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PHARMACOECONOMIC EVALUATION OF THERAPY SCHEME OF THE 2ND TYPE DIABETES IN THE VINNYTSIA REGIONAL CLINICAL ENDOCRINOLOGY CLINIC IN 2011-2012 (UKRAINE)

T.A. Germanyuk, T.I. Ivko

Department of Pharmacy, National Pirogov Memorial Medical University, Vinnytsia, Ukraine

Summary The pharmacoeconomic study on the medicine regimens of diabetes mellitus (DM) type 2 was conducted with the purpose of their improvement. The research was based on the retrospective analysis of 599 medical histories of patients of type 2 diabetes. These patients were treated at the Vinnytsia Regional Clinical Endocrinology Clinic in 2011-2012. The studies of medicine regimens were performed by the «cost-effectiveness» analysis. We have found that the scheme of pharmacotherapy metformin+gliclazide has cost-effective advantage over the scheme pharmacotherapy metformin+glimepiride.

Relevance. (T2DM) type diabetes mellitus is a medical and social problem. The prevalence of diabetes increased among the adult population aged 20-79 years from 7,6% in 2003 to 9,6% in 2011 in the European Union [1]. The proportion of patients with DM has increased by 26% for the past 5 years in Ukraine [2]. DM complications create dangers increasing mortality, disability and reducing quality of life significantly [3,4]. Economically and clinically grounded choice of schemes of the DM therapy is gaining great importance in modern conditions. The study of the costs and effectiveness of pharmacotherapy of T2DM is a weighty component of pharmacoeconomic analysis [5,6], which is the basis for selection of the least expensive and most effective schemes of pharmacotherapy. According to researches' opinion, pharmacoeconomic analysis is an essential link in the development of treatment standards and creating a national formulary of medicaments [7].

The purpose: to define pharmacoeconomically-based therapy scheme of T2DM.

Research objectives:

- 1) carrying out retrospective analysis of medical histories and treatment sheet of T2DM patients in hospital treatment conditions;
- 2) frequency analysis of the consumed treatment regimens;
- 3) analysis of patients included in the study, according to the certain parameters (age, gender, body mass index (BMI), fasting plasma glucose (FPG) when it's applied, hospital stay, complications) in the context of medicament regimens;
- 4) conducting ATC/DDD-analysis of oral hypoglycemic medicines (OHM) included in the studied schemes of pharmacotherapy; medicament regimens T2DM by the analysis of «cost - effectiveness.»

The object of the study: the pharmacotherapy of T2DM patients in stationary conditions.

The research materials:

1. official data on the prevalence of T2DM in Ukraine and worldwide
2. 599 medical histories and treatment sheets of T2DM patients treated in the Vinnytsia regional clinical endocrinology clinic (VRCEC) in 2011-2012.

Research methods:

1. retrospective analysis of medical histories and treatment sheets
2. frequency analysis of the consumed treatment regimens
3. ATC/DDD-analysis
4. «cost-effectiveness» analysis

Study results. To select the most frequently used medicine regimens we have conducted the frequency analysis of all (599) medical histories and treatment sheets of T2DM patients included in this study. The selection of treatment regimens was carried out by endocrinologists. All the patients treated in 2011-2012 in the VRCEC were included in the study.

As a result of the conducted frequency analysis it was concluded that the most frequently used were the following schemes of pharmacotherapy: metformin+glimepiride applied in 43,1% of cases, gliclazide+metformin - 16%, metformin monotherapy - in 15,5% of cases. The treatment was applied for all the patients, according to the state standard for the management of T2DM patients [8], which reckons for the application of monotherapy and combination therapy for the treatment. The above presented pharmacotherapy schemes were used for 445 patients. The other 144 patients received various pharmacotherapy schemes at a frequency from 0,2% to 8% (Picture1).

Thus, in the scopes of the study for the pharmacoeconomic analysis there were included three most commonly used medicament regimens: the first group of patients (91 patients) was on monotherapy with metformin, the second group (96 patients) received a combination of metformin+gliclazide, the third group (258 patients) - a combination of metformin+glimepiride.

