Trends in Use of Oral Hypoglycemic Agents 1964–1986

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Oral hypoglycemic (OH) agents have been available in the United States for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) for almost 30 yr. During this time they have been subject to considerable controversy. In this article, we present pharmaceutical marketing research data that provide a review of several facets of OH use. The number of OH prescriptions dispensed peaked in 1973, decreased through 1980, and has been increasing since that year. In 1986, OH agents accounted for 21.5 million prescriptions: 1% of all prescriptions dispensed that year. Chlorpropamide is currently the most frequently ingested OH agent; it is used by 33% of the market. The two OH agents introduced in 1984, glyburide and glipizide, had acquired 41% of the OH market by the end of 1986. The rate of OH use per 1000 diabetes mellitus visits increases with patient's age. Patients aged 60 yr and older received OH prescriptions at a rate of 478 per 1000 diabetes mellitus visits in 1986. Data estimating both the number of patients diagnosed with diabetes and the number of diabetic patients taking OH agents indicate that the percentage receiving OH treatment has increased over the past 5 yr, with ~35% of all diabetic patients taking OH agents in 1986. *Diabetes Care* 11:558–62, 1988

Oral hypoglycemic (OH) agents have been available in the United States for use in the management of non-insulin dependent diabetes mellitus (NIDDM) since tolbutamide was approved by the Food and Drug Administration (FDA) in 1957. The OH class expanded through the 1960s with the approval of the rest of the so-called first-generation sulfonylureas: chlorpropamide in 1958, acetohexamide in 1964, and tolazamide in 1966. In addition to these early sulfonylureas, a biguanide, phenformin, was approved by the FDA in 1959 for use in the management of NIDDM.

The ability of these agents to lower blood glucose is unquestioned. However, their long-term efficacy is not as straightforward. Only a portion of NIDDM patients can be expected to achieve satisfactory blood glucose control on a long-term basis (1). The ideal candidate for OH therapy is a patient who is older at the onset of the disease and who has had known diabetes for a short time (1).

The long-term safety of OH agents has also been questioned. The publication of the findings of the University Group Diabetes Project (UGDP) in 1970 suggested that there was an increase in cardiovascular mortality in patients treated with tolbutamide (2). Later, the same group reported a similar finding for phenformin (3). The UGDP findings were questioned regarding the validity of analysis and conclusions (4). The American Diabetes Association initially supported the results of the UGDP but reassessed its position in 1979 and recommended that any decisions regarding the use of tolbutamide based on the UGDP results be held in abeyance (5). No consensus on the UGDP results has ever been reached, and diabetologists to this day remain sharply divided on their acceptance of the UGDP conclusions (6,7). Separate from the UGDP, the association of phenformin with fatal lactic acidosis ultimately resulted in the product's formal recall in 1977 (8). Thus, the 1970s

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was a period when risks associated with the use of OH agents became recognized.

However, the appeal of oral medications to treat NIDDM continued to exist. Physicians perceive that their patients are more compliant in taking oral medications than in injecting insulin, and patients themselves prefer the convenience of oral treatment (9). In 1984, glipizide and glyburide, the so-called second-generation sulfonylureas, were approved for use in the United States. These drugs are much more potent than the older products in this therapeutic class, although the advantage of increased potency as opposed to duration of activity has been questioned (10). The primary therapeutic differences among the sulfonylureas are in duration of action, elimination half-life, and relative potencies (11).

We describe trends in the use of OH agents from 1964 to 1986, a period that includes the major events in the history of this therapeutic class.

MATERIALS AND METHODS

Drug use data were derived from three subscription pharmaceutical marketing research data bases that the FDA purchases from IMS America (Plymouth Meeting, PA): the National Prescription Audit (NPA), the National Disease and Therapeutic Index (NDTI), and the U.S. Pharmaceutical Market-Drugstores (USD).

