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The study of the effectiveness of the combined therapy of diabetes mellitus based on the pharmacoeconomic analysis in Ukraine

Diabetes mellitus (DM) is a national health priority in the world and in Ukraine too.

Aim. To substantiate the choice of regimens for combined therapy of type 2 DM (T2DM).

Materials and methods. The research materials were retrospective analysis of 1792 medical histories of the inpatients with T2DM. These patients were treated in the endocrinology clinics of the Podolsky region of Ukraine. The methods of frequency analysis; ATC/DDD-methodology; cost-effectiveness analysis were used. The cost of a defined daily dose (DDD) of drugs was studied in UAH according to the data of the average retail price of drugs in Ukraine as of May 2017.

Results and discussion. The frequency analysis showed that the monotherapy with metformin, glimepiride and gliclazide was used in 25 % of cases, and combined therapy with metformin + glimepiride, metformin + gliclazide and metformin + glibenclamide was used in 66 % of cases when treating T2DM. It was found that inpatients with metformin + glibenclamide regimen were significantly older, with the longer duration of T2DM, with the highest body mass index and highest levels of fasting plasma glucose (FPG). When comparing inpatients with metformin + gliclazide regimen and metformin + glimepiride regimen a significant difference between the duration of the disease and the level of FPG on admission was determined, no other significant differences were found by other parameters analyzed. The ATC/DDD-methodology showed that metformin + glimepiride regimen had the minimum cost of DDD, and metformin + gliclazide regimen had the maximum cost of DDD. The cost-effectiveness analysis showed that the costs-efficiency ratio (CER) for metformin + glibenclamide regimen varies from 560.10 to 2138.49 UAH, for metformin + glimepiride – from 821.07 to 2300.20 UAH, for metformin + gliclazide – from 798.65 to 2128.60 UAH in the context of minimal and maximal prices of generics.

Conclusions. The frequency analysis showed that the combined therapy of T2DM was used in 66 % of cases. It was found that patients with metformin + glibenclamide regimen were significantly older, they had a longer duration of T2DM, the highest BMI and the highest levels of FPG. The regimen of the combined therapy with metformin + glibenclamide has the cost-effective advantages compared to other treatment regimens.

Key words: *diabetes mellitus; ATC/DDD methodology; cost-effectiveness analysis*

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Дослідження ефективності комбінованої терапії цукрового діабету в Україні на основі фармакоеконічного аналізу

Цукровий діабет (ЦД) 2 типу є серйозною медичною та соціальною проблемою.

Мета: наукове обґрунтування вибору схем комбінованої терапії ЦД 2 типу.

Матеріали та методи. Матеріалом стали 1792 медичних історій стаціонарних пацієнтів з ЦД 2 типу, які лікувалися в ендокринологічних клініках Подільського регіону України. Методи дослідження: частотний аналіз; ATC/DDD-методологія; аналіз витрати-ефективність. Вартість середньої добової дози DDD лікарських засобів досліджувалась у гривнях за даними середньої роздрібною ціни ЛЗ в Україні станом на травень 2017 року.

Результати та їх обговорення. В результаті частотного аналізу було встановлено, що в 25 % випадків застосовувалась монотерапія з метформіном, глімепіридом та гліклазидом; комбінації метформін + глімепірид, метформін + гліклазид та метформін + глібенкламід застосовувались у 66 % випадків. При порівнянні показників груп хворих, які вживали комбіновану терапію, встановлено, що хворі, які отримували метформін + глібенкламід, були достовірно старші з найбільшою тривалістю захворювання, а також з найбільшим індексом маси тіла та з найбільшим рівнем глюкози плазми натще при поступленні. При порівнянні показників груп хворих, які отримували метформін + глімепірид та метформін + гліклазид, встановлено достовірну відмінність між тривалістю захворювання та рівнем глюкози плазми натще при поступленні, за іншими аналізованими показниками не виявлено достовірних відмінностей. За результатами ATC/DDD-методології встановлено, що мінімальна вартість DDD була у схеми метформін + глібенкламід, максимальна – у схеми метформін + гліклазид. У результаті аналізу витрати-ефективність встановлено, що коефіцієнт витрати-ефективність CER для схеми метформін + глібенкламід коливався від 560,10 до 2138,49 грн, метформін + глімепірид – від 821,07 до 2300,20 грн, метформін + гліклазид – від 798,65 до 2128,60 грн в розрізі мінімальних та максимальних вартостей генериків.

