Utilization of Drug Sales Data for the Epidemiology of Chronic Diseases: The Example of Diabetes

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An indirect method for estimating the prevalence rates of chronic diseases that are treated by specific drugs was proposed in 1988 to European countries in the framework of a European Community concerted action on diabetes epidemiology. Data on consumption of antidiabetic drugs were collected at the national level in nine countries and at a regional level in two. Using official drug sales data and recent demographic data, we estimated the diabetes prevalence rates in each country or region. The estimated diabetes prevalence in Europe varied from 1.6% in Northern Ireland to 4.7% in Malta. In four countries that already had diabetes prevalence data, the estimation through drug consumption provided figures 3–20% lower than those from field surveys. This study showed a large variety of prescribing habits for diabetic patients in Europe (for example, the proportion of insulin-treated patients varies from 13% to 36%) and underscores the need for a consensus on antidiabetic treatments based on valid clinical research. The proposed approach does not replace field surveys but provides an inexpensive and practical marker of disease frequency and therapeutic attitudes over space and time. (Epidemiology 1993;4:421–427)

Keywords: chronic diseases, diabetes mellitus, drug consumption, prevalence, pharmacoepidemiology, insulin, biguanides, sulfonylurea compounds.

Morbidity data for chronic diseases are poorly documented in many countries. In Europe, there are several registers on specific cancers, ischemic heart disease, and some other chronic diseases, but they are often restricted to regions. The other classical approach, through prevalence surveys on random population samples, is hardly feasible and very expensive. Nevertheless, knowledge of the public health impact of chronic diseases and their evolution is crucial for planning health care facilities and preventive strategies in aging populations.

This paper focuses on the utilization of drug sales data for epidemiology, here applied to diabetes. These data are routinely collected and available in most in-

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dustrialized countries, but generally neglected by epidemiologists. The definitions provided by the Drug Utilization Research Group of the World Health Organization (WHO)[1] were first applied to diabetes, which appeared to be a relevant model for this application.[2,3] The methodology was then developed for estimating the number of diabetic patients in France[4,5] and proposed to European countries, in the framework of the European Community (EC) concerted action program on diabetes epidemiology (EURODIAB).[6]

Methodology

Rationale

In chronic diseases, patients are often prescribed a daily treatment, taken all year long. If the treatment is a drug specific to the disease, and the total amount (T) of this drug sold in 1 year is known with accuracy, then it is possible to estimate the total number (N) of patients taking the drug. The key parameter is the average daily dose of the drug in the population having the studied disease. This parameter was called the Prescribed Daily Dose (PDD) by the experts of the WHO Drug Utilization Research Group.[1] It should not be confused with the Defined Daily Dose, which is the dose recommended for the major indication of the drug.

In the simplest situation, $N = T/(365 \times PDD)$. T is obtained from official statistics, and PDD can be estimated in random samples of patients. Finally, the prevalence rate is obtained by dividing N by the size of the total population.

The method is valid if (1) the treatment is specific to the disease; (2) the drug is taken daily all year long; and (3) reliable total drug sales data are available. If several drugs are prescribed for a disease and are combined in some patients, the calculations are a little more complicated, since they involve correction factors to avoid double counting.

Application to Diabetes

Diabetes is a chronic disease having all three characteristics described above. Three main classes of antidiabetic drugs are prescribed for diabetic patients: insulin (by injection), sulfonylureas, and biguanides (oral hypoglycemic agents). Insulin is given to insulin-dependent patients (Type 1), but also to non-insulin-dependent patients (Type 2) when they fail to respond to oral treatment. In addition, certain non-insulin-dependent patients are treated only with a restricted diet in the period following diagnosis.

The formulas used to calculate the number of diabetic patients in a population, through their prescription of insulin (I), sulfonylureas (S), and biguanides (B), are presented in the Appendix. They take into account all of the possible combinations of the three classes of drugs. The proportions of patients treated with combinations of drugs or by diet alone will be used as correction factors in the calculation of the number of subjects.