The NPA provides information on prescriptions dispensed by chain and independent pharmacies in the continental United States; other outlets such as discount stores and supermarkets with pharmacies are not included. Since 1981, the NPA has been based on prescriptions dispensed by a panel of 1200 computerized pharmacies. Because data collection is dependent on computerized pharmacies, the panel does not represent a true random sample. However, IMS America does ensure that the panel is representative of United States pharmacies in terms of geographic region, type of ownership, and pharmacy size. From 1973 to 1981, data were obtained from a representative sample of 800 pharmacies; each was audited for 2 days/month. Before 1973, a panel of 400 stores reported 4 days each month. Therefore, changes from 1980 to 1981 and from 1972 to 1973 in the number of prescriptions reported by the NPA may reflect methodologic revisions as well as actual changes in drug use. The NPA provided data for this study on the number of prescriptions dispensed and the average daily dose prescribed by physicians.

The NDTI provided descriptive information on disease patterns and treatment in office-based practice in the continental United States. Data were obtained from a panel of >2000 physicians representing 19 specialties. These physicians reported case-history information on each private patient seen or contacted in any setting during 2 consecutive working days each quarter. Data collected from the NDTI physician panel are projected to >250,000 office-based physicians in the United States. Drugs recorded by the physician during each patient contact (i.e., formal prescription, recommendation, direct administration) are termed *drug mentions*. A drug mention is not equivalent to patient use. We have assumed, however, that trends in drug mentions by physicians will reflect trends in actual drug use by patients. One or more diagnoses can be recorded per patient visit and no drugs, one drug, or several drugs may be mentioned in association with each diagnosis. Diagnoses are coded according to the World Health Organization's International Classification of Diseases, seventh edition (ICD-7). The NDTI projection methodology was substantially revised in 1974; therefore, any analyses conducted with NDTI data are limited to 1974–1986.

Data from the NDTI were used to characterize the age-specific use of OH agents in the treatment of diabetes mellitus (ICD-7 code 260.0). Drug data were standardized as drug mentions per 1000 visits per year for each age group.

The USD measured the flow of pharmaceuticals into drugstores (i.e., pharmacies, discount houses, and proprietary stores) by collecting monthly invoices from a panel of 840 drugstores and a near census of chain and wholesale warehouses. These data were then projected nationally. IMS America revised sampling methods for

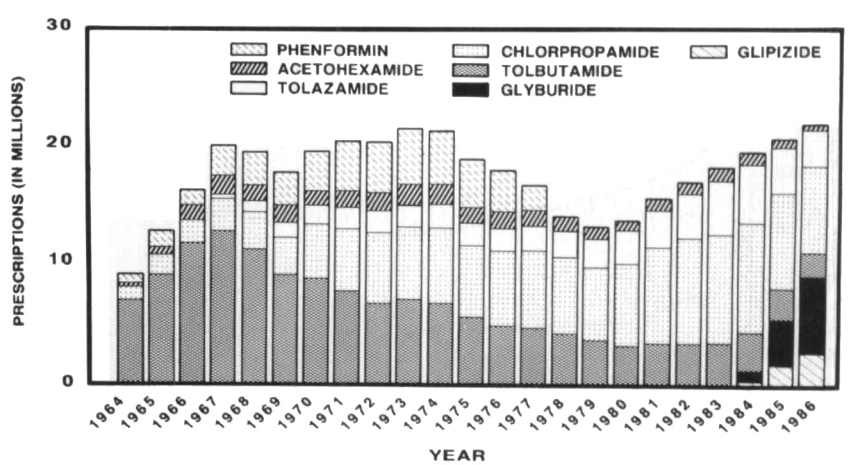

FIG. 1. Prescriptions for oral hypoglycemic agents from 1964 to 1986.

the USD data base in 1981 and 1982 to incorporate census-level data from wholesale and chain warehouses. Data before the 1982 change were not reprojected. Therefore, data analysis is limited to the 5-yr period from 1982 to 1986. USD data were used to calculate estimated population exposure to the OH agents.

For each year, the number of kilograms of each OH agent purchased by drugstores was divided by the average dose prescribed per day (from the NPA) and then by 365 days to provide an estimate of the number of people who could have been treated for an entire year given the quantity of drug purchased during that year.

An estimate of the number of patients diagnosed as having diabetes was determined by applying 1978 age- and sex-specific prevalence rates (12) to the yearly United States population based on the midyear civilian population each year (13).

To examine the distribution of OH mentions by product type (first-generation vs. second-generation OH agents) for patient's age group (<60 vs. ≥60 yr old), we used the χ^2-statistic. To examine the secular trend in the estimated proportion of diabetic patients treated with OH agents over the period 1982–1986, we used the arcsine transformation to normalize the data (14). Linear regression was then used with the transformed variable as the dependent outcome, and the *F* value was determined.

