

# Nationwide trends in antidiabetic drugs (type-2) utilization, Ukraine, 2014–2016

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## Abstract

**Introduction:** Type 2 diabetes is the most common form of diabetes. According to the guidelines of International Diabetes Federation, patients need to be given appropriate medical treatment, the purpose of which is to achieve the compensation of the disease and the treatment of its complications. The aim of this study was to analyze the consumption and expenditure per day of oral antidiabetic medicines in Ukraine during 2014–2016. **Materials and Methods:** Study of drug consumption was conducted using anatomical therapeutic chemical/defined daily dose (ATC/DDD) methodology by calculating such figures as utilization in DDD, DDDs per 1000 inhabitants per day, and expenditure per DDD. **Results and Discussion:** The consumption rates of DDDs/1000 PD of monoantidiabetic drugs fluctuated from 11.57 to 15.45 DDDs/1000 PD, and for combined antidiabetic drugs, it was changed from 1.02 to 1.11 DDDs/1000 PD during 2014–2016. The structure of consumption in Ukraine 2015–2016 shows increasing in consumption of biguanides (51.21%), sulfonylureas (74.57%), repaglinide (91.67%), liraglutide (40%), pioglitazone (33.3%), and dapagliflozin (35%). The analysis of expenditure per DDD shows that the most affordable unit of DDD was agents that contain pioglitazone, metformin, sulfonylureas group, and combined drugs. **Conclusion:** Nationwide trends in antidiabetic agents' utilization were analyzed in Ukraine during 2014–2016. It has been established a slight decreasing of A10B group agents' consumption in the period of 2014–2015. In 2016, there was a tendency to increase the value of DDDs/1000 PD.

**Key words:** Antidiabetic drugs, defined daily dose per 1000 inhabitants per day, drug consumption, expenditure per defined daily dose, type 2 diabetes

## INTRODUCTION

Diabetes mellitus is a complex disease which has become one of the most serious public health problems based on its increasing incidence, devastating complications, and even concerning the cost of antidiabetic therapy.<sup>[1,2]</sup> According to the data International Diabetes Federation (IDF) Diabetes Atlas,<sup>[3]</sup> there are 425 million people with diabetes in the world. There will be 629 million people with diabetes in the world in 2045. In Ukraine, the number of patients with diabetes aged from 20 to 79 years was 2756.7 in 1000s (2016), in 2017, the number of patients increased to 2836.3 in 1000s.

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes. Around 90% of people with diabetes have T2DM. The number of people with T2DM is growing, most likely

as a result of rising overweight and obesity rates, lifestyle and dietary changes, and an aging population.<sup>[2]</sup>

According to the guidelines of IDF, patients need to be given appropriate medical treatment, the purpose of which is to achieve the compensation of the disease and the treatment of its complications.<sup>[4]</sup>

The aim of our study was to analyze the consumption and expenditure per day of oral antidiabetic medicines in Ukraine during 2014–2016.

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## METHODS

The research was conducted by analyzing the quantitative sales of medicinal products that contain active substances of subgroup (A10 B) of oral antidiabetic drugs (type-2), approved by the State Department of Drugs and included in The State Register of Ukraine, The National list of a basic medicines, and the Compendium, during 3 years' period from 2014 to 2016.

The necessary data for the study were collected from The Database for retail "Pharmstandard" (Ukraine) for 2014–2016. The collected data were centralized and processed using Microsoft Office Excel 2010. The methods used in the research are described below.

The retrospective analysis: In this type of study, the data are collected from the past, from a previously established moment till the time of the research. In this case, the study was conducted on a specified timeframe, a period of 3 years relevant for the study carried out.

The sampling method: Implies that the sample selected should be representative for the target population on which the study is conducted and to which obtained results will be extrapolated. In the present case, for the research carried out the simple random sampling was used.

The comparison method: The obtained data were processed and interpreted according to the same criteria and taking into account the same parameters so that the results should be viable.

Descriptive methods: There were collected and analyzed the obtained data, there were observed the outcomes and the particularities of the results dependent on the criteria and the conclusions were drawn.<sup>[5]</sup>

According to introduction to drug utilization research,<sup>[6]</sup> study of drug consumption was conducted using anatomical therapeutic chemical/defined daily dose(DDD) methodology by calculating such figures as utilization in DDD, DDDs per 1000 inhabitants per day (DDD/1000 PD), and expenditure per DDD.

