Prescription patterns for *diabetes mellitus* and therapeutic implications: a population-based analysis

Padrões de prescrição e implicações terapêuticas para o diabetes melito: análise de base populacional

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ABSTRACT

Objective: To analyze drug prescriptions for insulin and oral antidiabetic drugs in type 1 and type 2 *diabetes mellitus* patients seen in the Brazilian Public Healthcare System (Unified Health System – SUS) in Ribeirao Preto, SP, Brazil. **Subjects and methods:** All the patients with diabetes seen in the SUS in the western district of Ribeirao Preto, SP, Brazil between March/2006 and February/2007 were included in the study. **Results:** A total of 3,982 patients were identified. Mean age of the patients was 60.6 years, and 61.0% were females. Sixty percent of the patients were treated with monotherapy. Doses of oral antidiabetic drugs were lower in monotherapy than in polytherapy. Ten patients received doses of glibenclamide or metformin above the recommended maximum doses, and in elderly patients there was no reduction in drug doses. **Conclusion:** Monotherapy with oral antidiabetic drugs was the predominant procedure, and the doses were not individualized according to age. Arq Bras Endocrinol Metab. 2012;56(2):120-7

Keywords

Unified Health System; *diabetes mellitus*; drug use, pharmacoepidemiology; drug prescriptions; database

RESUMO

Objetivo: Analisar as prescrições medicamentosas dos antidiabéticos orais e insulina em pacientes portadores de diabetes melito tipo 1 e tipo 2 atendidos pelo Sistema Único de Saúde (SUS) em Ribeirão Preto, SP, Brasil. **Sujeitos e métodos:** Todos os pacientes com diabetes atendidos no distrito sanitário oeste de Ribeirão Preto, SP, do SUS, entre março/2006 e fevereiro/2007, foram incluídos no estudo. **Resultados:** Foram identificados 3.982 pacientes com diabetes. Idade média dos pacientes foi de 60,6 anos e 61,0% do gênero feminino. Sessenta por cento foram tratados com monoterapia. A dose dos antidiabéticos foi menor em monoterapia quando comparada à politerapia. Dez pacientes receberam doses de glibenclamida e metformina acima da dose máxima recomendada. Além disso, em pacientes idosos, não houve redução da dose. **Conclusão:** A monoterapia com antidiabéticos orais foi prevalente e não houve individualização da dose de acordo com a faixa etária. Arq Bras Endocrinol Metab. 2012;56(2):120-7

Descritores

Sistema Único de Saúde; diabetes melito; uso de medicamentos, farmacoepidemiologia; prescrições de medicamentos; base de dados

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INTRODUCTION

Diabetes mellitus (DM), a chronic non-transmissible disease, is one of the most prevalent diseases in the world. According to the International Diabetes Federation, 6.6% of the worldwide adult population, and 6.0% of the Brazilian adult population had DM in 2010. It is estimated that by 2030, approximately 7.8% of the worldwide adult population will have DM (1).

Concerning DM treatment, it is important to emphasize that non-pharmacological treatment is essential

in the care of the disease. However, if non-pharmacological treatment does not lead to acceptable glycemic control, patients should receive oral antidiabetic drugs (OAD), or insulin, or both. In Brazil, the two pharmacologic classes of OAD available in the National List of Essential Medicines for DM treatment are biguanide (metformin), and sulfonylurea (glibenclamide and gliclazide), as well as the hormone insulin (2). The increasing number of subjects diagnosed with the disease suggests that it is necessary to study and understand the profile of OAD and insulin use. In addition, in a previous study in Brazil, the greatest part of direct costs of DM treatment was attributed to medication (48.2%) (3).

In the current context, pharmacoepidemiological studies are necessary and may be carried out using the computerized drug monitoring systems. Thus, it may possible to describe drug use patterns, analyze early signals of the irrational drug use, promote interventions to improve drug use, analyze quality control cycles, and promote continuous quality improvement (4-7).

Moreover, these studies are highly relevant in Brazil. According to the Ministry of Health, 80.0% of the Brazilian population use only the Brazilian Public Health System for their healthcare (8). Therefore, this study aimed at analyzing drug prescriptions for OAD and insulin in patients with DM types 1 and 2 seen in the Brazilian Unified Health System (SUS) of Ribeirao Preto, SP, Brazil.