The EURODIAB Subarea C Study

This methodology was proposed to the 12 EC countries in the framework of the IVth research program of the European Community. Some countries were not able to participate, but other neighboring countries joined the Study Group. Finally, 11 countries were included: Belgium, France, Germany, Luxembourg, Italy, Malta, Northern Ireland, Rumania, Spain, Sweden, and Switzerland.

The great heterogeneity of the health care systems, medical insurance, distribution of drugs, social perception of diabetes, and level of confidentiality in these countries prevented the preparation of a highly detailed, strictly standardized protocol. Therefore, a general outline was proposed to the group, with the following steps:

1. Estimate the prescribed daily doses of insulin, sulfonylureas, and biguanides in random samples of insulin-treated and non-insulin-treated patients, the proportions of patients treated with any combination of two or three antidiabetic treatments (I + S and/or B; S + B), and, where possible, the proportion of diabetic patients treated by diet alone.

2. Obtain drug consumption data from reliable existing sources; convert the number of boxes of hypoglycemic oral drugs sold in 1 year into the number of tablets, and the number of boxes of insulin into the number of insulin units.

3. Obtain recent demographic data from administrative sources.

The central coordinator examined in detail the feasibility of performing the study in each country. The final local protocol, established in collaboration with the national coordinator, involved either representative samples of patients by a cluster procedure, through samples of physicians (Luxembourg, Malta, Northern Ireland, Spain), pharmacists (Belgium, Switzerland), or the use of an existing database (France, Germany, Italy, Rumania, Sweden). In Italy and Spain, the data were collected in small regions (Cremona and Avila, respectively), representing less than 1% of the general population; therefore, the results cannot be generalized to the whole country. In Switzerland, data regarding prescriptions were collected in the largest canton, the

TABLE 1. Population Basis and Sampling for Determination of Prescribed Daily Doses of Antidiabetic Drugs, EURODIAB EC Concerted Action, 1988–1991

Country	Population	Year	Sample	Number of Patients
Belgium	10,000,000	1990	107 pharmacies	884
France	56,000,000	1986–1990	80 laboratories	1,172
Germany	61,000,000	1985–1986	National survey	91
Italy (Cremona)	162,000	1988–1989	2 diabetes centers + 143 physicians	2,358
Luxembourg	378,000	1990–1991	40 physicians	957
Malta	349,000	1989	7 health centers + 1 diabetes center	1,565
Northern Ireland	1,580,000	1990–1991	70 physicians	1,529
Rumania	23,000,000	1989	9 district centers	44,800
Spain (Avila)	182,000	1989	48 physicians	1,328
Sweden	8,600,000	1989–1990	National survey	415,000*
Switzerland	6,800,000	1990	38 pharmacies	370

* Patient-visits for diabetes.

Canton of Bern, which represents one-seventh of the total population and has been considered as representative of the country with respect to diabetes occurrence. The general features of the populations studied and sampling procedures are presented in Table 1. In countries where a specific survey was set up, the sampling of physicians or pharmacists was based on demographic data (stratified on population density) or medical structures (specialized centers/general practitioners).[7,8] The database from Germany (Federal Republic of Germany at the time of the survey) provided results from a national pharmacoepidemiologic survey including 4,760 subjects age 25–69 years.[9] The participants were selected at random from the general population. Of these, 91 were treated with drugs for diabetes. The French survey included patients recruited in 80 medical analysis laboratories.[5] In Sweden, the prescriptions were recorded in a national survey on drug utilization from 415,000 patient-visits for diabetes. In Italy, the data were derived from an ongoing census of all diabetic patients in the town of Cremona. A national diabetes register was used in Rumania. In five countries, Italy, France, Malta, Rumania, and Sweden, the prevalences obtained through drug consumption have been compared with previous direct estimates.

The mean value of the different PDDs and their 95% confidence intervals (mean ± 2 standard error of the mean) were used to calculate the 95% confidence interval for the final observed prevalence rate. The 95% confidence limits correspond to the limits of the 95% confidence interval of the PDDs, using the lowest and the highest values for all types of antidiabetic drugs.