## RESULTS

It was evaluated that consumption index DDDs/1000 PD for monoagents of A10B group decreased from 11.57 DDDs/1000 PD in 2014 to 10.99 DDDs/1000 PD in 2015, namely, with 0.58 DDD/1000 PD in absolute values or with 5% in relative one. It can be explained that according to statistics data of the Ministry of Statistics of Ukraine the number of population was decreased from 43 570 280 inhabitants in 2014 to 42 910 885 inhabitants in 2015 (declined by 1.5%). The thing to note here is that statistics data do not include population of the temporarily occupied territory of the Autonomous Republic of Crimea and uncontrolled parts of Donetsk and Luhansk regions (2014).

At the same time, the unstable economic situation in the country affected the consumption of drugs; the devaluation of the national currency during the period of 2014–2015 was approximately 58%, which resulted in a decrease of population's consumer purchasing abilities.

Consumption index DDDs/1000 PD of monoagents of A10B group in 2016 was 15.45 DDDs/1000 PD. This amount was increased by 4.46 DDDs/1000 PD in absolute values or with 40.58% in relative one comparing with the consumption of antidiabetic drugs in 2015.

In 2016, the population of Ukraine declined by 238 356 inhabitants (0.55%) as against 2015. Stabilization of the economic situation, minor fluctuations of the national currency (15%) and the introduction of a National Policy of Providing Population with affordable medicines in the framework of the prevention of the widening of T2DM had become a prerequisite for increasing the level of consumption of oral antidiabetic drugs (OADs) during 2015–2016 [Table 1].

The structure of OAD consumption in Ukraine 2015–2016 shows a jump in the consumer level in the *Biguanides* group (+51.21%), *Sulfonylureas* (+74.57%), *Repaglinide* agents (+91.67%), *Liraglutide* agents (+40%), *Pioglitazone* agents (+33.3%), and *Dapagliflozin* agents (+35%).

An insignificant decrease in consumption rates (DDD/1000 inhabitants/day) was in the group dipeptidyl peptidase-4 inhibitors (*DPP-4*) (saxagliptin, sitagliptin) – fell by 0.21%.

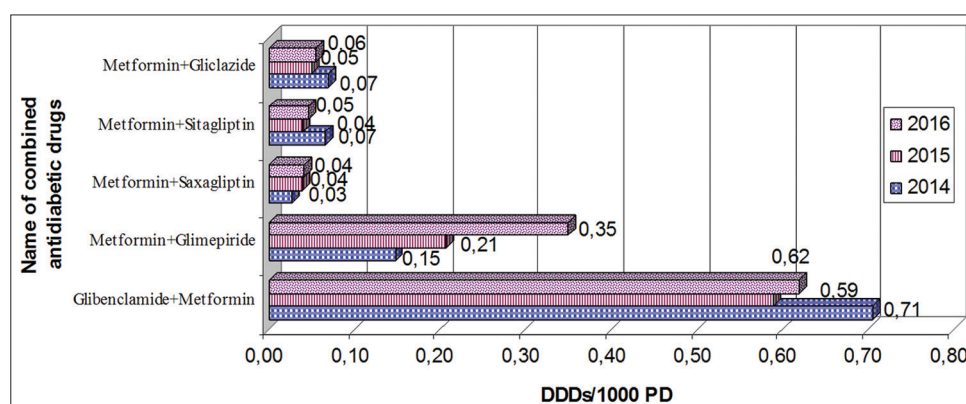
Analyzing the level of consumption of combined antidiabetic drugs the reducing of consumption during 2014–2015 by 9.3% can be observed. The DDDs/1000 PD consumption rate in 2016 was 1.11 DDDs/1000 PD, which in comparison with the consumption of antidiabetic drugs in 2015 increased by 0.19 DDDs/1000 PD in absolute values or with 18.7% in relative one [Figure 1]. The most significant increase in consumption was recorded for drugs containing a combination of metformin and glimepiride (68.60%).

The analysis of the expenditure per day indicator allowed the allocation of three groups of antidiabetic drugs, depending on the cost of 1 unit of DDD in T2DM monotherapy. The most expensive drug was Victoza® (liraglutide, 6 mg/ml, 3 ml, № 2, Novo Nordisk). It was observed increasing of the expenditure per day of Victoza® during 2014–2016. In 2015, it was 3034 UAH/DDD, which grew by 88% in relative one compared to 2014, and in 2016, the growth was 2%.