RESULTS

Prescription trends. Figure 1 shows trends in the use of the OH agents as measured by prescriptions dispensed by retail pharmacies from 1964 to 1986. Use of these drugs peaked in 1973 and then decreased. In the 1980s, these agents experienced a resurgence in popularity with a continuing increase in use. In 1986, the OH class accounted for 21.5 million prescriptions or ~1% of all prescriptions dispensed that year.

In 1964, tolbutamide was the most frequently used OH agent with 75% of the market. In 1973, tolbutamide was still the most frequently used OH agent, but its market share had dropped to 33%. By 1986 it accounted for only 10%. Chlorpropamide is currently the most frequently used OH agent, accounting for 33% of all 1986 prescriptions in this class. Before the introduction of the second-generation sulfonylureas, it had comprised as much as 53% of the market. The newer agents, glyburide and glipizide, have been readily accepted in the United States. By the end of 1986, glyburide and glipizide had garnered over 41% (glyburide with 29% and glipizide with 12%) of OH prescriptions.

Phenformin accounted for 9% of dispensed OH agents in 1964. At its peak in 1973 it was the second most frequently dispensed OH agent with almost 22% of the market. Its use declined until it was withdrawn from the general market. The drug is still available for certain patients under a "compassionate" provision in the FDA regulations. However, this use would not be measured by the NPA. Given the overall decline in the use of the OH therapeutic class through the 1970s, it is difficult to guess to which other products (if any) former phenformin users may have been switched. Tolazamide was the only one of the class that experienced an increase in use during the 1970s.

Use of oral hypoglycemic agents by age. In 1986, over half (56%) of mentions of the use of the OH agents by office-based physicians were for people ≥65 yr of age. An additional 14% were 60–64 yr old. Twenty-seven percent were between 40 and 59 yr old, and only 3% of the mentions were for people ≤39 yr old. That same year, patients for whom the second-generation products were mentioned were more likely to be <60 yr of age than those for whom the first-generation OH agents were mentioned ($P < .0001$). Not surprisingly, age distribution for diabetes mellitus [both insulin-dependent diabetes mellitus (IDDM) and NIDDM] office visits in 1986 had a somewhat different distribution than the distributions for OH mentions. Fifty-one percent of patients visiting doctors' offices were ≥65 yr, 13% were 60–64 yr old, 27% were 40–69 yr old, 7% were 20–39 yr old, and 2% were <20 yr old.

Figure 2 shows the rate of OH mentions per 1000 diabetes mellitus visits by age group by year. Data in Fig. 2 generally mirror the prescription data in Fig. 1 by showing decreasing rates of drug mentions in the 1970s.

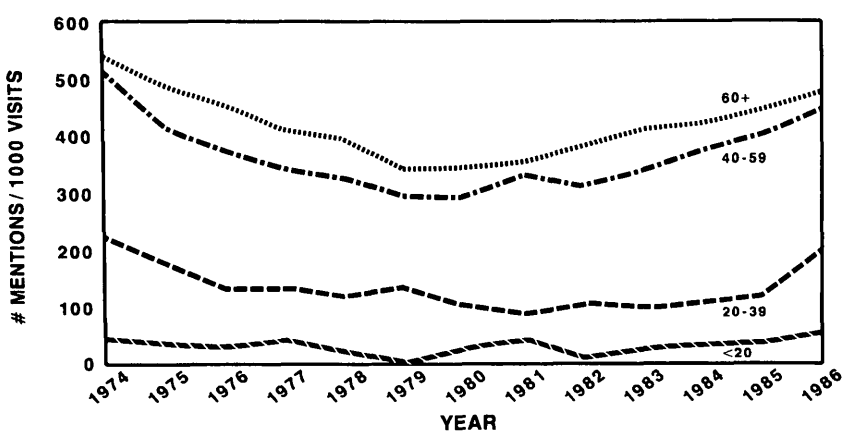

FIG. 2. Rate of oral hypoglycemic mentions per 1000 diabetes mellitus visits by age group.

In the 1980s the rate began increasing again. The data also show that, as would be expected, older diabetic patients receive OH agents more frequently than younger ones. Unfortunately, these data do not permit us to distinguish between IDDM and NIDDM.