Results

Prescribing Habits

The average prescribed daily doses for insulin, sulfonylureas, and biguanides are shown in Table 2. A relative homogeneity was observed for insulin prescription. As a whole, the PDDs of insulin were close to the Defined Daily Dose recommended by WHO (40 units).

The intercountry differences were larger for the PDDs of oral drugs. For sulfonylureas, the values ranged between one and two tablets per day, which is on the average a little lower than the dose defined by WHO, about two tablets per day. The prescription of biguanides was reported as negligible in Germany and Avila; consequently, the number of patients was too small for estimation of the PDD.

Note that the Italian figure for the PDD of oral drugs is for sulfonylureas and biguanides combined, because in that country, the distribution of the differ-

TABLE 2. Prescribed Daily Doses (PDD)

Country	Insulin	Sulfonylureas	Biguanides
Belgium	41 ± 16	1.9 ± 1.0	2.7 ± 1.3
France	40 ± 18	2.1 ± 1.1	2.0 ± 0.7
Germany	39 ± 14	1.5 ± 0.7	NA*
Italy (Cremona)	38 ± 19	1.8 ± 0.9	
Luxembourg	47 ± 15	1.9 ± 0.9	1.7 ± 0.7
Malta	35 ± 15	1.5 ± 1.0	1.3 ± 1.3
Northern Ireland	46 ± 22	1.8 ± 1.0	2.4 ± 0.9
Rumania	46†	2.8†	2.8†
Spain (Avila)	33 ± 19	1.2 ± 0.9	NA
Sweden	46†	1.6†	2.5†
Switzerland	40 ± 19	1.6 ± 0.9	1.9 ± 0.9

* NA: not assessed; sample size too small.
† Standard deviation not assessed.

TABLE 3. Percentages of Diabetic Patients Treated with a Combination of Drugs or with Diet Alone

Country	Percentage of Patients		
	P_{IBS}*	P_{BS}†	P_D‡
Belgium	15	20	NA§
France	6	32	15
Germany	5	3	NA
Italy (Cremona)	40	NA	21
Luxembourg	10	29	13
Malta	10	7	50
Northern Ireland	0	13	42
Rumania	Negligible	22	27
Spain (Avila)	Negligible	Negligible	42
Sweden	Negligible	19	41
Switzerland	23	6	38

* Percentage of insulin-treated patients receiving sulfonylureas (S) and/or biguanides (B).
† Percentage of orally treated patients receiving a combination of sulfonylureas (S) and biguanides (B).
‡ Percentage of non-insulin-treated patients treated by diet alone.
§ NA: not assessed.

ent types of tablets was not assessed (both drugs are often associated in the same tablet, generally in equivalent proportions).

The most striking differences were related to the prescription of combined antidiabetic treatments and to the proportion of patients on diet alone (Table 3). Tablets were prescribed in addition to insulin (p_{IBS}) in 0–40% of the insulin-treated patients, and sulfonylureas were combined with biguanides (p_{BS}) in 3–32% of the orally treated patients. Of the 11 countries, nine were able to provide the proportion of diabetic patients treated by diet alone (p_D; the figure for Switzerland was drawn from a previous survey of physicians[10]), which varied from 13% to 50% of the non-insulin-treated patients.

Estimated Prevalence Rates

Using data from Tables 2 and 3 and the total drug sales of each antidiabetic drug for the corresponding target populations (data not shown), the prevalence rates by treatment group and overall were calculated (Table 4). The available prevalence data are given in the last column. All were higher than the overall rate based on drug consumption. The difference was small in France, compared with the result of a national survey performed on a sample of physicians,[11] and in Sweden, compared with the average value of different studies performed in different areas.[12] In Italy, the prevalence was close to that from a census of all known cases in Cremona. In Malta, there was a 20% difference in comparison with previous studies.[13,14] For Rumania, the prevalence rate is not presented, since a large discrepancy exists between the estimation through drug consumption (0.05%), and the official figure (2.18%) from the national statistics (I Mincu, personal communication, 1990). Thus, it was clear that the proposed methodology was inadequate in Rumania.