The second group, by the expenditure of 1 unit of DDD, was consisted of sitagliptin, saxagliptin, repaglinide, and dapagliflozin. The mean value of the studied index for Forxiga® (dapagliflozin, tablet 5 mg № 30, AstraZeneca AB) was 35.3 UAH/DDD for 2015–2016. There should be noted an increase in the value of the studied indicator for Novonorm® (repaglinide, tablet 1 mg № 30, Novo Nordisk) by 88%

**Table 1:** The consumption rates of DDDs/1000 PD of oral monoantidiabetic drugs, 2016 *versus* 2015, 2014

Name	Calendar year			Abatements	
	2014	2015	2016	Absolute	Relative
	x	y	z	z-y	$((z-y)/y)*100$
Metformin	3.34	3.3	4.99	1.69	51.21
Glimepiride	3.24	3.3	5.6	2.3	69.70
Gliclazide	3.12	2.85	3.43	0.58	20.35
Glibenclamide	1.68	1.39	1.25	-0.14	-10.07
Gliquidone	0.05	0.04	0.035	-0.002	-5.41
Saxagliptin	0.036	0.028	0.03	0.0019	6.79
Sitagliptin	0.028	0.01	0.009	-0.0007	-7.00
Pioglitazone	0.028	0.024	0.032	0.008	33.33
Repaglinide	0.021	0.012	0.023	0.011	91.67
Dapagliflozin	0.02	0.04	0.054	0.014	35.00
Liraglutide	0.0002	0.0001	0.00014	0.00004	40.00
Total	11.57	10.99	15.45		

**Figure 1:** The consumption rates of DDDs/1000 PD of oral combined antidiabetic drugs, 2016 *versus* 2015, 2014

for 2014–2015, and for the next period of 2015–2016, the growth amounted to 8.3–10.4%. The expenditure per day for Onglyza® (saxagliptin, tablet 2.5 mg № 30, AstraZeneca AB) varied from 26.07 UAH/DDD in 2014 to 34.79 UAH/DDD in 2016. Among the reported doses of Januvia® (sitagliptin, Merck and Co), the highest values of expenditure per day were obtained for the tablet 25 mg, № 14, that was amounting to 60.99 UAH/DDD in 2014, but in the following years, there was a tendency of growth of 21.6–49% in relative one. Drugs included in the second group by the cost of 1 unit DDD were the original medicines that appeared on the pharmaceutical market of Ukraine during the last decade and were represented by world pharmaceutical companies.

Pioglitazone, metformin, and sulfonylureas composed the third group by the cost of 1 unit of DDD. The pharmaceutical market of Ukraine has registered six medicines containing pioglitazone. The highest values of expenditure per day were obtained for Pioglar (tablet 15 mg, № 30, Sun Pharmaceutical Industries Ltd), which was 8.09 UAH/DDD in 2014, during next years an increasing the index by 82.7% in relative one was observed. The value of the studied indicator varied within

the range of 4.28–5.87 UAH/DDD for Glutazone (tablet 15, 30, and 45 mg, № 28, Kusum Pharm) in 2014. The growth rate of the studied indicator for these drugs is 19.4–27.5% in 2015, and for the next period 2015–2016, the growth was 1.9–7.1%.

Among the metformin agents, the highest values of expenditure per day were evaluated for such brands as Glucophage XR and Siofor, as well as a number of other drugs were presented by foreign manufacturers [Figure 2].

For drugs containing metformin of domestic production, the expenditure per day ranged from 1.79 to 6.53 UAH/DDD in 2014. The growth rate of the studied indicator for these drugs, sometimes up to 84% in 2015, and the next period of 2015–2016 the researched index was decreased.

In the sulfonylureas group, the highest values of expenditure per day were obtained for the medicine with trade name Glurenorm (Gliquidone, tablet, 30 mg, № 60, Boehringer Ingelheim), which was 4.1 UAH/DDD in 2014. The value of the index in 2015 was increased by 72% in relative one, and in 2016, the value was decreased by 10%.

