diabetology

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The Prescription and Safety of Oral Antidiabetic Drugs in Outpatients with Type 2 Diabetes Mellitus: An Observational, Retrospective, Multicenter Study on the Role of Adherence in a Real-Life Primary Care Setting

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Abstract: Introduction: Type 2 diabetes mellitus (T2DM) is a common disease burdened with significant morbidity and mortality. Despite the substantial number of new available drug treatments, adherence to therapy and adverse drug reactions (ADRs) are the major constraint in the management of this disease. We evaluated the use, the adherence, and the safety of antidiabetic drugs in patients with T2DM. Methods: We performed an observational, retrospective, multicenter study on medical records of outpatients referred to general practitioners in Catanzaro (Calabria, Italy). Drug adherence was measured considering the packages of antidiabetic drugs prescribed at the time of admission, after three months, and 1 year later. ADRs were evaluated using the Naranjo probability scale. Collected data were analyzed using the Statistical Package for the Social Sciences. Results: During the study, we evaluated 12,170 medical records of seven general practitioners. The most prescribed drug was metformin alone (28.4%) or with other oral antidiabetics (19.6%) and then insulin (*n:* 354; men 190, women 164). Logistic regression showed an association between T2DM less than or equal to 5 years and low adherence ($p = 0.023$). During the study, we recorded 26 ADRs that were correlated with sex (women) and insulin treatment. Conclusions: this real-life study shows that patients with T2DM have a high adherence, probably related to their having a low number of ADRs.

Keywords: adherence; adverse drug reactions; type 2 diabetes mellitus; therapy

Citation: Marcianò, G.; Vocca, C.; Casarella, A.; Gallelli, L.; Rania, V.; De Sarro, C.; Citraro, R.; Palleria, C.; Bianco, R.C.; Fera, I.; et al. The Prescription and Safety of Oral Antidiabetic Drugs in Outpatients with Type 2 Diabetes Mellitus: An Observational, Retrospective, Multicenter Study on the Role of Adherence in a Real-Life Primary Care Setting. *Diabetology* **2024**, *5*, 333–343. https://doi.org/10.3390/diabetology5030025

Academic Editor: Yoshifumi Saisho

Received: 14 May 2024
Revised: 24 July 2024
Accepted: 5 August 2024
Published: 7 August 2024

1. Introduction

Diabetes mellitus is a multi-factorial chronic metabolic disorder related to hyperglycemia [1,2] and leading to several complications. The complications can be classified as acute (e.g., hypoglycemia, diabetic coma, ketoacidosis) or chronic according to the time of onset [3,4]. Chronic complications may be further classified as microvascular (nephropathy, retinopathy, neuropathy, skin alterations), macrovascular (coronary artery disease, stroke, peripheral artery disease) or non-vascular (e.g., steatosis and infections) [3,4]. Furthermore,

diabetic patients may develop food-related disorders since the necessity of monitoring blood levels and holding specific dietary behaviors may determine the negative attitude of these patients toward food and body image [5]. Moreover, diabetic gastroparesis generated by diabetic neuropathy may seriously impair gastric emptying in patients with diabetes [6,7]. Globally, type 2 diabetes mellitus (T2DM) is the most prevalent, constituting over 90% of all diabetes cases [8], with more than 3 million 200 thousand people affected in Italy [9].