Pattern of Treatments

The distribution of the different treatments among the drug-treated diabetic population is derived from the preceding results. It appears that the proportion of insulin-treated patients was very different among European countries. The highest percentages were observed in Northern Ireland (46% of the drug-treated patients), Sweden (40%), Belgium (39%), Switzerland (38%), and, to a lesser degree, Luxembourg (33%); in the other countries, insulin treatment was under 30%: France and Malta (19%), Italy (21%), Germany (26%), and Spain (27%).

Conversely, the highest proportions of orally treated patients were found in France, Malta, and Cremona.

TABLE 4. Diabetes Prevalence (Percentage) by Treatment Group and Overall Prevalence

Country	Insulin Treated (1)	Orally Treated (2)	Drug Treated (1) + (2)	Diet Alone (3)	Overall (1) + (2) + (3)	Direct Estimate
Belgium	0.7	1.0	1.7 (1.6–1.8)†	NA*	NA	
France	0.4	1.3	1.7	0.2	1.9 (1.8–2.0)†	2.1[11]
Germany	0.7	2.2	2.9	NA	NA (2.5–3.2)†	
Italy (Cremona)	0.5	1.7	2.2	0.5	2.7 (2.6–2.8)†	2.8‡
Luxembourg	0.5	1.1	1.6	0.2	1.8 (1.7–1.9)†	
Malta	0.5	2.1	2.6	2.1	4.7 (4.4–5.1)†	5.9[13,14]
Northern Ireland	0.5	0.6	1.1	0.5	1.6 (1.5–1.7)†	
Spain (Avila)	0.6	1.5	2.1	1.1	3.2 (2.8–3.6)†	
Sweden	0.8	1.2	2.0	0.9	2.9	3.0[12]
Switzerland	0.5	0.7	1.2	0.4	1.6 (1.5–1.8)†	

* NA: not assessed.
† 95% confidence interval.
‡ Result of a census: 4,547 diabetic patients in 164,000 inhabitants.

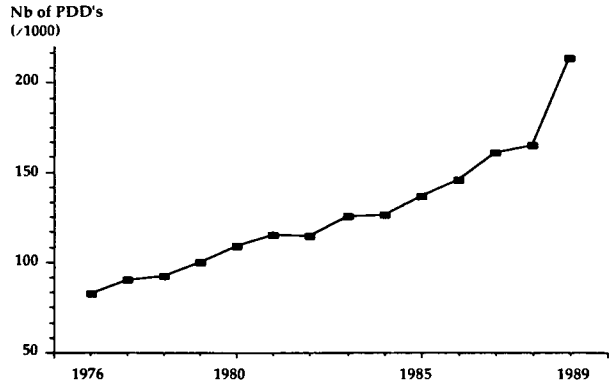

FIGURE 1. Insulin consumption in France from 1976 to 1989 (number of PDDs per 1,000 patients).

Analysis of the prescription pattern for the different oral antidiabetic drugs among drug-treated patients by country revealed the following features: sulfonylureas were widely used in all countries; biguanides (alone or in combination) were not prescribed in Avila and were given rarely in Malta and Germany, but frequently in Belgium and Luxembourg (37% of the orally treated patients) and in France (56%). The combination of both drugs was used in less than 10% of patients on oral treatment in Germany, Malta, Spain, and Switzerland.

Follow-up of Drug Consumption

In France, the antidiabetic sales of insulin from 1976 to 1990, provided by the French Ministry of Health (Figure 1), showed a regular increase of about 6% per year up to 1988. At that time, human insulin and the insulin pen were put on the French market, inducing a sudden 30% increase in the sales of insulin. This phenomenon could not be explained by a corresponding increase in the number of insulin-dependent patients.

