression of diabetic complications (11,13–15). The importance of achieving glycemic control was determined by the landmark UKPDS and the Diabetes Control and Complications Trial (11,13–15), which were conducted in the 1990s.

The prescription data presented in this article are limited by the following methodological considerations: the data are based on prescriptions rather than persons; the data do not address duration of use; and the sampling schemes are not statistical samples, so the results may not be representative. Furthermore, the sampling schemes have changed over time and these changes could affect trend data. Pertinent to the data presented in this report, the mail order and long-term care channels were added during the 1990s; however, they constitute a relatively small proportion of total prescriptions, and inclusion of these channels is in the direction of greater population coverage and

more accurate estimates. For less-popular singular drugs, the descriptive information from NDTI is based on relatively small samples with wide confidence intervals about the estimates; in contrast, NDTI estimates for the class of oral antidiabetic drugs included in this article are based on large numbers of patient-physician visits, which result in narrow confidence intervals and more accurate estimates. The IMS Health data are purchased by pharmaceutical companies, the FDA, and other government agencies to obtain timely drug use information. The IMS Health databases yield results that are generally consistent with other health surveys and databases.

With these data, we are able to track drug use over time. Since their introduction some 40 years ago, the first-generation (primarily chlorpropamide) and then the second-generation (glyburide and glipizide) sulfonylurea drugs have been the mainstays of type 2 diabetes management. With the approval in 1995 through 2001 of new medications with different mechanisms of action, options for management of type 2 diabetes have expanded.

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