Висновки. В результаті частотного аналізу встановлено, що для лікування ЦД 2 типу у 66 % випадків застосовувалась комбінована терапія. Встановлено, що пацієнти, які застосовували схему метформін+глібенкламід були значно старшими, мали більшу тривалість ЦД 2 типу, найвищий індекс маси тіла та найвищі рівні глюкози плазми натще. Фармакоеконічну перевагу серед комбінованих схем терапії має схема метформін+глібенкламід.

Ключові слова: *цукровий діабет; ATC/DDD-методологія; аналіз витрати-ефективність*

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Исследование эффективности комбинированной терапии сахарного диабета в Украине на основе фармакоэкономического анализа

Сахарный диабет (СД) 2 типа является серьезной медицинской и социальной проблемой.

Цель: научное обоснование выбора схем комбинированной терапии СД 2 типа.

Материалы и методы. Материалом стали 1792 медицинских историй стационарных пациентов с СД 2 типа, получавших лечение в эндокринологических клиниках Подольского региона Украины. Методы исследования: частотный анализ; АТС/DDD-методология; анализ затраты-эффективность. Стоимость средней суточной дозы DDD лекарственных средств (ЛС) исследовалась в гривнах по данным средней розничной цены ЛС в Украине по состоянию на май 2017 года.

Результаты и их обсуждение. В результате частотного анализа было установлено, что в 25 % случаев применялась монотерапия с метформином, глимепиридом и гликлазидом; комбинации метформин + глимепирид, метформин + гликлазид и метформин + глибенкламид применялись в 66 % случаев. При сравнении показателей групп больных, принимавших комбинированную терапию, установлено, что больные, получавшие метформин + глибенкламид были достоверно старше и с наибольшей продолжительностью заболевания, с наибольшим индексом массы тела и с наибольшим уровнем глюкозы плазмы натощак при поступлении. При сравнении показателей групп больных, получавших метформин + глимепирид и метформин + гликлазид, установлено достоверное отличие между длительностью заболевания и уровнем глюкозы плазмы натощак при поступлении, по другим анализируемым показателям не выявлено достоверных различий. По результатам АТС/DDD-методологии установлено, что минимальная стоимость DDD была у схемы метформин + глибенкламид, максимальная – у схемы метформин + гликлазид. В результате анализа затраты-эффективность установлено, что коэффициент затраты-эффективность CER для схемы метформин + глибенкламид колебался от 560,10 до 2138,49 грн, метформин + глимепирид – от 821,07 до 2300,20 грн, метформин + гликлазид – от 798,65 до 2128,60 грн в разрезе минимальных и максимальных стоимостей генериков.

Выводы. В результате частотного анализа установлено, что для лечения СД 2 типа в 66 % случаев применялась комбинированная терапия. Установлено, что пациенты, которые применяли схему метформин + глибенкламид, были значительно старше, имели большую продолжительность СД 2 типа, высокий индекс массы тела и высокие уровни глюкозы плазмы натощак. Фармакоэкономическое предпочтение среди комбинированных схем терапии имеет схема метформин + глибенкламид.

Ключевые слова: сахарный диабет; АТС/DDD-методология; анализ затраты-эффективность

Diabetes mellitus is a national health priority in the world and in Ukraine too. According of the data of the International Diabetes Federation (IDF) 415 million adults have diabetes. By 2040 this will rise to 642 million. There were more than 2 757.7 million people with DM in Ukraine in 2017. Approximately, from 87 to 91 % of all people with DM are estimated to have T2DM. The number of people with T2DM is growing [3]. Increase in prevalence determined the choice of the study object. Monotherapy and the combined therapy are used for the treatment of T2DM [2, 3, 4]. T2DM needs effective and economically substantiated therapy in the limited financing of healthcare. The scientific novelty of the research was in substantiation of the choice of regimens of the combined therapy of T2DM in Ukraine on the basis of the retrospective analysis of medical histories of patients with T2DM and the pharmacoeconomic analysis of the regimens used.