All the patients had complications of T2DM. Hence, in the 1st group retinopathy was found in 34% of patients, angiopathy - in 86%, neuropathy - in 88%, nephropathy - in 14,5%, cardiovascular complications - in 83,5%. In the 2nd group retinopathy was observed in 66,7% of patients, angiopathy - in 98%, neuropathy - in 97%, nephropathy - in 19%, cardiovascular complications - in 83%. In the 3rd group retinopathy was found in 45% of patients, neuropathy - in 91% angiopathy - in 88,8%, nephropathy - in 17,4%, cardiovascular complications - in 91,5%. Taking into account the commonness of pathogenesis in the current research, the percentage of patients with complexity in every group was 100%.

Patients of the 1st and 2nd groups had authentic distinctions in age, BMI, FPG while admission, on average reduction in FPG during the treatment period, duration of illness, hospital stay and the number of effective patients but they did not differ authentically on indicators of FPG at discharge when comparing groups of patients (Table 1). The patients of the 1st and 3rd groups authentically distinguished from each other on all the analyzed parameters. The patients of the 2nd and 3rd groups had authentic distinctions on the number of patients with the effectiveness and had not authentic distinctions on all the other analyzed indicators.

Drug Combination	Percentage
metformin+glimepiride	43,00%
metformin+gliclazide	16,00%
metformin+glibenclamide	15,00%
metformin+pioglitazone	3,50%
glibenclamide	1,50%
gliclazide	1,50%
metformin+glimepiride+pioglitazone	1,50%
metformin+glimepiride+glibenclamide	1,50%
metformin+glimepiride+gliclazide	1,50%
gliquidone	1,50%
metformin+gliquidone	1,00%
glimepiride+pioglitazone	1,00%
metformin+repaglinide	1,00%
gliclazide+gliquidone	0,50%
metformin+glibenclamide+pioglitazone	0,50%
metformin+gliclazide+pioglitazone	0,50%
sitagliptin	0,50%
metformin+gliclazide+gliquidone	0,50%
saxagliptin in combination	8,00%

Consequently, the patients who were on the 1 treatment regimen were significantly younger, had the highest BMI, the lowest FPG while hospital admission, the lowest duration of T2DM illness, the lowest FPG at discharge and authentically a lower average FPG reduction during the treatment period (Table 1).

names (IUN) amounted to 2,000mg of metformin, 60mg of gliclazide, 2mg of glimepiride. Their prices were researched in hryvnas (UAH) at the regional pharmaceutical market Vinnitsia and Vinnitsia region with calculation value of each pharmacotherapy regimens (Table 2, 3, 4).

Table 1. Characteristics of patients at different pharmacotherapy regimens.

Indicators	Pharmacotherapy schemes			The significance of differences
	Metformin Scheme 1	Metformin + gliclazide Scheme 2	Metformin + glimepiride Scheme 3	
The number of patients	91	96	258	
Age (years)	55,62±1,17	60,58±0,85	59,30±0,53	p1-2<0,05 p1-3<0,05 p2-3>0,05
Gender (woman/man,%)	40/51 44/56	51/45 53/47	142/116 55/45	
BMI (kg/m2)	33,92±0,55	30,75±0,38	31,65±0,33	p1-2<0,05 p1-3<0,05 p2-3>0,05
FPG on hospital admission (mmol/L)	9,35±0,21	11,39±0,34	11,12±0,19	p1-2<0,05 p1-3<0,05 p2-3>0,05
Duration of illness (years)	6,63±0,62	9,60±0,74	8,42±0,35	p1-2<0,05 p1-3<0,05 p2-3>0,05
Hospital stay (days)	10,36±0,25	11,33±0,15	10,99±0,10	p1-2<0,05 p1-3<0,05 p2-3>0,05
FPG on exit (mmol/L)	6,71±0,15	6,98±0,17	7,26±0,10	p1-2>0,05 p1-3<0,05 p2-3>0,05
Mean reduction FPG during the treatment period (mmol / L)	2,63±0,18	3,67±0,30	3,86±0,17	p1-2<0,05 p1-3<0,05 p2-3>0,05
Number of effective patients (%)	63±2,92	54±3,95	48±1,98	p1-2<0,05 p1-3<0,05 p2-3<0,05

Table 2. DDD cost for 1st scheme of pharmacotherapy.