SUBJECTS AND METHODS

Settings

Based on the SUS guidelines, the municipal health office of Ribeirao Preto, SP, divided the city into five healthcare districts: north, south, east, west and central, within which its 550,000 inhabitants were distributed in 2007. The five districts are meant to ensure that both primary and emergency care are close to people's homes. This study was carried out in the western district, which comprises a population of approximately 140,000 inhabitants and 8 healthcare units.

Subjects

All patients with DM types 1 and 2 used in the study were seen in the western district of Ribeirao Preto, SP. They were selected from the district database, and all patients who received at least one of the OADs (glibenclamide 5 mg; metformin 850 mg; gliclazide 80 mg) or insulin from March 2006 and February 2007 were included. There were 3,918 patients with DM types 1 or 2. Patients with DM type 2 who received prescriptions for gliclazide (26 patients) were not included in the statistical analysis due to the small size of group, and the total number of patients was reduced to 3,892.

Data source

The municipal health office of Ribeirao Preto, SP, has a computer database that includes all the information on medical prescriptions issued by the SUS in the city of Ribeirao Preto, SP. Information in this database includes patient identification, gender, age, generic drug prescribed, drug dispensing date, dose regimen, amount of drug dispensed, and the health unit where the drug was dispensed. Database information was updated simultaneously with patient care.

Drugs were dispensed monthly by the healthcare unit pharmacies upon presentation of a prescription, and were simultaneously recorded in the database. All the drugs on the National List of Essential Medicines are dispensed free of charge by the SUS (2). All the necessary information was collected from the database of a single pharmacist.

Data analysis

The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD)

The ATC/DDD is a system used to classify therapeutic drugs. It was used to stratify patients with DM into therapeutic groups according to the drug or drug combination prescribed: insulin, glibenclamide, metformin, metformin plus glibenclamide, glibenclamide plus insulin, metformin plus insulin, and metformin plus glibenclamide plus insulin. In addition, doses of glibenclamide, metformin and insulin were also analyzed using the ATC/DDD system, especially to define consumption doses (DDD per 1,000 inhabitants per day) (9).

Analysis of drug dose for the treatment of diabetes mellitus

Drug prescriptions were evaluated for each month of the study. It was possible to analyze insulin and OAD doses according to age and therapeutic group. Dose regimen for oral antidiabetic drugs and insulin in the treatment of DM has been well established using a number of individual dosing studies and analyses of the worldwide clinical database.

In the treatment with metformin, the usual starting dose is 500 mg orally twice a day, or 850 mg orally once a day. To get to the maintenance dose, doses should be

increased by 500 mg weekly or 850 mg every two weeks for patients who do not show adequate therapeutic response. The therapeutic dose range is from 1 to 2.55 g orally a day, divided into two to three doses, usually administered after the main meals (10,11).

In the treatment with glibenclamide, the usual starting dose is 2.5-5.0 mg daily. The dose is usually increased by 2.5 milligrams at weekly intervals, depending on the patient's response. The therapeutic dose range is from 1.25 to 20.0 mg a day, which may be given as single or multiple doses, usually before the main meals (10,12).

In the treatment with insulin, the dose is individualized according to the patient's needs. The average dose per patient with DM ranges from 0.7 to 1.5 U/kg/day. Obese patients may require doses of 2.0 U/kg/day due to insulin resistance. In the association of insulin with OAD, patients should continue taking OAD in the same dose (possibly reduced), administering insulin in a single dose at bedtime (starting with about 10.0 to 15.0U, or 0.2 U/kg in obese patients). The insulin dose is adjusted using 2.0, 4.0, or 6.0U (if capillary blood glucose level is consistently higher than 120, 140 or 160 mg/dL, respectively), every three days until target fasting plasma glucose level is reached (13,14).

Analysis of variation in dose and number of drugs used for *diabetes mellitus* treatment

As described above, drug prescriptions were evaluated for each month of the study. OAD and insulin doses were analyzed per patient to observe in which patients the doses were decreased, increased or maintained during the period. Furthermore, it was possible to analyze the number of drugs used for the DM treatment, classifying treatment as monotherapy or polytherapy and, at the end of the study, it was possible to examine in which patients the number of drugs prescribed for the treatment of DM was modified, and if changes were classified as simple addition (combination with another drug), addition by substitution (replacement with another drug), or drug withdrawal.

Ethics committee approval

This study was approved by the Research Ethics Committee of the Health Training Center at the School of Medicine of Ribeirao Preto, SP, Universidade de Sao Paulo, Brazil.