The aim of the work was to substantiate the choice of regimens for combined therapy of T2DM.

Materials and methods

The object of the study was the pharmacotherapy of T2DM. The study was conducted in 6 stages (Fig.).

The research materials were retrospective analysis of 1792 medical histories of the inpatients with T2DM. These patients were treated in the endocrinology clinics of the Podolsky region of Ukraine. The exclusion criteria for patients with T2DM were insulin therapy; dia-

betic foot of stages II-V; heart failure of stage III; patients older than 75 and younger than 30 years. Considering the short period of staying in hospital and the necessity of selecting the effective pharmacotherapy during this period the criterion for estimation was the level of fasting plasma glucose (FPG).

The methods of the frequency analysis, АТС/DDD-methodology, cost-effectiveness analysis were used. The cost of a defined daily dose (DDD) of drugs was studied in UAH at the pharmaceutical market of the Podolsky region of Ukraine in the context of price for generics according to the data of the average retail price of drugs in Ukraine as of May 2017 published in a weekly journal "Pharmacy". To analyze the results of the study the methods of mathematical statistics were used. Statistical data processing was performed using the Microsoft Excel 2007 software. The distribution of data was assessed using the Pearson's chi-squared test (χ^2). For statistical analysis of the results the parametric methods of statistics (normal distribution) were used. The Fisher's exact test was used to test the hypothesis about the identity of two variances to one general population (their equality or inequality). The confidence estimation of differences between samples was performed using the Student t-test. The quantitative values were presented in the form of ($x \pm m$) where x – the arithmetic mean, m – the average error. The comparison was considered at the significance level of 0.05.

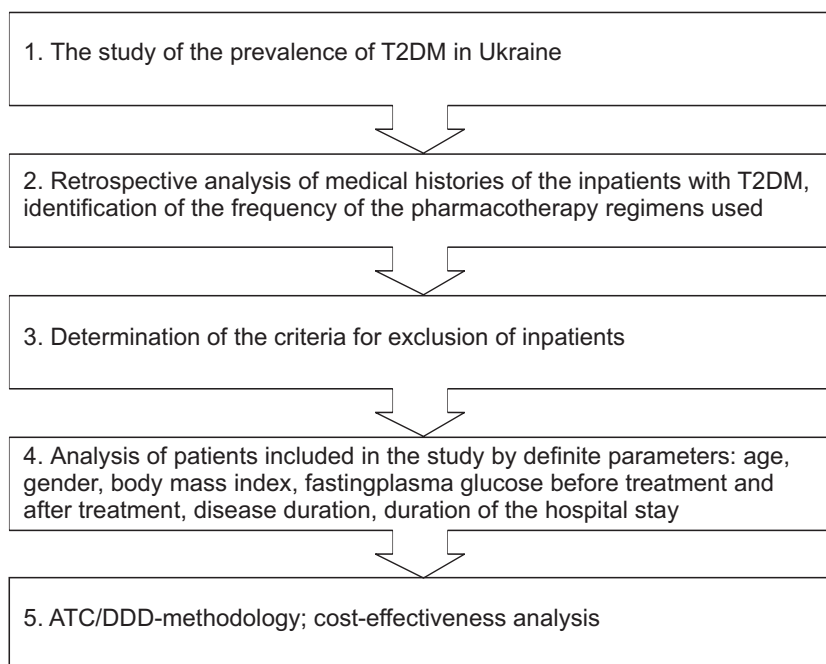


Fig. The study design

The research objectives were as follows:

- the retrospective analysis of medical histories and treatment sheets of inpatients with T2DM;
- the frequency analysis of the treatment regimens used;
- determination of criteria for exclusion of inpatients with T2DM from the study;
- the analysis of the patients included in the study according to definite parameters: age, gender, body mass index (BMI), FPG on admission to hospital, disease duration, period of staying in hospital;
- the study of treatment regimens by cost-effectiveness analysis.