Among the products of Gliclazide, the highest values of the expenditure per day for 2014–2016 were obtained for Diabeton MR (tablet, 60 mg, № 30, Servier) - 3.1–3.7 UAH/DDD, Oziclide MR (tablet, 30 mg, № 60, Sun Pharmaceutical Industries Ltd) - 2.3–2.6 UAH/DDD, and Diaglizide MR (tablet, 60 mg, № 60, Pharmak JSC) - 2.14–2.46 UAH/DDD. For other domestic medicines containing Gliclazide, the value of the studied index ranged from 0.6 to 2.15 UAH/DDD.

The analysis of the index expenditure per day for glimepiride agents indicates about considerable financial costs for consumer purchases for such branded medicines as Amaryl, Sanofi-Aventis (2.49–3.21 UAH/DDD), Glemaz, Quimica Montpellier (1.53–4.75 UAH/DDD), Glimepiride, Sandoz (2.1–2.39 UAH/DDD), Oltar (Glimepiride), and Berlin-Chemie (2.28–4.08 UAH/DDD).

According to the results of the analysis of the expenditure per day, consumers had the lowest financial costs for glibenclamide agents. Somewhat, higher rates were obtained for the brand Maninil (Berlin-Chemie) at a dose of 3.5 mg № 120, which fluctuated within the range of 1.05–1.97 UAH/DDD during 2014–2016. For other domestic medicines

containing glibenclamide, the value of the studied index ranged from 0.3 to 0.6 UAH/DDD.

Among the combined antidiabetic drugs, the results of the expenditure per day were the highest for original drugs: Janumet (Merck & Co) – combination of metformin with sitagliptin; Komboglyze XR (AstraZeneca AB) – combination of metformin and saxagliptin [Figure 3]. Combined preparations of metformin with glimepiride are commercially available Amaryl M 2/500, Amaryl M SR (Sanofi-Aventis), and Duglimax (Kusum Pharm). Fluctuations in the value of the studied indicator for these drugs increased by 11–25% in 2015, but for the next period 2015–2016, the growth was insignificant.

Fluctuations of the expenditure per day for combined metformin and glibenclamide named as Glibomet (Berlin-Chemie), Glucovance (Takeda), and Gliboform (Farmak JSC) increased by 62–69% in relative one during 2014–2015, and in 2016 increased just by 18–21%. The combination of metformin with Gliclazide is represented by the trademark Dianorm M (Micro Labs); the dynamics of the analyzed index are shown in Figure 3.

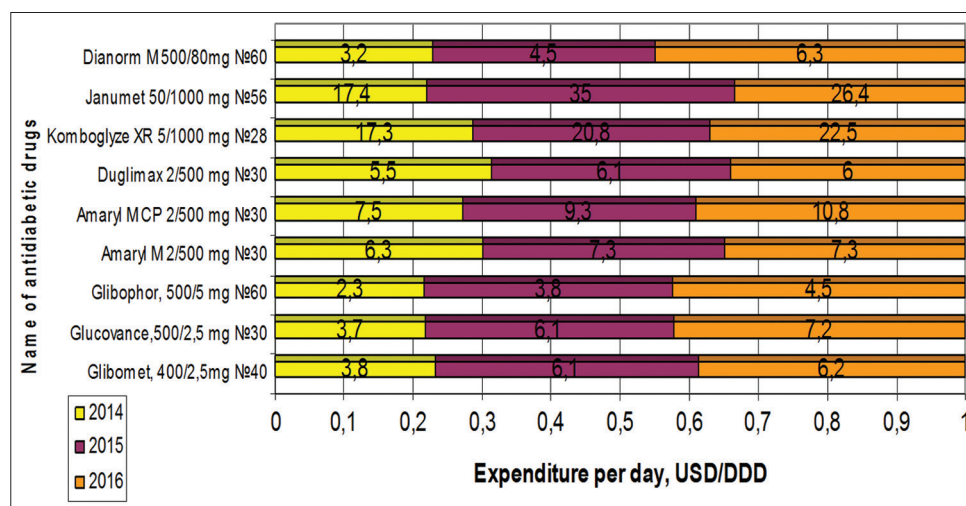


Figure 2: The expenditure per day for oral antidiabetic drugs, 2016 versus 2015, 2014