Discussion

The present study started in 1988, just 1 year before WHO and the International Diabetes Federation (IDF) decided to promote an international diabetes task force. Two meetings led to the well-known Saint Vincent Declaration for the improvement of diabetes care in Europe.[15] Unfortunately, the real size of the problem was not assessed on the basis of reliable data in most of the populations represented at that assembly. As successively stressed in different reviews on diabetes epidemiology,[16-18] more descriptive data and etiologic research are needed, especially on Type 2 diabetes, which is the more prevalent and, so far, the least investigated form of the disease. Except for the prevalence rates mentioned in the present paper, there are very few data assessed at the national level in Europe.

In this European study, we had to overcome many difficulties, due to the disparity of the national health care systems. We tried to obtain comparable data in different ways. The drug consumption approach, although imperfect, provides an approximation to the frequency of diagnosed disease, which probably correlates well with its actual socioeconomic cost. Of course, this method is inadequate for detecting undiagnosed cases. Thus, the objectives were not to establish the individual risk of diabetes for comparison among different populations, but rather to assess the burden of this pathology in each country. Along this line, it appeared interesting, from the public health point of view, to examine the crude prevalence rates of known cases. The age distribution was not available in all samples, so we were not able to estimate adjusted prevalence rates. The interpretation of the differences between countries should therefore take into account the differences of age in general populations. They are similar in most European countries, with some exceptions. The low diabetes prevalence in Northern Ireland, together with a high proportion of insulin-treated patients, could be partly explained by the proportion of people under 15 years of age, which reaches 25% in this population. In contrast, the Swedish and German populations are characterized by an excess of elderly people (more than 20% over age 60), which results in a higher population at risk, particularly for Type 2 diabetes.

The necessary conditions for the validity of the method are met in most industrialized countries: supply of drugs to any patient requiring them, and reliability and availability of official drug sales data and of recent demographic data. The failure of the method in Rumania, a country that is experiencing a very difficult period in its evolution, is a striking illustration. In Malta, we suspect that the 20% difference could be due to an underdeclaration of privately imported medication, rather than to a poor estimation of the prescribed daily doses. When the data are reliable, an underestimation by no more than 10% seems systematic, in comparison with field surveys. One possible cause of underestimation could be linked to some biases in the recruitment of the samples, since the agreement of many participants was required to obtain the data: physicians or pharmacists at the first stage,

patients at the second stage. The classical problem in these surveys is the possibility of a selection bias, tending to recruit more strictly treated patients (those who go regularly to the doctor or to the pharmacist). Any systematic registration of the physician's prescription (as in Northern Ireland) represents a more adequate tool than a sampling procedure. Another bias, perhaps the more important, is related to the poor compliance to drug treatment in a portion of the orally treated subjects, as has been observed in hypertensive patients.[19] In both cases, it is likely that the prescribed daily dose would be overestimated, leading to an underestimation of the total number of diabetic subjects. Studies on drug compliance, however, are scarce and difficult to obtain. Once the magnitude of the underestimation has been estimated, it is possible to correct the prevalence rate from antidiabetic drug sales figures.

Another feature of the drug consumption method is the possibility of studying the distribution of the different treatments among the population having the disease. In the early 1990s, there was a large variety of therapeutic approaches for diabetic patients in Europe. This diversity had already been observed in Nordic countries and Northern Ireland some years before in a study based on three case histories submitted to random samples of physicians.[20] The differences related to insulin prescription can be partly explained by a different distribution of Type 1 and Type 2 diabetes in the populations, Type 1 being more prevalent in the north than in the south of Europe.[21] Another important factor could be the tendency to shift poorly controlled non-insulin-dependent patients to the most efficient hypoglycemic drug: insulin. Usually considered as a classical therapeutic policy in northern countries, it remains a rather exceptional procedure in southern countries. Tablets are often used in Mediterranean countries: France, Italy, and Malta. In this context, the data from Avila are surprising because they are quite similar to those from Germany. But we must keep in mind that the survey was performed locally and cannot be generalized to all of Spain. The same restriction holds for the survey in Cremona, but to a lesser extent, since the observed pattern of treatment is consistent with that observed in two previous studies performed in Italy, one in the south,[22] and the other at the national level.[23]

Other between-country differences can be highlighted: (1) use of a single antidiabetic drug in Germany, Northern Ireland, and Spain, but use of an association of two or three drugs in Belgium, France, and Italy; (2) prescription of low daily doses in Germany, Malta, and Spain, and of high doses in Belgium, Northern Ireland, Rumania, and Sweden; (3) use of diet alone, low in France, Italy, and Luxembourg, but common in the other countries.