The results of this study allowed substantiating the complex approach to optimization of drug provision for inpatients with T2DM in Ukraine. The propositions for improvement of the section “Treatment” of the Unified Clinical Protocol of the primary and secondary (specialized) medical care to patients with diabetes mellitus on the basis of evidence-based medicine and formation of the list of drugs in the section “Endocrinology” of the State Drugs Formulary were made. In addition, the results of the studies were introduced in practical activities of the Vinnytsya regional clinical endocrinology highly specialized center; the Khmelnytsky regional hospital; the Ternopil University hospital; the Vinnytsya clinical hospital 1; the Vinnytsya pharmacy “Be healthy”; the Vinnytsya Medical College named after academician D. K. Zabolotny; the Lviv National Medical University named after Danylo Halytsky; the Odessa National Medical University, the Ivano-Frankivsk National Medical University.

Results and discussions

The frequency analysis of 1792 medical histories and treatment sheets of inpatients with T2DM who were included in this study allowed us to select the most frequently used drug regimens. These inpatients were treated at the

Podolsky region of Ukraine (Vinnytsya Regional Endocrinology Clinic, Endocrinological Department of the Khmelnytsky hospital and Ternopol regional hospital). The frequency analysis showed that the monotherapy with metformin, glimepiride and gliclazide was used in 25 % of cases, the combined therapy with metformin + glimepiride, metformin + gliclazide and metformin + glibenclamide was used in 66 % of cases in the treatment of T2DM. Other 9% of cases of the therapy of inpatients with T2DM received various pharmacotherapy regimens with a frequency that was less than 3 % of each.

Thus, the pharmaco-economic study included three most commonly used treatment regimens of T2DM: metformin + glimepiride (45 % of cases), metformin + gliclazide (15 %) and metformin + glimepiride (6 %). The analysis of T2DM treatment protocols showed compliance with the recommended drugs used in practice.

The inpatients were examined by the following parameters: age, duration of T2DM, BMI, FPG, duration of the hospital stay. It was found that inpatients with metformin + glibenclamide regimen were significantly older, with the longer duration of T2DM, with the highest BMI and the highest levels of FPG on admission before treatment. When comparing inpatients with metformin + gliclazide regimen and metformin + glimepiride regimen it was found that the patients who received the combined therapy with metformin + gliclazide had longer duration of disease, but the patients with metformin + glimepiride regimen had more FPG on admission before treatment. No other significant differences in the parameters analyzed were found (Tab. 1).

DDD of oral hypoglycemic drugs by International Nonproprietary Name (INN) was studied for ATC/DDD-methodology [1]. Taking into account the absence of DDD for combined regimens of pharmacotherapy of T2DM,

Table 1

Characteristics of inpatients with T2DM using different regimens of the combined therapy

| Parameters | Combined therapy regimens | | | The significance of difference |
|---------------------------------------|---------------------------|------------------------|---------------------------|---|
| | metformin + glimepiride | metformin + gliclazide | metformin + glibenclamide | |
| The number of patients | 807 | 259 | 110 | |
| Age, years | 56.86 ± 0.62 | 57.68 ± 1.16 | 59.33 ± 1.81 | p ₁₋₂ > 0.05 p ₁₋₃ < 0.05 p ₂₋₃ > 0.05 |
| Duration of T2DM, years | 6.87 ± 0.34 | 7.81 ± 0.75 | 9.43 ± 1.35 | p ₁₋₂ < 0.05 p ₁₋₃ < 0.05 p ₂₋₃ < 0.05 |
| BMI, kg/m ² | 32.97 ± 0.47 | 31.07 ± 0.65 | 32.03 ± 1.18 | p ₁₋₂ < 0.05 p ₁₋₃ > 0.05 p ₂₋₃ > 0.05 |
| FPG before treatment, mmol/L | 10.71 ± 0.19 | 10.32 ± 0.34 | 11.11 ± 0.57 | p ₁₋₂ < 0.05 p ₁₋₃ > 0.05 p ₂₋₃ < 0.05 |
| FPG after treatment, mmol/L | 7.15 ± 0.12 | 6.77 ± 0.10 | 7.20 ± 0.44 | p ₁₋₂ > 0.05 p ₁₋₃ < 0.05 p ₂₋₃ < 0.05 |
| Duration of staying in hospital, days | 10.90 ± 0.13 | 10.82 ± 0.22 | 10.90 ± 0.39 | p ₁₋₂ > 0.05 p ₁₋₃ > 0.05 p ₂₋₃ > 0.05 |

the frequent use of them and the need to calculate the cost of pharmacotherapy we considered separately the cost of DDD for metformin, and the cost of DDD for each drug was added in obedience to the treatment regimens (according to the results of the retrospective analysis). DDD for metformin was 2.000 mg, DDD for glimepiride – 2 mg, DDD for gliclazide – 60 mg, DDD glibenclamide – 10 mg. The total number of calculated variants of generics at the Ukrainian pharmaceutical market for the regimen with metformin+glimepiride was 207, with metformin+gliclazide – 70, metformin+ glibenclamide – 72. Their DDD cost was significantly different (Tab. 2).

