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Article

Prescription and Safety of Oral Antidiabetic Drugs in Outpatients with Type 2 Diabetes Mellitus: The Role 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 constrain in the management of this disease. We evaluated the use, the adherence and the dsaftey of antidiabetic drugs in patients with T2DM. **Methods:** we performed an observational, retrospective, multicenter study on medical records of outpatients referred to general practitioners. Drug adherence was measured in agreement to the European Society for Patient Adherence, Compliance and Persistence Medication Adherence Reporting Guideline. 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 7 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). Enrolled patients were stratified as high (35%), medium (41%) and low (24%) adherence. 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 was correlated with sex (women) and insulin treatment. **Conclusion:** this real-life study shows that patients with T2DM have high adherence probably related dto a low number of ADRs.

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

1. Introduction

Diabetes mellitus is a multi-factorial chronic metabolic disorder caused characterized by hyperglicemia [1,2], leading to chronic microvascular, macrovascular and neuropathic life threatening complications (e.g. nephropathy, neuropathy, cardiovascular and renal complications, retinopathy, food related disorders) [3]. Globally, type 2 diabetes mellitus (T2DM) is the most prevalent, constituting over 90% of all diabetes cases [4], with over 3 million 200 thousand people affected in Italy [5].

To control hyperglicemia and its complications, an appropriate treatment is essential and today several drugs are available as monotherapy or add on to the first line therapy (metformin) (Table 1)

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[6]. Drug treatment must be continued, and a decrease in drug adherence increases the risk of complications [7–9].

Table 1. Drugs used in the management of type 2 diabete mellitus.

Classes	Mechanism of action	Drugs
Biguanides	Reduces hepatic glucose production	Metformin
Sulfonylureas	enhance release of insulin from pancreatic islets	Glibenclamide, Glipizide, Glimepiride
α-glucosidase inhibitors	interferes with absorption of glucose and carbohydrate in the gut	Acarbose
Metiglinides	enhance release of insulin from pancreatic islets	Repaglinide
peroxisome proliferator-activated receptor-γ (PPARγ) agonists	increase the sensitivity of cells to insulin	Pioglitazone, Rosiglitazone and Ciglitazone.
Dual PPARα/γ agonists	maintains the lipid metabolism, insulin sensitivity, inflammation control.	Muraglitizar, Tesaglitazar, Aleglitazar, Ragaglitizar, Naveglitazar and Saroglitazar
Incretin mimetics: glucagone like peptide 1 agonists (GLP1A)	GLP-1 is an enzyme that triggers the synthesis and secretion of insulin from β cells of pancreas	Exenatide, Lixisenatide, Dulaglutide and Liraglutide
Incretin mimetics: dipeptidyl peptidase 4 inhibitors (DPP IV-i)	increases the activity of GLP-1	Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin, Gemigliptin, Anagliptin, Teneligliptin, Alogliptin, Trelagliptin and Omarigliptin
Sodium-glucose co-transporter-2 inhibitors (SGLT2-i)	inhibit the SGLT2 present in proximal convoluted tubule, which prevents reabsorption of glucose and enhances the excretion of glucose in urine	Canagliflozin, Dapagliflozin, Empagliflozin, Ipragliflozin, Luseogliflozin and Tofogliflozin

Drug adherence in long-term therapies is defined as "the extent to which a person's behaviour (taking medication, following a diet, and/or executing lifestyle changes), corresponds with agreed recommendations from a health care provider" [10]. Some authors suggested that better adherence to anti-diabetic drugs is associated with better health outcomes: e.g., improved glycaemic control and reduced complications [11].

Medication nonadherence is a common problem associated with managing chronic illnesses, particularly in older people due to the risk of adverse drug reactions (ADRs) (Table 2) [6]. In fact, patients may discontinue taking the drug due to the increased risk of hospitalisation for ADRs with the lose of potential benefit.

Table 2. Adverse drug reactions related to the administration of antidiabetic drugs in patients with type 2 diabete mellitus.