Obviously, in spite of efforts to reach a consensus,[24] there is so far no policy for diabetes treatment in Europe. In particular, the choice between either insulin or large doses of sulfonylureas (mainly glibenclamid) in Type 2 patients with repeated acute hyperglycemic episodes deserves more clinical research in the framework of strictly controlled therapeutic trials. A large debate looms, since both insulin and sulfonylureas have been questioned as possible risk factors for cardiovascular complications.[25,26] Insulin tends to be prescribed more often than in the past, at least in France, but this change is probably due to the practical advantage of the insulin pen, as metabolic control is not necessarily improved with insulin.[27]

Besides these conclusions regarding diabetes, the methodology based on drug consumption could be appropriate for other diseases. A similar approach based on drug prescription in the province of Rome has been validated recently to identify cases of tuberculosis.[28] The markers of disease frequency will never replace field surveys, but they can provide useful information, in particular for detecting variations over time.

References

1. World Health Organization Regional Office for Europe. Studies in Drug Utilization: Methods and Applications. Regional Publications. European Series. Geneva: World Health Organization, 1979;8.
2. Bergman U, Sjöqvist K. Measurement of drug utilization in Sweden: methodological and clinical implications. Acta Med Scand 1984;683:15–22.
3. Stika L. Patterns in drug utilization—national and international aspects: antidiabetic drugs. Acta Med Scand 1984;683:53–57.
4. Fontbonne A, Papoz L, Eschwège E. Drug sales data and prevalence of diabetes in France. Rev Epidemiol Santé Publique 1986;34:100–105.
5. Papoz L, Vauzelle F, Vexiau P, Cathelineau G. Pattern of treatment among diabetic patients in France. Diabetes Care 1988;11:586–591.
6. Fuller JH. European Community Concerted Action Programme in Diabetes (EURODIAB). Diabetic Med 1989;6:278.
7. Walckiers D, Van der Veken J, Papoz L, Stroobant A. Prevalence of drug-treated diabetes mellitus in Belgium. Eur J Pharmacol 1992;43:613–619.
8. de Beaufort C, Michel G, Haas N, Wirion R, Glaesener G. Consommation des médicaments antidiabétiques au Grand Duché de Luxembourg. Bull Soc Sci Med Grand-Duché Luxemb 1991;2:5–9.
9. Melchert HU, Hoffmeister H. Validation of questionnaire data on consumption of pharmaceuticals in a pharmacoepidemiological study by determination of serum levels of selected active substances. J Clin Res Drug Dev 1988;2:184–185.
10. Teuscher T, Teuscher AU, Teuscher A. Diabetes-Häufigkeit in der Schweiz. In: Stahelin HB, Lüthy J, Casabianca A, Monnier