Pharmacological and non-pharmacological treatments are necessary to reduce hyperglycemia and prevent its complications [10]. The most common drug categories are biguanides (e.g., metformin), sulfonylureas (e.g., glibenclamide*, glipizide*, glimepiride*), α-glucosidase inhibitors (e.g., acarbose*), metiglinides (e.g., repaglinide*), peroxisome proliferator-activated receptor-γ (PPARγ) agonists (pioglitazone*, rosiglitazione, ciglitazone), dual PPARα/γ agonists (muraglitizar, tesaglitazar, aleglitazar, ragaglitizar, naveglitazar, and saroglitazar), incretin mimetics: glucagone-like peptide 1 agonists (GLP1A) (exenatide*, lixisenatide*, dulaglutide*, semaglutide* and liraglutide*), incretin mimetics: dipeptidyl peptidase 4 inhibitors (DPP IV-i) (sitagliptin*, vildagliptin*, saxagliptin*, linagliptin*, alogliptin*, gemigliptin, anagliptin, teneligliptin, trelagliptin, and omarigliptin) and sodium-glucose co-transporter-2 inhibitors (SGLT2-i) (canagliflozin*, dapagliflozin*, empagliflozin*, ertugliflozin*, ipragliflozin, luseogliflozin, and tofogliflozin) (* = available on market) [10–16]. These compounds display a variety of effects and adverse drug reactions (ADRs) through various mechanisms of action. Biguanides lower the levels of glucose produced by the liver and have been linked to lactic acidosis, renal failure, cramps, diarrhea, nausea, vomiting, increased flatulence, and poor vitamin B12 absorption. Metiglinides and sulfonylureas improve the release of insulin from pancreatic islets, but their use could be related to dizziness, agitation and anxiety, weight gain, skin reactions, and black urine. On the other hand, α-glucosidase inhibitors prevent the stomach from absorbing glucose and carbs, which is why the amount of unmetabolized sugar that remains in the lumen might induce gastrointestinal manifestations (e.g., flatulencea and bloating) [10–16].

A variety of pathways are activated by peroxisome proliferator-activated receptor-γ (PPARγ) agonists, which raise cells' sensitivity to insulin. They might induce heart failure, weight gain, and edema. When used with other anti-diabetic medications, they may increase the risk of bone fractures as well as hypoglycemia. By acting on both isoforms, dual PPARα/γ agonists modulate further lipid metabolism and lessen adverse effects. Incretin mimetics work by either employing long-half-life analogs or by inhibiting the enzyme that metabolizes GLP1, DPP-4, to increase the action of GLP1. Possible adverse drug reactions (ADRs) include diarrhea, vomiting, nausea, headaches, dizziness, increased perspiration, indigestion, constipation, loss of appetite, and pancreatitis. Finally, SGLT2-inhibitors, blocking the SGLT2 present in the proximal convoluted tubule, prevent the reabsorption of glucose and enhance its excretion in urine. Urinary infections are a common side effect [10–16]. The development of these ADRs induces a decrease in drug adherence, with an increased risk of complications. Glycated hemoglobin (HbA1c) $\leq$ 7% has been consistently associated with a reduction in the risk of microvascular and macrovascular complications [17–19]. The reduction in drug adherence is therefore associated with the increase in diabetic complications, since HbA1c levels are dependent on drug adherence and their increase is correlated with the onset of complications. The risk of acute coronary syndrome, kidney failure, stroke, leg amputation, vision loss, and nerve damage is increased by non-adherence [20]. Drug adherence in long-term therapies is defined as "the extent to which a person's behavior (taking medication, following a diet, and/or executing lifestyle changes) corresponds with agreed-upon recommendations from a health care provider" [21]. Recently, Al-Azayzih et al. [22] using a questionnaire, divided TDM2 patients into three groups of adherence: high adherence: if the patient does not forget to take the medication(s), does not modify the dose or stop the medication; moderate adherence: if patients occasionally forget to take the medication(s); low adherence: if patients frequently forget to take the medication(s), or intentionally skip doses, or change the dosing regimens. Some authors suggested that higher adherence to anti-diabetic drugs is associated with better health outcomes, e.g.,

improved glycemic control and reduced complications. Lin et al. [23], in a retrospective study, analyzed 2463 patients and showed that the prevalence of medication adherence was 65% among newly diagnosed patients. The HbA1C levels of patients characterized by poor adherence profile showed an increase of 0.4 over two years. Patients may discontinue taking the drug due to the increased risk of hospitalization for ADRs with the loss of potential benefit. Notably, an ADR is defined as an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product [24]. The incidence of antidiabetic drug ADRs may vary greatly considering different studies and patient characteristics. Chaturvedi et al. [25], in a clinical trials performed on 200 patients with T2DM, documented the development of ADRs in 19.5% of these.

In our study, we evaluated both the use of antidiabetic drugs and the level of adherence in patients with T2DM. Moreover, we also evaluated the correlation between drug adherence and the development of ADRs.

2. Materials and Methods

2.1. Study Design

We performed an observational, retrospective, multicenter study on the medical records of outpatients referred to general practitioners from June 2018 to June 2023.

2.2. Protocol

Data regarding the following were recorded in clinical records and were analyzed in agreement with previous papers [26–31]: age, gender, diabetes duration, antidiabetic drugs, ADRs (in agreement with Naranjo probability score), comorbidities, polytherapy, and laboratory findings.