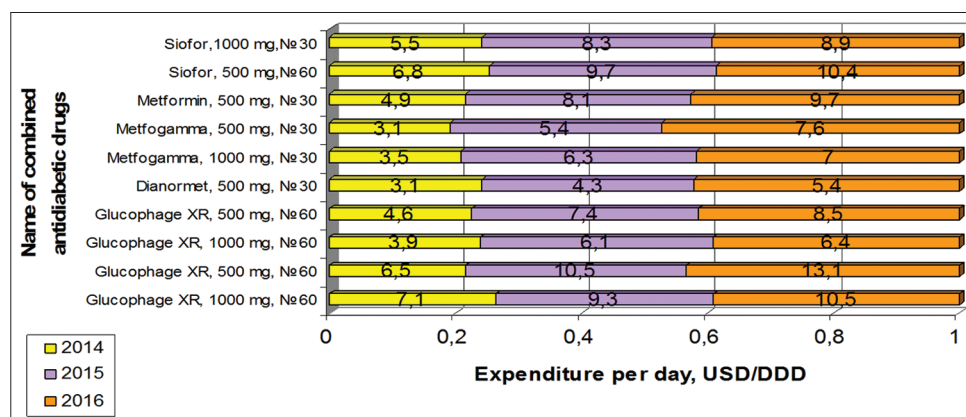


Figure 3: The expenditure per day for combined oral antidiabetic drugs, 2016 versus 2015, 2014



## DISCUSSION

With respect to cost, quality of life, and the number of hypoglycemic events averted, metformin remains the recommended first-line agent in the pharmacologic management of T2DM in the elderly.<sup>[7-9]</sup> The study conducted by López-Sepúlveda *et al.*<sup>[10]</sup> showed increasing the consumption of metformin (alone) from 4.3 DDD to 23.7 DDD and reducing of usage sulfonylureas from 30.1 DDD to 16.4 DDD. Metformin was the most consumed agent in 2014. A rise in consumption of DPP-4 inhibitors and “other hypoglycemic agents” was also noticed.<sup>[10]</sup> Likewise, the most prescribed medications according to research of Gaviria-Mendoza *et al.*<sup>[11]</sup> were metformin 81.3%, insulins 3.3%, and sulfonylureas 21.8%. Lunger *et al.*<sup>[12]</sup> presented results of research where metformin was used most frequently (47.9% of the study population), followed by gliptines (27.2%). Results of research in Australia also confirmed 5-fold increasing of metformin utilization between 1995 and 2012.<sup>[13]</sup> According to American findings from 2006 to 2013, use increased for metformin (from 47.6 to 53.5%), DPP-4 inhibitors (0.5–14.9%), and insulin (17.1–23.0%) but declined for sulfonylureas (38.8–30.8%) and thiazolidinediones (28.5–5.6%).<sup>[14]</sup> The study by Weng *et al.*<sup>[15]</sup> revealed that the use of a single oral antidiabetic drug was the most common diabetes medication-related claim (46.2% of patients in 2007; 56.7% of patients in 2012). Among monotherapy users, metformin was the most commonly used and increased from 2007 (74.7% of OAD monotherapy users) to 2012 (90.8%).

In our study, the consumption of metformin (alone) was increased from 3.34 DDDs/1000 PD (2014) to 4.99 DDDs/1000 PD (2016) as well. In the same time, the usage sulfonylureas were increased from 8.09 DDDs/1000 PD (2014) to 10.32 DDDs/1000 PD (2016). Interestingly that in our case, metformin was the most consumed agent in 2014–2015, but in 2016, glimepiride was the most drug utilization agent. It can be confirmed by American scientists<sup>[16]</sup> results that sulfonylureas still represented 47% of all second-line drug starts, with proportionately higher use in patients  $\geq 75$  years of age (63% of drug starts). According to the statement of the American Diabetes Association and European Association for the Study of Diabetes guidelines also endorses metformin is the first-line drug for T2DM patients and has the lowest risk of hypoglycemia, it does not cause weight gain and weight loss, has the beneficial effect of lowering the lipid levels and available at a low cost.<sup>[17,18]</sup>

A nationwide population-based study from Taiwan indicated that sulfonylureas were the most common alternatives to metformin for monotherapy.<sup>[19]</sup> The study which provided the estimation of health care use and expenditure for diabetes in Bangladesh shows that 9.8% patients reported not taking any antidiabetic medications, 46.4% took metformin, and 38.7% sulfonylurea, over the preceding 3 months.<sup>[20]</sup>