Population exposure. Table 1 provides estimates of the number of patients diagnosed yearly as having diabetes from 1982 to 1986. Estimates are also given in this table for the number of people taking OH agents each year. As can be seen, both the estimated number of diabetic patients and the estimated number of people taking OH agents have increased slightly over this 5-yr period. The proportion of diabetic patients treated with OH agents from 1982 to 1986 increased ($P = .009$) in this period.

DISCUSSION

The official labeling for all OH agents provides a specific reminder that these drugs are not first-line therapy (15).

> In initiating treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential for the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible.

However, for the NIDDM patient whose blood glucose levels do not fall into a satisfactory range after an appropriate trial of diet and exercise, the treating physician must decide to initiate drug therapy or to leave the patient with blood glucose levels that can potentially cause hyperglycemic symptoms. Current medical wisdom suggests that even if a physician is not convinced that tight control changes the incidence or severity of diabetes complications, the patient should not be left with elevated blood glucose levels (16). Some of these patients may have few problems with using insulin to control their symptoms, but others may have great difficulty in adapting and adhering to an insulin regimen. The greatest benefit of OH agents may well be in the treatment of this latter group. However, OH therapy obviously cannot control blood glucose adequately for all diabetic patients, and it is known that the primary and secondary failure rates for these agents are high (1). From our data it appears that the limitations of the OH agents are recognized and that the use is restricted to a subgroup of patients.

Data also indicate that the number of prescriptions dispensed for OH agents as a class decreased in the 1970s during the UGDP controversy. The 1980s have seen a steady increase in prescription volume for these products. We can speculate that much of this increase is due to the increasing number of diabetic patients in an aging population coupled to a lesser extent with a waning influence of the UGDP. The newer products seem to have claimed part of the market formerly held by the older products. Our data suggest that physicians are more likely to prescribe the newer OH agents to younger patients (i.e., those <60 yr of age) and to maintain or start older patients on the first-generation OH agents. The prescribing of OH agents is compatible with their effectiveness in patients with NIDDM and lack of effectiveness in patients with IDDM.

Unfortunately, we do not have any data on the effect of marketing (e.g., dollars spent on advertising, number of visits by pharmaceutical-company representatives) on the use of each of the sulfonylureas. We believe marketing plays a significant role in the choice of one OH agent over another. Promotion of the second-generation products glipizide and glyburide has no doubt contributed to their rapid acceptance and to the percentage of the market share they now hold.

It is important to note the limitations of our data. The NPA provides data on outpatient drug use only, so use in hospitals and nursing homes is not covered. Because the NPA provides information only on prescriptions dispensed by chain and independent pharmacies, other important drug sources such as supermarkets and mail-order houses are not included. For the variables discussed in this article, trends observed in drugs dispensed from the retail pharmacies covered by the NPA would probably be seen in other marketing outlets as well. The NDTI data are derived entirely from the prescribing practices of office-based physicians, which may or may not be similar to prescribing by hospital-based physicians. Finally, our estimates of the percentage of diagnosed diabetic individuals treated and OH agents from 1982 to 1986 assumed that the age- and sex-specific

TABLE 1
Estimated percentage of diagnosed diabetic patients treated with oral hypoglycemic agents: 1982–1986

	Year				
	1982	1983	1984	1985	1986
Estimated number of diagnosed diabetic patients* (in millions)	5.55	5.62	5.68	5.74	5.83
Estimated number of patients taking oral hypoglycemic agents† (in millions)	1.64	1.81	1.83	2.02	2.08
Estimated percentage treated with oral hypoglycemic agents	29.5	32.2	32.2	35.2	35.7

*Estimation based on sex- and age-adjusted prevalence rates for diagnosed diabetes (1978 NCHS: National Health Interview Survey; 12) applied to midyear U.S. civilian population data (13).
†Quantity of drugs purchased by drugstores each year divided by the average prescribed dose for each drug that year divided by 365 equals the estimated number of patients who could have taken the drugs for an entire year.

prevalence rates of diabetes in the 1980s have remained constant and that treated diabetic patients actually took their prescribed daily dose every day of the year. Despite these limitations, these data provide useful information on the national use of OH agents that has previously been lacking in the literature.

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