Statistical analysis

The statistical package for Social Sciences® (SPSS, version 11.5, 2002) and Microsoft Excel® (Microsoft Corporation, 2007) were used to record and analyze data. ANOVA was used to test the differences between the means of continuous variables with Gaussian distribution, and statistical significance was considered when $p < 0.05$.

RESULTS

There were 3,918 patients identified with DM types 1 or 2. After excluding patients to whom gliclazide was prescribed (26 patients), 3,892 patients were analyzed. There was a large proportion (55.0%) of elderly (≥ 60 years) individuals with mean age of 60.6 (± 13.2), and a higher proportion of females (61.0%).

Table 1 shows the Anatomical Therapeutic Chemical groups of this study in relation to the number of DM patients, their mean age, minimum and maximum ages.

Table 1. Age group profile and number of patients with *diabetes mellitus* in each Anatomical Therapeutic Chemical group

Anatomical Therapeutic Chemical groups		n = 3,892 (%)	Age (years)		
			Mean (SD)	Minimum	Maximum
Monotherapy	Insulin	131 (3.4)	51.2 (20.3)[a]	07	93
	Glibenclamide	959 (24.6)	64.1 (12.5)[b]	18	96
	Metformin	1,245 (32.0)	57.7 (13.5)[a]	14	96
Polytherapy	Metformin plus glibenclamide	1,112 (28.6)	61.3 (11.6)	23	92
	Glibenclamide plus insulin	60 (1.5)	64.2 (10.7)	40	90
	Metformin plus insulin	267 (6.9)	61.6 (12.1)	13	90
	Metformin plus glibenclamide plus insulin	118 (3.0)	60.6 (11.3)	27	85
Total		3,892	60.6 (13.2)	07	96

[a] $p < 0.05$ when compared with all Anatomical Therapeutic Chemical groups.
[b] $p < 0.05$ when compared with metformin, and metformin plus glibenclamide groups.
SD: standard deviation.

Box 1 shows therapeutic profiles of the patients with DM types 1 and 2 correlated with the age group and the respective mean dosages of metformin, glibenclamide, and insulin.

Figure 1 shows total consumption of defined daily doses per 1,000 inhabitants per day (DDD/1,000 inhabitants/day) of OAD and insulin.

Glibenclamide and metformin were prescribed to four and six patients at doses above 20.0 mg/day and 2,550 mg/day, respectively. In addition, metformin was prescribed to other 128 patients at a dose below 500 mg/day.

At the end of the study, it was possible to analyze in which patients the number of drugs prescribed was changed. There were 11.7% of changes in the therapeutic regimen of glibenclamide, and changes were simple addition (5.2%), addition by substitution (2.8%), and glibenclamide withdrawal (3.7%). With respect to metformin, there were 11.2% of changes in the therapeutic regimen, and changes were simple addition (6.0%), addition by substitution (2.1%), and metformin withdrawal (3.1%). For insulin, there were 18.4% modifications in the therapeutic regimen, and changes were simple addition (9.8%), addition by substitution (6.4%), and insulin withdrawal (2.2%).

Changes in OAD and insulin doses were analyzed during the period studied. Approximately 15.3%, 18.2%, and 13.3% of the patients receiving glibenclamide, metformin and insulin, respectively, had their doses increased. In addition, 4.7%, 3.4% and 10.9% of the patients receiving glibenclamide, metformin, and insulin, respectively, had their doses reduced.

DISCUSSION

In the present study, 60.0% of the patients identified were treated with only one drug, demonstrating a prevalence of monotherapy. Previous reports in the literature cited by Vauzelle-Kervröedan and cols., Bosi and cols., and Baviera and cols., also indicated a prevalence of monotherapy in 69.6%, 61.8% and 51.5% of the patients, respectively (15-17). However, in Colombia, Alba and cols. observed that polytherapy was more frequent, since 52.0% of the patients used a combination of OADs (18).

In the present study, 32.0% and 24.6% of the patients used metformin and glibenclamide, respectively, in monotherapy (Table 1). Other reports in the literature indicated values of 25.1%, 17.6%, and 32.8% for monotherapy with metformin, and 44.5%, 20.0%, and 18.9% for sulfonylurea (15,18,19). These results illustrate differences in OAD prescriptions. Indeed, biguanides and sulfonylurea are first-choice treatments, while metformin is mainly indicated for obese and insulin resistance patients, and glibenclamide is mainly used in patients with a normal body mass (13,20,21).