№	Medicine trade name	Cost of DDD (UAH)	The cost of 10 days of pharmacotherapy (UAH)
1.	Glucophage 850 mg t.№30	4,26*	42,6*
2.	Glucophage 500 mg t.№30	3,63	36,3
3.	Glucophage 1000 mg t.№30	3,38	33,8
4.	Siofor 500 mg t.№60	2,97	29,7
5.	Siofor 850 mg t.№60	2,15	21,5
6.	Siofor 1000 mg t.№30	2,46	24,6
7.	Metformin Sandoz 500 mg t.№120	2,47	24,7
8.	Metformin Sandoz 850 mg t.№120	1,88	18,8
9.	Diaformin 1000 mg t.№60	2,28	22,8
10.	Diaformin 850 mg t.№30	1,45	14,5
11.	Diaformin 500 mg t.№30	2,0	20,0
12.	Metformin Kutno 500 mg t.№30	1,43	14,30
13.	Metformin Teva 500 mg t.№30	1,25*	12,50*

* – marked minimum and maximum price scheme 1

As a result of ATC/DDD-analysis it was found that the cost for DDD of monotherapy with metformin ranged from 1,25 to 4,26 UAH.

Table 3. DDD cost for the 2nd scheme of pharmacotherapy.

№	Medicine trade names	Cost of DDD (UAH)	The cost of 10 days of pharmacotherapy (UAH)
1.	Glucophage 850 mg t.№30+ Diabeton MR 60 mg t. № 60	5,34*	53,4*
2.	Glucophage 500 mg t.№30+ Diabeton MR 60 mg t. № 60	4,71	47,1
3.	Glucophage 1000 mg t.№30+ Diabeton MR 60 mg t. № 60	4,46	44,6
4.	Siofor 500 mg t.№60+ Diabeton MR 60 mg t. № 60	4,05	40,5
5.	Siofor 850 mg t.№ 60+ Diabeton MR 60 mg t. № 60	3,23	32,3
6.	Siofor 1000 mg t.№30+ Diabeton MR 60 mg t. № 60	3,54	35,4
7.	Siofor 500 mg t.№60+ Diaglizid MR 30mg t № 60	4,30	43,0
8.	Siofor 850 mg t.№ 60+ Diaglizid MR 30mg t № 60	3,48	34,8
9.	Siofor 1000 mg t.№30+ Diaglizid MR 30mg t № 60	3,79	37,9
10.	Diaformin 1000 mg t.№60+ Diabeton MR 60 mg t. № 60	3,36	33,6
11.	Diaformin 850 mg t.№ 30+ Diabeton MR 60 mg t. № 60	2,53*	25,3*
12.	Diaformin 500mg t.№30+ Diabeton MR 60 mg t. № 60	3,08	30,8

* – marked minimum and maximum price scheme 2

DDD (defined daily dose, average daily dose) was studied to carry out the ATC/DDD-analysis [10]. DDD for medicines with the international unlicensed

As a result of ATC/DDD-analysis it was found that the cost for the DDD scheme 2 ranged from 2,53 to 5,34 UAH.

Table 4. DDD cost for the 3rd scheme of pharmacotherapy.