The Naranjo scale is used to estimate the probable causality between drug administration and adverse reactions. It consists of 10 questions answered "Yes", "No", or "Do not know". Different points are assigned to each question (−1, 0, 1, or 2). Total scores range from −4 to +13. The causality of the ADRs is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less [32].

The inclusion criteria were as follows: age $\geq$ 18 years; diagnosis of T2DM, in agreement with the World Health Organization and American Diabetes Association criteria; treatment with antidiabetic drugs.

Patients with diabetes caused by radiotherapy, pancreatic surgery, pancreatic tumor, pancreatitis, glucose infusion, and steroids were excluded, according to a different etiology. The study protocol was approved by the Ethics Committee Calabria Centro, protocol number 2017/238.

The primary endpoint was the medication adherence rate. The secondary endpoint was the correlation between low adherence and ADRs.

2.3. Adherence to Therapy

The European Society for Patient Adherence, Compliance and Persistence Medication Adherence Reporting Guideline (EMERGE) [33] was used to evaluate the adherence to the treatment. Adherence is defined, according to the World Health Organization (WHO), as the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider [21,34]. In agreement with other studies [35,36], the adherence was calculated by the medication possession ratio (MPR = total days' supply/study time; study time of 3 months and 1 year) considering the packages of antidiabetic drugs prescribed at the time of admission, 3 months and 1 year later. High medication adherence was defined as an MPR value $\geq$ 0.8; medium medication adherence was defined as an MPR between 0.4 and 0.7, while low medication adherence was defined as an MPR $\leq$ 0.3.

2.4. Adverse Drug Reactions

ADRs were collected in agreement with our previous studies [31,37,38]. Briefly, general practitioners evaluated the clinical records, and the development of ADRs was recorded.

Records positive for ADRs were reviewed by clinician pharmacologists, who identified ADRs reported in clinical records and applied the Naranjo ADR probability scale.

The pharmacologists assessed the impact of each ADR on the patient in terms of disability, likely cause, place and date of occurrence, and type of ADR.

Written informed consent was taken by each general practitioner, at the time of the first admission in clinical room. All the procedures were performed according to the Declaration of Helsinki and in accordance with the Good Clinical Practice guidelines.

2.5. Statistical Analysis

Descriptive statistical analyses were performed to evaluate clinical and demographic characteristics, with continuous data presented as mean ± standard deviation (SD), while ordinal data were expressed as numbers (percentage). The skewness of continuous variables was assessed by the Kolmogorov–Smirnov test, highlighting variables not normally distributed. Thus, a non-parametric approach was applied using the Mann–Whitney *U* test or the independent-samples Kruskal–Wallis Test for continuous variables and the two-tailed Pearson chi-squared test or Fisher's test for categorical variables, as appropriate.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariate and multivariate regression models to evaluate the contribution of independent variables in predicting ADR insurgence and achieving medium or high adherence (using a multinomial logistic regression [low adherence as reference category]). A p-value < 0.05 was considered as statistically significant. All tests were two-tailed. Statistical analysis was conducted with the Statistics Package for Social Sciences (SPSS) version 26.0 (IBM Corp. SPSS Statistics, Armonk, NY, USA).

3. Results

3.1. Demographic and Clinical Characteristics

During the study period, we analyzed 12,170 clinical records referred to general practitioners' ambulatory care. Using the paired sample test, we evaluated that there was no difference between males and females enrolled (p = 1.235), while the mean age of enrolled patients was 69.35 ± 13.82 years. Of 12,170 enrolled patients, 86% had at least one comorbidity; the most common were hypertension (15.8%) and cancer (3.8%) (Table 1).

Table 1. Comorbidity in clinical records analyzed at the first control (n: 12,170). Data are expressed as the percentage of enrolled patients.