Gliclazide, another OAD available on the National List of Essential Medicines, was little prescribed in either monotherapy or polytherapy. The use of glicazide in the SUS is restricted to elderly patients. This OAD was only prescribed to 26 patients, and five of them used it in an inappropriate combination with glibenclamide. According to the Brazilian Society of Diabetes and the American Diabetes Association, when a combination of two or three OADs is required in the treatment of DM, agents from different classes should be used (13,20,22).

Since glibenclamide, gliclazide, and metformin are the only OADs available in the SUS, therapeutic options are limited. This probably explains the rather high number of individuals using monotherapy with glibenclamide or metformin. Another monotherapy identified in the study was insulin, but its use was discrete (3.4%) when compared to the other therapies.

Generally, doses used in OAD monotherapy are reduced, to prevent or control adverse side effects, and these doses are changed or not according to the patient's response to the treatment. A retrospective study demonstrated that patients with DM type 2 treated with metformin or sulfonylurea monotherapy did not need additional treatment for 14.5 to 20.5 months, respectively, and, after these periods, glycosylated hemoglobin (HbA1c) exceeded 8.0% for both therapeutic options. DM is a progressive disease that can cause deterioration of glycemic control (glucose toxicity), making it necessary to change pharmacotherapy with time (23,24).

There were no statistical differences in the dose *versus* age group in patients treated with metformin or glibenclamide in monotherapy (Box 1A and 1B). Despite the fact that the authors did not have access to appropriate clinical information to verify the need to change the dose, reductions in the sulfonylurea dosages have been recommended in elderly patients, especially for OAD showing long elimination half-lives, such as glibenclamide, because of increased risks of adverse reactions such as hypoglycemia (25). In addition, some authors warn against the use of metformin in elderly patients due to an increasing risk of lactic acidosis (20).

Box 1. Profile of the therapeutic prescriptions of metformin (A), glibenclamide (B) and insulin (C) for patients with *diabetes mellitus* according to the Anatomical Therapeutic Chemical group and age

A. Profile of the therapeutic prescriptions of metformin for patients with *diabetes mellitus* type 2 according to their Anatomical Therapeutic Chemical group and age

Age Group	Anatomical Therapeutic Chemical groups			
	Metformin Mean dose (mg) (SD)	Glibenclamide plus metformin Mean dose (mg) (SD)	Metformin plus insulin Mean dose (mg) (SD)	Glibenclamide plus metformin plus insulin Mean dose (mg) (SD)
< 40	1,446 (593)[b]	1,853 (683)	2,401 (318)[e]	1,643 (927)
40-49	1,520 (642)[a]	1,945 (565)	1,744 (588)	1,654 (708)
50-59	1,429 (639)[c]	1,917 (631)	1,884 (638)	2,108 (621)
60-69	1,395 (637)[c]	1,843 (609)	1,858 (591)	1,936 (608)
70-79	1,452 (605)[b]	1,743 (643)[d]	1,781 (691)	1,720 (761)
> 80	1,353 (504)[a]	1,761 (648)	1,438 (556)	1,700 (694)

[a] $p < 0.05$ when compared with the glibenclamide plus metformin group.
[b] $p < 0.05$ when compared with the glibenclamide plus metformin, and metformin plus insulin groups.
[c] $p < 0.05$ when compared with the Anatomical Therapeutic Chemical groups.
[d] $p < 0.05$ when compared with the 40-49 and 60-69 age group.
[e] $p < 0.05$ when compared with 70-79 and > 80 age groups.
SD: standard deviation.

B. Profile of the therapeutic prescriptions of glibenclamide for patients with *diabetes mellitus* type 2 according to their Anatomical Therapeutic Chemical group and age

Age group	Anatomical Therapeutic Chemical groups			
	Glibenclamide Mean dose (mg) (SD)	Glibenclamide plus metformin Mean dose (mg) (SD)	Glibenclamide plus insulin Mean dose (mg) (SD)	Glibenclamide plus metformin plus insulin Mean dose (mg) (SD)
< 40	8.6 (4.0)[a]	11.7 (5.0)	-	12.5 (3.5)
40-49	8.3 (4.0)[b]	11.9 (4.4)	10.8 (4.9)	12.6 (5.8)
50-59	9.1 (4.1)[b]	11.6 (4.4)	12.2 (4.9)	13.1 (3.2)
60-69	8.8 (4.2)[c]	11.9 (4.1)	13.5 (3.8)	12.9 (4.1)
70-79	8.5 (4.0)[c]	11.9 (3.9)	11.4 (4.6)	11.3 (4.6)
> 80	7.7 (4.0)[b]	11.2 (4.3)	5.0 (0.0)	13.8 (4.8)

[a] $p < 0.05$ when compared with the glibenclamide plus metformin group.
[b] $p < 0.05$ when compared with glibenclamide plus metformin, and glibenclamide plus metformin plus insulin groups.
[c] $p < 0.05$ when compared with all Anatomical Therapeutic Chemical groups.
SD: standard deviation.