N, Müller HR, Schutz Y, Sieber R, eds. Dritter Schweizerischer Ernährungsbericht. Bern: Federal Office of Public Health, 1991;413–422.
11. Mesbah M, Chwalow J, Vauzelle-Kervroedan F. Prevalence of diabetes in France with associated risk factors by regions. Presented at the XIIth Scientific Meeting of the International Epidemiological Association, Los Angeles, August 1990.
12. Workshop: Treatment of Non-Insulin Dependent Diabetes Mellitus. Uppsala: Medical Product Agency, 1990;1–213.
13. Schranz AG, Prikatsky V. Type I diabetes in the Maltese Islands. Diabetic Med 1989;6:228–231.
14. Schranz AG. Abnormal glucose tolerance in the Maltese: a population-based longitudinal study of the natural history of NIDDM and IGT in Malta. Diabetes Res Clin Pract 1989;7:7–16.
15. Workshop Report. Diabetes care and research in Europe: the Saint Vincent Declaration. Diabetic Med 1990;7:360.
16. Rewers M, LaPorte RE, King H, Tuomilehto J. Trends in the prevalence and incidence of diabetes: insulin-dependent diabetes mellitus in childhood. World Health Stat Q 1988;41:179–189.
17. King H, Zimmet P. Trends in the prevalence and incidence of diabetes: non-insulin-dependent diabetes mellitus. World Health Stat Q 1988;41:190–196.
18. Papoz L. Recent trends in the epidemiology of diabetes mellitus in European and Mediterranean countries. Acta Diabetol 1991;28:140–142.
19. Degoulet P, Menard J, Vu HA, Goldmard JL, Devries C, Chatellier G, Plouin PF. Factors predictive of attendance at clinic and blood pressure control in hypertensive patients. Br Med J 1983;287:88–93.
20. World Health Organization Drug Utilization Research Group (DURG). Therapeutic traditions in Northern Ireland, Norway and Sweden. I. Diabetes. Eur J Clin Pharmacol 1986;30:513–519.
21. Green A, Gale EAM, Patterson CC for the EURODIAB ACE Study Group. Incidence of childhood-onset insulin dependent diabetes mellitus. Lancet 1992;339:905–908.
22. Vaccaro O, Imperatore G, Ferrara A, Palombino R, Riccardi G. Epidemiology of diabetes mellitus in southern Italy: a case-finding method based on drug prescriptions. J Clin Epidemiol 1992;45:835–839.
23. Garancini P, Gallus G, Calori G. Incidence and prevalence of diabetes mellitus in Italy from routine data: a methodological assessment. Eur J Epidemiol 1991;7:55–63.
24. Alberti KGMM, Gries FA. Management of non-insulin-dependent diabetes mellitus in Europe: a consensus view. Diabetic Med 1988;5:275–281.
25. Stout RW. Insulin and atheroma: 20-yr perspective. Diabetes Care 1990;13:631–654.
26. Ferner RE, Alberti KGMM. Sulphonylureas in the treatment of non insulin-dependent diabetes. Q J Med 1989;73:987–995.
27. UK Prospective Diabetes Study Group. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. Diabetologia 1991;34:877–890.
28. Maggini M, Salmaso S, Alegiani SA, Caffari B, Raschetti R. Epidemiological use of drug prescriptions as markers of disease frequency: an Italian experience. J Clin Epidemiol 1991;44:1299–1307.

Appendix

Estimating Prevalence Rates

Define the following terms:

PDD_I = the average prescribed daily dose of insulin in number of insulin units (I)

PDD_S = the average prescribed daily dose of sulfonylureas (S), in number of tablets

PDD_B = the average prescribed daily dose of biguanides (B), in number of tablets

N = the population of the country or region considered

S_I = the total number of units of insulin sold in 1 year

S_S = the total number of tablets of sulfonylureas sold in 1 year

S_B = the total number of tablets of biguanides sold in 1 year

p_{IBS} = the proportion of *insulin-treated* patients receiving, in addition, sulfonylureas, biguanides, or both

p_{BS} = the proportion of patients treated with *oral agents* (not insulin treated) using a combination of sulfonylureas and biguanides

p_D = the proportion of *non-insulin-treated* diabetic patients who are treated by diet alone.

Then, the estimated prevalence rates of diabetic patients, by treatment group, are:

Insulin: $P_I = S_I/(365 \times PDD_I \times N)$

Oral agents: $P_O = \{(S_S/PDD_S + S_B/PDD_B)/[365 \times N \times (1 + p_{BS})]\} - p_{IBS} \times P_I$

Non-insulin: $P_{non\text{-}I} = P_O/(1 - p_D)$

Overall: $P = P_I + P_{non\text{-}I}$.