Clinical Characteristics	Data
Age	69.35 ± 13.82 years
Body mass index	
Normal (18.5 to 24.9)	45.3%
Overweight (25.0 to 29.9)	39.2%
Obese (30 or higher)	15.5%
Smokers	
Yes	5.4%
No	94.6%
Blood hypertension	15.8%
Cancer	3.8%
Atrial fibrillation	3.4%
Hypothiroidism	3.4%
Cardiovascular disease	2.5%
COPD	1.9%
Depression	1.8%

Table 1. *Cont.*

Clinical Characteristics	Data
Gastroesophageal reflux disease	1.7%
Asthma	1.4%
Hert failure	0.9%
Low back pain	0.9%

We documented the 1234 patients (age 71.9 ± 11.9 years) of the 12,170 total patients (10.1%) who had a diagnosis of Type 2 diabetes mellitus (men: 648, 52.5%, age 70.4 ± 11.8 years; women: 586, 47.5%, age 73.5 ± 11.8 years, $p = 1.312$). In T2DM patients (n = 1234), we documented that 9.1% (n = 112) did not receive any treatment, while the other enrolled patients (n = 1122) received at least one antidiabetic drug. The most prescribed drug was metformin (n = 593) alone (351; 28.4%) or with other oral antidiabetics (242; 19.6%) and then insulin (n = 354, 28.7%; men = 190, women = 164) (Table 2).

Table 2. Drug prescription in Type 2 diabetes mellitus patients enrolled in the study (n: 1234). Data are expressed as a total number and as a percentage.

Drugs	Alone		In Combination	
	Number	Percentage	Number	Percentage
Metformin	227	18.4	242	24.2
Sulphaniluree	28	2.3	67	5.4
Insulin	39	3.2	291	23.6
Repaglinide	24	1.9	38	3.1
DPPI-4 inhibitors	21	1.7	54	4.4
GLP1-agonist	16	1.3	56	4.6
SGLT-2	2	0.2	43	3.5
Pioglitazone		--	86	7

Metformin was more frequently ($p < 0.01$) prescribed in men compared to women (Table 3), but women were older than men (men: range 38–96 years; women: range 29–98 years).

Table 3. Difference by sex in patients with T2DM using antidiabetic drugs enrolled in the study (n: 1234). Data are expressed as an absolute number. The percentage difference is reported with respect to the value for men. * $p < 0.05$; ** $p < 0.01$.

Drugs	Men	Women	Percentage Difference Men vs. Women
Metformin	300	287	4.3
Insulin	190	164	13.7 *
Sulphaniluree	47	51	−8.5
Repaglinide	33	30	9.1
DPPI-4 inhibitors	46	33	−28.3 **
GLP1	10	12	20 **
SGLT2	35	15	57.1 **
Pioglitazone	3	4	33.3 **

Concerning age, we documented that metformin and insulin were significantly prescribed in both elderly men and women (Table 4); we did not record any other difference in the prescription of the other antidiabetic drugs (Table 4).

Table 4. Difference in age (years) in patients with T2DM using antidiabetic drugs (n: 1234). Data are expressed as mean ± standard deviation.

Drugs	Men	Women	*p*
Metformin	69.0 ± 11.2	72.1 ± 11.9	0.000516
Insulin	70.3 ± 13	75.4 ± 11.8	0.00000
Sulphaniluree	77.5 ± 8.2	79.1 ± 10.9	0.230403
Repaglinide	76.3 ± 12.3	76.8 ± 13.3	0.424246
DPPI-4 inhibitors	72.5 ± 10.5	75.8 ± 10.5	0.106064
GLP1	67.7 ± 18.9	61.2 ± 18.8	0.87754
SGLT2	65 ± 9.9	67.9 ± 15.2	0.132805
Pioglitazone	72.7 ± 10.7	71 ± 15.2	0.56786

Among the collected data, all patients reported HbA1c values measured within the last 6 months. Target HbA1c levels (<7) were achieved by 70.3% of patients (Table 5), of whom 71.3% were highly adherent ($p = 0.005$).

Table 5. Percentage of T2DM patients with HbA1c values < 7 after drug treatment.

Drug	Adherence	Adherence Levels		
	Total	High	Moderate	Low
DPPI-4	54.6%	50	30	20
GLP1	19%	30	30	40
SGLT2	25%	35	30	35

3.2. Adherence to Antidiabetic Medications and Related Variables

T2DM-enrolled patients (1234) were stratified as having high (n = 296; 24%), medium (n = 432; 35%), and low (n = 506; 41%) adherence. Low adherence was recorded in patients with complex polytherapy, particularly those using the combinations of sitagliptin, metformin, and insulin (79%); dapaglifozin, metformin, and insulin (15%); or metformin and insulin (6%). In contrast, we failed to describe a correlation between medium adherence and polytherapy ($p = 1.031$), comorbidity ($p = 0.917$), age ($p = 1.20$), sex ($p = 0.81$), or job ($p = 0.613$). With respect to ethnicity and religiosity, we did not evaluate it because all the enrolled patients were Italian with a Catholic credence. However, in a sub-analysis of the data, logistic regression showed an association between having T2DM for less than or equal to 5 years ($p = 0.023$) and low adherence.