№	Medicine trade name	Cost DDD (UAH)	The cost of 10 days of pharmacotherapy (UAH)
1.	Glucophage 500mg t № 30 + Amaryl 2mg t № 30	5,88	58,8
2.	Glucophage 500mg t № 30 + Amaryl 3mg t № 30	5,65	56,5
3.	Glucophage 500mg t № 30 + Amaryl 4mg t № 30	5,66	56,6
4.	Glucophage 850mg t № 30 + Amaryl 2mg t № 30	6,51*	65,1*
5.	Glucophage 850mg t № 30 + Amaryl 3mg t № 30	6,28	62,8
6.	Glucophage 850mg t № 30 + Amaryl 4mg t № 30	6,29	62,9
7.	Glucophage 1000mg t № 30 + Amaryl 2mg t № 30	5,63	56,3
8.	Glucophage 1000mg t № 30 + Amaryl 3mg t № 30	5,4	54
9.	Glucophage 1000mg t № 30 + Amaryl 4mg t № 30	5,41	54,1
10.	Siofor 500mg t № 60 + Amaryl 2mg t № 30	5,22	52,2
11.	Siofor 500mg t № 60 + Amaryl 3mg t № 30	4,99	49,9
12.	Siofor 500mg t № 60 + Amaryl 4mg t № 30	5,0	50
13.	Siofor 850mg t № 60 + Amaryl 2mg t № 30	4,4	44
14.	Siofor 850mg t № 60 + Amaryl 3mg t № 30	4,17	41,7
15.	Siofor 850mg t № 60 + Amaryl 4mg t № 30	4,18	41,8
16.	Siofor 1000mg t № 30 + Amaryl 2mg t № 30	4,71	47,1
17.	Siofor 1000mg t № 30 + Amaryl 3mg t № 30	4,48	44,8
18.	Siofor 1000mg t № 30 + Amaryl 4mg t № 30	4,49	44,9
19.	Glucophage 500mg t № 30 + Diapirid 2mg t № 30	4,79	47,9
20.	Glucophage 500mg t № 30 + Diapirid 3mg t № 30	4,45	44,5
21.	Glucophage 500mg t № 30 + Diapirid 4mg t № 30	4,73	47,3
22.	Glucophage 850mg t № 30 + Diapirid 2mg t № 30	5,42	54,2
23.	Glucophage 850mg t № 30 + Diapirid 3mg t № 30	5,08	50,8
24.	Glucophage 850mg t № 30 + Diapirid 4mg t № 30	5,36	53,6
25.	Glucophage 1000mg № t 30 + Diapirid 2mg t № 30	4,54	45,4
26.	Glucophage 1000mg № t 30 + Diapirid 3mg t № 30	4,20	42
27.	Glucophage 1000mg № t 30 + Diapirid 4mg t № 30	4,48	44,8
28.	Diaformin 500mg t № 30 + Diapirid 2mg t № 30	3,16	31,6
29.	Diaformin 500mg t № 30 + Diapirid 3mg t № 30	2,82	28,2
30.	Diaformin 500mg t № 30 + Diapirid 4mg t № 30	3,10	31
31.	Diaformin 850mg t № 30 + Diapirid 2mg t № 30	2,61	26,1
32.	Diaformin 850mg t № 30 + Diapirid 2mg t № 30	2,27*	22,7*
33.	Diaformin 850mg t № 30 + Diapirid 2mg t № 30	2,55	25,5
34.	Diaformin 1000mg t № 60 + Diapirid 2mg t № 30	3,44	34,4
35.	Diaformin 1000mg t № 60 + Diapirid 3mg t № 30	3,10	31
36.	Diaformin 1000mg t № 60 + Diapirid 4mg t № 30	3,38	33,8

* – marked minimum and maximum price scheme 4

As a result of ATC/DDD-analysis it was found that the cost for DDD of the scheme 3 fluctuated from 2,27 to 6,51 UAH.

In the scopes of the “cost-effectiveness” analysis we have calculated the cost of blood sugar decrease on 1 mmol / L, the number of effective patients and cost in case of normoglycemia for every scheme of pharmacotherapy (Table 5). The cost of blood sugar decrease on 1 mmol / l was calculated based on the following formula:

$$T = A/B, \text{ where:}$$

T – the cost of blood sugar decrease on 1 mmol / l in UAH.