Patients with T2DM typically use several drug treatments during their lifetime.<sup>[21]</sup> There is a debate about the best second-line therapy after metformin monotherapy failure due to the increasing number of available antidiabetic drugs and the lack of comparative clinical trials of secondary treatment regimens.<sup>[21]</sup> German scientists presented results that over the course of treatment, the number of patients receiving multiple medications increased from 5% to 30%. The most frequent combinations were metformin/DPP-4 inhibitor, metformin/sulfonylureas, and metformin/insulin.<sup>[22]</sup> The most common treatment regimen in this population was the dual therapy of metformin and another OAD (17.2%), followed by metformin monotherapy (16.6%) and triple therapy of metformin and two additional OAD (11.0%).<sup>[12]</sup> In our research, the higher consumption rates of OAD were received for such combinations as glibenclamide with metformin and glimepiride with metformin.

It was also confirmed by clinical studies of Danish scientists<sup>[23]</sup> that the level of consumption of glucose-lowering drug increased every year. Metformin uses increased more than 7-fold during the period and was used by 30 of 1000 inhabitants in 2014, while the prevalence of insulin use increased 1.8-fold to 13 per 1000 in 2014. After peaking in 2007, use of sulfonylurea halved to 6 per 1000 in 2014.<sup>[23]</sup> Among newer drug classes of OAD, the most consumed were glucagon-like peptide 1 (GLP-1) receptor agonists, the DPP-4 inhibitors, and the sodium-glucose cotransporter 2 (SGLT-2) inhibitors.<sup>[24]</sup> According to research of Boulin M *et al.*, DPP-4 inhibitors showed favorable cost-effective profiles for adults aged 80 years and older in both the US and Canada, as well as for adults aged 65–79 years in Canada only.<sup>[25]</sup> However, DPP-4 inhibitors were not found to be cost-effective in adults aged 65–79 years in the US because of higher drug acquisition costs.<sup>[25]</sup> The research of changes in the pharmacotherapy and glycemic control trends in elderly patients with T2DM in Japan shows that in the  $\geq 75$  age group, DPP-4 inhibitors became the most frequently prescribed drug (49.1%) in 2013, and sulfonylureas remained the second-most frequently prescribed drug (37.8%) with decreased prescribed doses.<sup>[26]</sup> A pharmacoeconomic study of DPP-4 inhibitor cost-effectiveness in Minas Gerais state, Brazil, confirmed the higher position of sitagliptin/metformin combination.<sup>[27]</sup>

In Ukraine, we could observe the same trend. GLP-1 receptor agonists incurred slightly higher rates of hypoglycemia and relative to sulfonylureas were only cost-effective in the US for adults aged 80 years and older.<sup>[25]</sup> We found out that consumption of DPP-4 class agents had reached a considerable position in 2014 - 0.064 DDDs/1000 PD, against lower results during 2015–2016 years - 0.038–0.039 DDDs/1000 PD, respectively. However, the use of other classes such as GLP-1, SGLT-2, and thiazolidinediones was increased approximately by 35%.

The research of the expenditure of OAD in Colombian population shows the cost per 1000 inhabitants/day was

1.21 USD for metformin, 3.89 USD for insulins, and 0.02 USD for glibenclamide.<sup>[11]</sup> According to López-Sepúlveda *et al.*,<sup>[10]</sup> research of overall expenditure in antidiabetic medications increased notably from 4.5 million euros in 2001 to 14.4 million euros in 2014. In our study of Ukrainian pharmaceutical market about overall expenditure of oral antidiabetic medications, we can see its notable rising up from 22.6 million USD in 2014 to 56.1 million USD in 2016.

## CONCLUSION

The features of consumption of oral antidiabetic medicines in Ukraine during 2014–2016 have been analyzed. A slight decreasing of A10B group agents' consumption in the period of 2014–2015 has been established. In 2016, there was a trend to increase the value of DDDs/1000 PD for monopreparations by 40.58% versus 2015 in relative one, and for combined - 18.7% in relative one. The most common used antidiabetic drugs were glimepiride, metformin, and gliclazide, which were combined of glibenclamide/metformin or metformin/glimepiride.

An analysis of the consumption of drugs for the treatment of T2DM, depending on the expenditure per DDD was also carried out. The highest results of expenditure per DDD were the original branded medicines Victoza®, Forxiga®, Novonorm®, Onglyza®, and Januvia®. Pioglitazone, metformin, sulfonylureas, and combined drugs were the most affordable ones according to the studied index.

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