The ATC/DDD-methodology showed that metformin + glimepiride regimen had the minimum cost of DDD, and metformin + gliclazide regimen had the maximum cost of.

The cost-effectiveness analysis was carried out for pharmaco-economic substantiation of the combined treatment regimens for inpatients with T2DM [6].

The percent of effective patients was taken as the unit of effectiveness. The effective patients were patients whose FPG levels after selection and correction of pharmacotherapy reached ≤ 7mmol/L (short-term results) [2, 3, 4].

According to the “Unified Clinical Protocols of the primary and secondary (specialized) medical care to patients with diabetes” the aim of therapy is the level of glycosylated hemoglobin (glycated hemoglobin, HbA1c), which is an integral factor and reflects the long-term outcome. The target level in adults is considered to be the level of HbA1c ≤ 7%. The value of HbA1c ≤ 7% corresponds to the FPG level ≤ 7mmol/l [2-4]. Therefore, for estimation of the clinical efficacy the FPG level ≤ 7 mmol/l was selected as the short-term clinical outcome corresponding to the short period of the hospital stay and the necessity of selection of the effective pharmacotherapy of T2DM. The number of effective patients and efficiency in percent for each regimen were identified. The number of effective patients was determined in the context of the treatment regimens of T2DM analyzed.

It was found that the clinical efficacy of metformin + glimepiride combination was 50.3% (this regimen was used in 807 inpatients, the number of inpatients with the FPG level of pharmacotherapy of ≤ 7mmol/L was 406 patients), metformin + gliclazide regimen had the clinical efficacy of 59.1% (of 259 inpatients there were 153

Table 2

The DDD cost of the combined regimens of pharmacotherapy of T2DM

| INN of drugs | Minimum cost of DDD (UAH) | Maximum cost of DDD (UAH) |
|---------------------------|---------------------------|---------------------------|
| metformin + glimepiride | 4.13 | 11.57 |
| metformin + gliclazide | 4.72 | 12.58 |
| metformin + glibenclamide | 2.75 | 10.50 |

effective patients), and the clinical efficacy of metformin + glibenclamide regimen was 49.1 % (of 110 inpatients there were 54 effective patients).

The costs-efficiency ratios (CER) in the context of minimal and maximal prices of generics were calculated by the formula [5]:

$$CER = DC/Ef,$$

where: DC – is the direct cost of pharmacotherapy; Ef – is the indicator of the treatment efficiency.

The cost-effectiveness analysis showed that the cost of CER for metformin + glibenclamide regimen ranged from 560.10 to 2138.49 UAH, for metformin + glimepiride – from 821.07 to 2300.20 UAH, for metformin + gliclazide – from 798.65 to 2128.60 UAH, in the context of minimal and maximal prices of generics.

The results obtained indicate the cost-effective advantages of the regimen for combined therapy with metformin + glibenclamide.

Unfortunately, we cannot compare our results with those in Ukraine because of their absence.

Most of the world scientists perform the cost effectiveness analysis of pharmacotherapy of T2DM taking into account the quality of life. There is no information concerning the cost effectiveness analysis where the criterion of effectiveness is the level of glucose in the available literature.

CONCLUSIONS

1. The frequency analysis showed that the combined therapy of T2DM was used in 66 % of cases.

2. It was found that patients with metformin + glibenclamide regimen were significantly older, they had a longer duration of T2DM, the highest BMI and the highest levels of FPG.

3. The regimen of the combined therapy with metformin + glibenclamide has the cost-effective advantages compared to other treatment regimens.

Conflict of Interests: authors have no conflict of interests to declare.

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