Classes	Adverse drug reactions
Biguanides	Lactic acidosis and renal failure; diarrhea, cramps, nausea, vomiting, increased flatulence and decreased absorption of vitamin B12
Sulfonylureas	dizziness, sweating, confusion and nervousnes, hunger, weight gain, skin reaction, stomach upset and dark colored urine.
α-glucosidase inhibitors	bloating, flatulence, gastrointestinal irritation

Metiglinides	dizziness, sweating, confusion and nervousnes, hunger, weight gain, skin reaction, stomach upset and dark colored urine.
peroxisome proliferator-activated receptor-γ (PPARγ) agonists	edema, weight gain, macular edema and heart failure. They may cause hypoglycemia when combined with other anti-diabetic drugs as well as they decrease hematocrit, decrease hemoglobin levels and increase bone fracture risk
Dual PPARα/γ agonists	Reduced side effects respect to PPARγ agonists
Incretin mimetics: glucagone like peptide 1 agonists (GLP1A)	diarrhoea, nausea, vomiting, headaches, dizziness, increased sweating, indigestion, constipation and loss of appetite
Incretin mimetics: dipeptidyl peptidase 4 inhibitors (DPP IV-i)	
Sodium-glucose co-transporter-2 inhibitors (SGLT2-i)	Urinary infections

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

2. Materials and Methods

2.1. Study design

We performed an observational, retrospective multicenter study on medical records of outpatient referred to general practitioners up to June 2023.

2.2. Protocol

Data recorded in clinical records were analyzed in agreement with previous papers [12–17]ì: age, gender, diabetes duration, antidiabetic drugs, ADRs (in agreement with Naranjo probability score), comorbidities, polytherapy and laboratory findings.

Inclusion criteria were as follows: age ≥18 years; diagnosis of T2DM, in agreement with the World Health Organization and American Diabetes Association criteria; start of treatment with antidiabetic drugs.

Patients with diabetes caused by radiotherapy, pancreatic surgery, pancreatic tumor, pancreatitis, glucose infusion and steroid were ruled out. The study protocol was approved by the local Ethics Committee, 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) [18], was used to evaluate the adherence to the treatment. In agreement with our previous studies [19,20], the adherence was calculated considering the packages of antidiabetic drugs prescribed at the time of admission, three months and 1 year later.

2.4. Adverse drug reactions

Adverse drug reactions (ADRs) were recorded in agreement with our previous studies [17,21,22]. The study was performed on clinical recorders of general practitioners, therefore written informed consent was take from each general practitioner, at the time of the first admission in clinical

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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 expressed as number (percentage). Skewness of continuous variables was assessed by the Kolmogorov-Smirnov test, highlighting not normally distributed variables. 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 the 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 ADRs 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 we analyzed 12,170 clinical records. Using the paired sample test, we evaluated that there was no difference between male and female enrolled (P=1.235), while the mean age of enrolled patient was 69.35 ± 13.82 years. Of 12,170 enrolled patients, 86% had at least one comorbidity, the most common were hypertension (15.2%) and cancer (3.8%) (Table 3).

Table 3. Comorbidity in patients enrolled in this study. Data are expressed as percentage of enrolled patients (n.12,170).

Disease	Percentage
Blood Hypertension	15.8
Cancer	3.8
Atrial fibrillation	3.4
Hypothiroidism	3.4
Cardiovascular disease	2.5
COPD	1.9
Depression	1.8
Gastroesophageal reflux disease	1.7
Asthma	1.4
Hert failure	0.9
Low back pain	0.9

We documented those 1,234 patients, (age 71.9 ± 11.9 years), have 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: 1,234), 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; men 190, women 164) (Table 4).

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Table 4. Drug prescription in Type 2 diabete mellitus enrolled patients. Data are expressed as percentage respet to the enrolled patients.

Drugs	Alone	In combination
Metformin	28.4	19.6
Sulphaniluree	2.3	5.4
Insulin	3.2	24.7
Repaglinide	1.9	3.1
DPPI-4 inhibitors	1.7	4.6
GLP1-agonist	1.3	4.6
SGLT-2	0.2	3.5
Pioglitazone	--	7

Metformin was commonly (P<0.01) prescribed in men respect to women (Table 5), but women were older than men (men range 38-96 years; women range 29-98 years). We did not record any difference respect to the age in the prescription of the other antidiabetic drugs (Table 6).

Table 5. Sex difference in patients with T2DM using antidiabetic drugs enrolled in the study. Data are expressed are absolute number. Percentage difference is reported respect to men value. *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**

Table 6. Difference of age (years) in patients with T2DM using antidiabetic drugs. Data are expressed are 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 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 7) of which 71.3% were highly adherent (p=0.005).