3.3. Adverse Drug Reactions

At least one ADR has been experienced by 26 patients (0.21%), with 27 ADRs reported overall. The most frequently reported ADRs identified were GI disorders (15; 55.6%), and the most involved drug was metformin (Table 6). Women were commonly involved in the development of ADRs ($p < 0.01$) in the metformin group and in metformin + insulin, while men were in the other treatments ($p < 0.01$).

T2DM patients with ADRs were not older compared to T2DM patients without ADRs (73.0 ± 7.7 vs. 71.9 ± 11.9) and had an earlier diagnosis of diabetes (49.9 ± 13.3 vs. 53.9 ± 13.3 years, $p = 0.001$). Using the univariate regression, we reported that ADRs were associated with women (OR 2.65; CI: 1.44–4.89; $p = 0.002$), polytherapy (OR 1.6; CI: 1.3–1.97; $p = 0.008$), and insulin treatment (OR 1.60; CI: 1.15–2.22; $p = 0.005$). A correlation with

treatment was also found in the multivariate analysis for metformin (OR 1.70; CI: 1.04–2.78; $p = 0.03$) and insulin (OR 1.86; CI: 1.03–3.35; $p = 0.04$).

Table 6. The drugs involved in the development of adverse drug reactions (n: 27) in enrolled patients with type 2 diabetes mellitus (n: 1234).

Drugs	Gastrointestinal Disorders		Skin Reactions		Fatigue		Hypoglycemia		Headache		Weight Increase	
	M	F	M	F	M	F	M	F	M	F	M	F
Metformin	1	10	2		2	1	-	1	-	1	-	1
Metformin + Insulin	1	-	1	-	-	-	-	1	-	-	-	-
Metformin + Repaglinide	-	2	-	1	-	-	-	-		-	-	-
Metformin + Pioglitazone	1	-	2	-	-	-	-	-		-	-	-

4. Discussion

In this study, we analyzed, in TDM2 outpatients, the use of antidiabetic drugs, their levels of adherence, and their correlation with the development of ADRs. Adherence is usually related to clinical, economic, and drug-related factors (e.g., the development of ADRs). In particular, ADRs can induce self-treatment discontinuation or self-dosage reductions [39–41]. Furthermore, reduced adherence can delay the achievement of glycemic targets and increase the risk of diabetes-related complications [42,43]. Janoo and Khan [44] showed in 497 subjects with T2DM (mean age 55.5 years) a moderate adherence level to medication and demonstrated a significant correlation ($p = 0.000$) between low adherence and ethnicity (Malay patients). In our study, we failed to report an association between adherence and ADRs, suggesting that socio-economic factors and ethnicity probably play a role in adherence to the treatment. In agreement with our data, a systematic review [35] highlighted a wide range (38.5 to 93.1%) of adherence among patients' groups, suggesting that several factors play a role in adherence.

Various authors reported that changes in lifestyle, knowledge about drug properties, psychological alterations, support from family and other figures, medication cost, and social status affect medication adherence in older people with uncontrolled T2DM [35,45–47].

We did not find any correlation between age and nonadherence in this trial, and we assume that this is likely due to patients' views toward medication use as well as the low rates of ADRs. It is crucial to keep in mind that low adherence is frequently linked to both patient and non-patient factors, such as patient demographics, critical patient beliefs about their medications, and perceptions of patients' burdens regarding obtaining and taking their medications. Examples of non-patient factors include integrated care, clinical inertia among health care professionals, and medicine costs. The cost of medications may be a significant barrier to diabetic therapy adherence. In a retrospective study of 20,326 patients with diabetes, Taha et al. [48] showed that a low income, high costs of medical bills, the absence of insurance, the presence of a comorbidity, and being of the female sex were associated with cost-related non-adherence (CRN), independently of age. In patients $\leq$65 years of age with diabetes, current smoking, hypercholesterolemia, and hypertension were associated with higher odds of reporting CRN among the elderly but not among the elderly. In patients $\geq$65, insulin use significantly increased the risk of cost-based nonadherence. Furthermore, the price of antidiabetic drugs may vary hugely worldwide, reducing the availability of these compounds. However, the drug's availability may also depend on its distance from urban centers. [49].