A – the cost of DDD for 10 days of pharmacotherapy in UAH.

B – the level of FPG of blood decrease during the period of hospital stay in mmol/l.

In regards to the number of effective patients we considered the percentage

of patients whose FPG level after pharmacotherapy became <7mmol/l (normoglycemia in T2DM patients [8,11]). For the calculations of the cost of 1 case normoglycemia the following formula was used:

$$M = D \times C / K, \text{ where:}$$

M – cost of one effective patient (UAH)

D – cost of a 10-day course of treatment of OHM based on DDD (UAH)

C – total number of patients treated with some medicine regimens

K – number of effective patients treated, according to the current regimens of pharmacotherapy

The calculations based on the minimum and maximum prices of OHM at the regional pharmaceutical market became the results of analysis.

The “cost-effectiveness” analysis of monotherapy with metformin revealed that the cost of blood sugar decrease on 1 mmol/L fluctuated from 4,75 to 16,20 UAH, the number of effective patients for this scheme was 63%, and for the 1-case of normoglycemia - from 19,95 to 68,02 UAH. (Table 5).

Table 5. The results of the “cost-effectiveness” analysis for the scheme 1.

Scheme of pharmacotherapy (INN)	Scheme of pharmacotherapy (trade names)	Cost of DDD (UAH)	Cost of DDD10 days (UAH)	Decrease of sugar of blood for 10 days of treatment (mmol / l)	Cost of decrease of blood sugar on 1 mmol / L (UAH)	Number of effective patients (%)	Cost of 1- case normoglycemia (UAH)
metformin	Metformin Teva 500mg t. №30	1,25	12,50	2,63±0,18	4,75	63	19,95
	Glucophage 850mg t. №30	4,26	42,60		16,20		68,02

The “cost-effectiveness” analysis of the scheme 2 revealed that the cost of blood sugar decrease on 1 mmol/L was from 6,80 to 14,55 UAH, the number of effective patients for this scheme was 53% and the cost of 1-case of normoglycemia - from 46,70 to 98,58 UAH. (Table 6).

The “cost-effectiveness” analysis of the scheme 3 revealed that the cost of blood sugar decrease on 1 mmol/L was from 5,88 to 16,86 UAH, the number of effective patients for this scheme was 48% and the cost for the 1-case of normoglycemia - from 47,60 to 136,55 UAH. (Table 6).

Table 6. The results of the “cost-effectiveness” analysis for the 2nd and 3rd schemes.

Scheme of pharmacotherapy (INN)	Scheme of pharmacotherapy (trade names)	Cost of DDD (UAH)	Cost of DDD10 days (UAH)	Decrease of sugar of blood for 10 days of treatment (mmol / l)	Cost of decrease of blood sugar on 1 mmol / L (UAH)	Number of effective patients (%)	Cost of 1- case normoglycemia (UAH)
metformin + gliclazide	Diaformin 850mg t № 60 + Diabeton MR 60mg t № 60	2,53	25,30	3,67±0,30	6,89	53	46,70
	Glucophage 850mg t № 30 + Diabeton MR 60mg t № 60	5,34	53,40		14,55		98,58
metformin + glimepiride	Diaformin 850mg t № 30 + Diapirid 3mg t № 30	2,27	22,70	3,86±0,17	5,88	48	47,60
	Glucophage 850mg t № 30 + Amaryl 2mg t № 30	6,51	65,10		16,86		136,55

To compare the schemes 2 and 3 we calculated the coefficients of “costs – efficiency” (CER2 and CER3, respectively), which is the ratio of the cost of treatment for the course of pharmacotherapy (DC2 and DC3, respectively) to the achievement of individual indicator of efficiency (Ef2 and Ef3).