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

Drug	Percentage
DPPI-4	54.6%
GLP1	19%
SGLT2	25%

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3.2. Adherence to antidiabetic medications and related variables

In agreement with EMERGE Guideline [18], enrolled patients (12,170) were stratified as high (n: 4,260; 35%), medium (n: 4,990; 41%) and low (n: 2,921; 24%) adherence. Low adherence patients taking at least two antidiabetic drugs, particularly the association sitagliptin, metformin and insulin (79%), or dapaglifozin, metformin and insulin (15%), metformin and insulin (6%). We failed to report any correlation between low therapy and polytherapy (P=1.031), comorbidity (P=0.917), age (P=1.20), sex (P=0.81), job (P=0.613). Respect to ethnicity and religiousity we did not evaluate it because all enrolled patients were Italian with a catholic credence. However, in a subanalysis of the data logistic regression showed an association between T2DM less than or equal to 5 years (P = 0.023) and low adherence.

3.3. Adverse drug reactions

At least one ADRs has been experienced by 26 patients (0.21%) with overall 27 ADRs reported. The most frequently reported ADRs identified were GI disorders (15; 55.6%) and other ADRs (12; 44.4%) including asthenia, hypersensitivity, dermatologic reactions, headache, ponderal increase, drowsiness. One patient experienced hypoglycemia. The drugs most commonly involved in the development of ADRs was metformin (Table 8).

Table 8. Drugs involved in the development of adverse drug reactions (n: 26) in enrolled patients. *P<0.01.

Drugs	Men	Women
Metformin	5	13*
Metformin + Insulin	2*	1
Metformin + Repaglinide	--	2*
Metformin + Pioglitazone	3*	--

Patients that experienced a ADRs were not older compared to the mean of diabetes affected patients age (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), poly-therapy (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). 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).

4. Discussion

In this study we evaluated, in TDM2 outpatients, the use of antidiabetic drugs and their levels of adherence and its 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 the self-treatment discontinuation or self-dosage reductions [23–25]. Furthermore, reduced adherence can delay the achievement of glycemic targets and improve the risk of diabetes-related consequences (*e.g.* micro and macrovascular disorders and altered lipid metabolism) [26,27]. Janoo and Khan [28] 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 (Malays's patients). In our study we we failed to report an association between adherence and ADRs suggesting that probably socio-economic factors and ethnicity play a role in the adherence to the treatment. In agreement with our data, a systematic review [29], highlighted a wide range (38.5 to 93.1%) of adherence among patients' groups suggesting that several factors play a role in adherence.

More recently Upamai et al., [30] reported that changes in lifestyle affect medication adherence in older people with uncontrolled T2DM.

In the present study, we did not report any association between age and nonadherence, and we suppose that this could be probably related to both low levels of ADRs and patients' attitudes toward the use of medicines. It is important to remember that poor adherence is commonly related to nonpatient factors e.g., integrated care and clinical inertia among health-care professionals, patient demographic factors, critical patients' belief about their medications, and perceive patients' burden regarding obtaining and taking their medications. Concerning the patient'attitude, we recorded an increased information given from general practitioners to the patient regarding the correct use of drugs. In fact, in Calabria (South of Italy) in the last five years was started an activity of information on diagnostic and therapeutic processes supporting the role of information and follow-up to improve the adherence in the population. Finally, we documented a correlation between low adherence and a recent diagnosis of diabetes; to reduce the risk of complications, particularly in young patients, is necessary that physicians as well as general practitioners provide counseling to patients at each visit and correctly assess the drug adherence.

According to our univariate and multivariate analysis, the strongest and only factor in the multivariate analysis predicting moderate/high adherence was the absence of reported 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 drugs used may have been underestimated according to the low number of patients with ADRs. Although a correlation between insulin and insurgence of ADRs was confirmed in our analysis.

Using the univariate regression, we documented an association between ADRs and sex (women) and poly-therapy. The association ADRs with sex has been investigated by several authors [31,32]. Watson et al., [33], suggesting a gender-related variables, such as weight, height, body surface area, fat mass, plasma volume and total amount of body water. 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 [32]. In agreement with Italian data, Watson et al., [33] 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 respect to the country. The authors suggest that the most common development of ADRs could be explained by a higher use of drugs in the women population compared to the men population. In particular, psychotropic drugs (eg., antidepressants) and sex hormones and modulators of the genital system are commonly used in women [33] with an increased risk of drug interaction and adverse drug reactions [34]. In our study we documented a correlation between insulin and ADRs, this could be related to the characteristic of the drug. In fact, has been reported that subcutaneous injection and complexity of dosing schedules could be involved in ADRs onset during insulin therapy [35–38].

Or study has some limitations, mainly related with the design (data recorded on clinical records). In conclusion, we reported that antidiabetic drugs are commonly used in a real life setting without the development of adverse drug reactions resulting in a satisfactory adherence to the therapy.

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Conflicts of Interest: All other authors have no conflicts to declare.

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