Concerning the patient's attitude, we recorded increased information given by general practitioners to the patient regarding the correct use of drugs. Finally, we documented a correlation between low adherence and a recent diagnosis of diabetes. We suppose that, to reduce the risk of complications, particularly in young patients, physicians as well as general practitioners need to provide counseling to patients at each visit and

correctly assess drug adherence. Evidence from the literature is mixed since authors report a positive [50], negative [51], or not significant [52,53] relationship between diabetes duration and adherence.

According to our univariate and multivariate analyses, the strongest factor in the multivariate analysis predicting low adherence was the development of ADRs, indicating that among all potential factors influencing adherence, it is probably the most important. In fact, expected negative influencing factors such as age did not have an impact on adherence, while the drugs used may have been underestimated due to the low number of patients with ADRs. That said, a correlation between insulin or metformin and the emergence of ADRs was confirmed in our analysis. These data are explained by considering the possible side effects of insulin (including hypoglycemia and an increase in body weight) or metformin (e.g., gastrointestinal side effects). Nevertheless, less frequent effects have also been described (lactic acidosis for metformin and allergic reactions for insulin) and have a possible impact on therapeutic adherence [54,55]. Furthermore, the early initiation of insulin has also been related to weight gain and cancer risk [56]. According to Bonnet and Scheen [57], metformin determines gastrointestinal side effects, considering its capacity to affect gut microflora, bile acid, and increase the levels of glucagon-like peptide 1 (GLP-1). The anaerobic utilization of glucose may increase the production of lactate, resulting in side effects. The rate of side effects is more probable in predisposed subjects, including those with organic cation transporter (OCT) 1 polymorphisms, specific comorbidities, those consuming other medications, or those having previously undergone bariatric surgery. Frail patients with kidney injury may also undergo rarer adverse events like lactic acidosis or acute kidney failure [58].

Using the univariate regression, in agreement with other studies [59,60], we documented an association between ADRs and the female sex. Clinical practice, epidemiological data, and the suspected adverse events reported through the Italian National Pharmacovigilance Network (RNF) show a higher incidence and greater severity of ADRs amongst women, who appear to be more prone to possible pharmacological interactions [60]. In agreement with Italian data, Watson et al. [61], in a large study on VigiBase, the WHO global database of individual case safety reports, documented that ADRs are more common ($p < 0.01$) in women (9,056,566 (60.1%) women, and 6,012,804 (39.9%) male) without difference with respect to country. In this study, the authors [61] suggested that the most common development of ADRs could be explained by a higher use of drugs in women, but also suggested that gender-related variables, such as weight, height, body surface area, fat mass, plasma volume, and total amount of body water, could play a role.

Moreover, psychotropic drugs (e.g., antidepressants) and sex hormones were commonly used in women [61] with an increased risk of drug interaction and ADRs [62]. In our study, we documented a correlation between insulin and ADRs, probably related to the characteristics of the drug. In fact, it has been reported that subcutaneous injection and the complexity of dosing schedules could be involved in ADR onset during insulin therapy [63–66].

5. Limitations

Our study has some limitations, mainly related to the design (data were recorded on clinical records). Furthermore, we did not collect information about socio-economic status or education. The dimension of our population is not small, but a higher number of patients may be recruited to obtain more complete information. Finally, we did not evaluate other medications consumed by our patients.

6. Conclusions

In conclusion, we reported that antidiabetic drugs are commonly used in a real-life setting without the development of adverse drug reactions, resulting in satisfactory adherence to the therapy.

Author Contributions: G.M., C.V., A.C., L.G., V.R., C.D.S. and R.C.: conceptualization, data curation, software; G.M. and C.P.: writing of the original version; L.G., B.D. and G.D.S.: formal analysis, review and editing; M.A.: English editing; R.C.B., I.F., A.G., L.M., G.N. and C.L.R.: investigation. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the local Ethics Committee Calabria Centro, protocol number 2017/238.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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