C. Profile of the therapeutic prescriptions of insulin for patients with *diabetes mellitus* type 1 or type 2 according to their Anatomical Therapeutic Chemical group and age

Age group	Anatomical Therapeutic Chemical groups			
	Insulin Mean dose (UI) (SD)	Metformin plus insulin Mean dose (UI) (SD)	Glibenclamide plus insulin Mean dose (UI) (SD)	Glibenclamide plus metformin plus insulin Mean dose (UI) (SD)
< 40	54.0 (24.0)	48.0 (32.0)	-	33.0 (22.0)
40-49	46.0 (18.0)	53.0 (30.0)	17.0 (14.0)[a,f]	36.0 (24.0)
50-59	63.0 (40.0)	52.0 (32.0)	48.0 (31.0)	29.0 (18.0)[b]
60-69	53.0 (24.0)[d]	55.0 (29.0)[d]	29.0 (14.0)	28.0 (17.0)
70-79	67.0 (49.0)[c]	47.0 (25.0)[e]	31.0 (17.0)	28.0 (16.0)
> 80	41.0 (15.0)	42.0 (19.0)	25.0 (11.0)	24.0 (7.0)

[a] < 0.05 when compared to the metformin plus insulin group.
[b] $p < 0.05$ when compared to the insulin and metformin plus insulin groups.
[c] $p < 0.05$ when compared to all Anatomical Therapeutic Chemical groups.
[d] $p < 0.05$ when compared to the glibenclamide plus Insulin and glibenclamide plus metformin plus insulin groups.
[e] $p < 0.05$ when compared to the glibenclamide plus metformin plus insulin group.
[f] $p < 0.05$ when compared to the 50-59 age group.
SD: standard deviation.

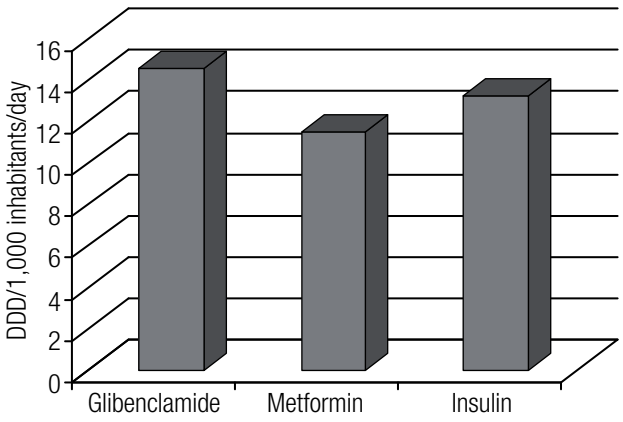

Figure 1. Use of oral antidiabetic drugs and insulin in defined daily doses per 1,000 inhabitants per day (DDD/1,000 inhabitants/day).

From the patients selected in this investigation, 28.6% used a combination of metformin plus glibenclamide. Other studies reported values of 28.4%, 39.0%, and 14.5% for the combination of metformin plus sulfonylurea (15,18,19). A United Kingdom Prospective Study demonstrated that the combination of these drugs improved the levels of HbA1c over a three-year period (23). In another study, the combination of metformin plus glibenclamide reduced the levels of HbA1c to less than 6.0% in 40.0% of the patients, while monotherapy with metformin or glibenclamide produced the same results only in 10.0% and 17.0% of the subjects using this treatment, respectively (26).

The dosages of OAD were lower in monotherapy when compared with those prescribed in polytherapy (Box 1A and 1B). When glycemic control is not possible, another OAD should be added, provided that the first one was used in the maximum recommended dose, indicating dose optimization (13,21). However, this was not obvious in the database since the doses of metformin and glibenclamide were far from optimum when the second OAD was added. This may be partially explained if one considers that patients with DM type 2 show different pathological mechanisms, warranting an early introduction of polytherapy, or when drug optimization is carried out according to patient tolerance.