In case of taking into account the maximum cost of OHM, the effectiveness ratio would be the following:

$$CER2 (\text{metformin+gliclazide}) = DC2/Ef2 = 53,40/0,53 = 100,75 \text{ UAH.}$$

$$CER3 (\text{metformin + glimepiride}) = DC3/Ef3 = 65,10/0,48 = 135,63 \text{ UAH.}$$

The comparison of CER2 and CER3 at maximum prices of OHM showed that in that case the metformin+gliclazide scheme was cheaper and more efficient, and metformin+glimepiride scheme was more expensive and less effective.

In case of taking into account the minimum cost of OHM, the effectiveness would be:

$$CER2 (\text{metformin+gliclazide}) = DC2/Ef2 = 25,30/0,53 = 47,74 \text{ UAH.}$$

$$CER3 (\text{metformin + glimepiride}) = DC3/Ef3 = 22,70/0,48 = 47,29 \text{ UAH.}$$

The obtained analysis results on determining the efficiency of the coefficients 2 and 3 of the pharmacotherapy regimens at minimal cost generics showed that the 2 and 3 medicine regimens were different by 2,6 UAH (a 10-day course of treatment of one patient), and the efficiency based on one patient with the pharmacotherapy scheme 2 was 0,53, and for the scheme 3 of pharmacotherapy – 0,48 ($p < 0,05$). Taking into account above stated, the incremental analysis of these medicine regimens [13] was conducted.

The calculations of the incremental “cost-effectiveness” ratio, which allowed to determine the cost of an additional unit of effectiveness became the result of the analysis based on more effective medicine regimens. It was calculated according to the following formula:

$$ICER = (DC2 - DC3) / (Ef2 - Ef3), \text{ where:}$$

ICER – cost of an additional unit of effectiveness

DC2, DC3 – cost of the scheme 2 and 3 in UAH, respectively

Ef2, Ef3 – efficiency indicators of the schemes 2 and 3, respectively, calculated per patient

Hence,

$$ICER = (DC2 - DC3) / (Ef2 - Ef3) = (25,30 - 22,70) / (0,53 - 0,48) = 52 \text{ UAH.}$$

The incremental value coefficient indicated the cost-effective benefits of the scheme 2 of pharmacotherapy (metformin + gliclazide) compared with the scheme 3 of pharmacotherapy (metformin + glimepiride).

Conclusions:

1) In the issue of frequency analysis it has been found that among included in research patients the following schemes of pharmacotherapy were applied the most frequently: metformin+glimepiride was applied in 43,1% of cases, gliclazide+metformin - in 16%, metformin monotherapy - in 15,5% of cases.

2) The patients of the 1st and 2nd groups had authentic distinctions in age, BMI, FPG while hospital admission, with the average reduction in FPG during the treatment period, the least duration of illness, hospital stay and the number of effective patients. The patients of the groups 1 and 3 had authentically differed from each other in all the analyzed parameters. The patients of the 2nd and 3rd groups had authentic distinctions in the number of effective patients and had not authentic distinctions in all other analyzed indicators.

3) As a result of the ATC/DDD-analysis it was found that the cost for DDD of the monotherapy with metformin ranges from 1,25 to 4,26 UAH, for the metformin+gliclazide – from 2,53 to 5,34 UAH, for the metformin+glimepiride – from 2,27 to 6,51 UAH.

4) As a result of the “cost-effectiveness” analysis of the monotherapy with metformin it was found that cost of blood sugar decrease on 1 mmol/L ranged from 4,75 to 16,20 UAH, the number of effective patients for this pharmacotherapy scheme was 63%, and the cost of the 1-case of normoglycemia which from 19,95 to 68,02 UAH.

5) As a result of the “cost-effectiveness” analysis for the medicine regimens 2 and 3 it was found that the scheme 2 was cheaper and more efficient in case of using the maximum cost of OHM.

6) The incremental value coefficient indicated the cost-effective benefits of the scheme 2 of pharmacotherapy (metformin + gliclazide) compared with the scheme 3 of pharmacotherapy (metformin + glimepiride) in case of using the minimum cost of OHM.

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