The third step in the treatment of patients with uncontrolled DM type 2 would be the introduction of a third OAD or insulin (13,20,21). The only option for SUS patients is to receive insulin, because the system does not have a third standardized class of OAD. In this instance, the practitioner may decide to add the hormone, or choose complete insulinization. The Collaborative Drug Therapy Management Service showed that the introduction of insulin or dose adjustment in patients with DM type 2 improves glycemic control in patients with HbA1c levels over 9.0% (27). However, in these cases, the introduction of insulin is less frequent than recommended, and usually started late in the course of the disease. This treatment is invasive and painful, and frequently negatively affects the patient--physician relationship and, consequently, the physician is reluctant to start it. Other concerns are also involved, since physicians, patients and families worry about the side effects, such hypoglycemia and weight gain, specially in elderly patients (13,28-30).

Insulin polytherapy was used to treat 11.4% of the patients identified (Table 1), and an appreciable proportion of subjects required close attention in relation to glycemic control in a treatment considered to be more aggressive. Note that the database used in the present study did not provide laboratory results. According to the Brazilian Society of Diabetes, the combination of a biguanide or sulfonylurea agent with insulin contributes to reducing hormone doses, facilitating the transition to full insulin treatment, besides increasing treatment acceptance and compliance (13). Other studies also reported reduction in insulin doses in patients treated with metformin (31,32). In the present study, 6.9% of the patients were treated with metformin and insulin (Table 1). However, recent data have shown favorable outcomes related to the recovery and maintenance of β-cell function and protracted glycemic remission in newly diagnosed patients with DM type 2, which made therapy with OAD plus insulin comparable with OAD alone (20,24).

Concerning insulin doses, they were higher in the monotherapy group than the polytherapy group, with the exception of the combination metformin plus insulin. In general, patients with DM types 1 or 2 in advanced stages require full insulinization with high doses (13,21). A reduction in insulin levels was not seen in the combination metformin plus insulin, when compared with glibenclamide plus insulin. The reduction in insulin doses when the hormone was combined with glibenclamide was statistically significant in the 40-79 age group (Box 1C). It is known that glibenclamide aids insulin secretion by pancreatic β-cells, and this factor may be related with a reduction in insulin doses.

The use of OAD and insulin during the period studied was 14.5, 11.5, and 13.2 DDD/1,000 inhabitants/day for glibenclamide, metformin and insulin, respectively (Figure 1). A study carried out in 2003 in 10 European countries found variations in the use of sulfonylurea from 9.0 to 24.5 DDD, metformin from 5.5 to 14.0 DDD, and insulin from 6.5 to 23.0 DDD (33). In relation to changes in the number of drugs used, a second or third drug was added to 14.0% of the patients treated. In addition, approximately a quarter of the patients had their OAD and insulin doses modified, with greater prevalence for increased doses. Boccuzzi and cols. found increased doses in 30.7% and 23.6% for patients using metformin and glibenclamide, respectively (34).

In addition, 3.5% of the prescriptions showed errors in the OAD recommended doses, 10 of which had high doses of metformin and glibenclamide, and 128 had low doses of metformin. These findings have clinical relevance, since they represent evidence of a risk of toxicity or ineffectiveness of the therapy.

There were some limitations in the present study since the database did not provide clinical diagnoses or laboratory results. However, the study does have its strengths. Methodology used was fast and low-cost, which made it easy to manage a large number of patients. The study was developed in a district with 140,000 inhabitants, a population size representative of hundreds of Brazilian cities. Computer databases are also low-cost systems, enabling management and analysis of drug use at the municipal, state and federal levels. It is unfortunate that the system has limited use in countries like Brazil, being only used in drug purchase and control of drug inventories. However, a computer system known as HORUS was developed in 2009 by the Department of Pharmaceutical Assistance of the Brazilian Ministry of Health, the first countrywide system aiming at improving drug management, intensifying actions related to drug use and rational use.

CONCLUSIONS

OAD monotherapy was the predominant treatment for DM in this study. The doses used in monotherapy were lower than those used in polytherapy. There was no individualization of doses according to age group, particularly in elderly patients. It was possible to estimate the use of OAD and insulin that may contribute to improving issues related to drug management. Therefore, the database enabled the analysis of drug therapy, drug doses, drug management, and prescription failures being valuable tools for the pharmacist to investigate prescription profiles, contributing to patient care.

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