Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ

ОРИГИНАЛЬНАЯ СТАТЬЯ

DOI: 10.19163/2307-9266-2021-9-5-377-386

TYPE 2 DIABETES MELLITUS'S DECOMPENSATED FORM: ON THE PROBLEM OF EFFECTIVE PHARMACOTHERAPY IN REAL CLINICAL PRACTICE

A.V. Safronenko, E.V. Gantsgorn, E.A. Sanina, M.A. Khachumova, S.O. Panenko, I.I. Kuznetsov, A.A. Kivva, V.I. Polyakova

Rostov State Medical University
29, Nakhichevansky st, Rostov-on-Don, Russia, 344022

E-mail: gantsgorn@inbox.ru

Received 23 May 2021 Accepted 07 Oct 2021

The aim of this retrospective study was to analyze the pharmacotherapy regimens of the decompensated form of type 2 diabetes mellitus (DM2) and to evaluate its effectiveness, its compliance with clinical recommendations.
Materials and methods: A retrospective analysis of 54 medical cards of patients with decompensated DM2 was conducted. The 1st group (n=24; 44%) included the patients who had a decrease in glycated hemoglobin (HbA1c) by 50% or more in 3 months after hypoglycemic therapy; and the 2nd group (n=30; 56%) – the patients whose HbA1c level decreased by less than 50%.
Results. A HbA1c level was 10.4% in the 1st group and 13.2% in the 2nd group (p<0.001). However, the target levels of venous blood plasma glucose and HbA1c were not achieved in any of the patient groups. The total number of the drugs prescribed to the patients ranged from 4 (in 25% (n=6) and 10% (n=3) cases in the 1st and the 2nd groups, respectively) to 8 (in 12.5% (n=3) and 20% (n=6) cases in the 1st and the 2nd, groups, respectively). However, in a number of cases some violations of clinical recommendations were recorded: the prescription to the obese patients of insulin drugs, the administration of sulfonylureas derivatives to patients with a history of cardiovascular diseases of the atherosclerotic origin, but modern hypoglycemic drugs with proven benefits in reducing cardiovascular risks were rarely prescribed.
Conclusion. The tactics of pharmacotherapy in the patients with a decompensated form of DM2 does not fully comply with the approved clinical guidelines, which requires the effectiveness of treatment optimization of this medically and socially significant pathology.
Keywords: glycated hemoglobin; hypoglycemic drugs; insulin; polypragmasia; type 2 diabetes mellitus
Abbreviations: HbA1 – glycated hemoglobin; DM – diabetes mellitus; DM1 – type 1 diabetes mellitus; DM2 – type 2 diabetes mellitus; BMI – body mass index; iSGLT-2 – sodium glucose cotransporter inhibitor type 2; GLPra-1 – glucagon-like peptide-1 receptor agonist; iDPP-4 – dipeptidyl peptidase-4 inhibitor; BABs – beta-adrenoblocker; ACEi – angiotensin converting enzyme inhibitor; MRA – mineralocorticoid receptor antagonist; CCB – calcium channel blocker; HDL – high density lipoprotein; LDL – low density lipoprotein; p-value – level of static significance; OR – odds ratio; CI – confidence interval; Q1–Q3 – interquartile range; M – median; SD – standard deviation; QoL – quality of life.

ДЕКОМПЕНСИРОВАННАЯ ФОРМА САХАРНОГО ДИАБЕТА 2 ТИПА: К ВОПРОСУ ОБ ЭФФЕКТИВНОЙ ФАРМАКОТЕРАПИИ В РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ

А.В. Сафроненко, Е.В. Ганцгорн, Е.А. Санина, М.А. Хачумова, С.О. Паненко, И.И. Кузнецов, А.А. Кивва, В.И. Полякова

Федеральное государственное бюджетное образовательное учреждение высшего образования «Ростовский государственный медицинский университет» Министерства здравоохранения Российской Федерации
344022, Россия, г. Ростов-на-Дону, пер. Нахичеванский, 29

E-mail: gantsgorn@inbox.ru

Получено 23.05.2021 Принята к печати 07.10.2021

Для цитирования: А.В. Сафроненко, Е.В. Ганцгорн, Е.А. Санина, М.А. Хачумова, С.О. Паненко, И.И. Кузнецов, А.А. Кивва, В.И. Полякова. Декомпенсированная форма сахарного диабета 2 типа: к вопросу об эффективной фармакотерапии в реальной клинической практике. *Фармация и фармакология.* 2021;9(5):377-386. **DOI:** 10.19163/2307-9266-2021-9-5-377-386

For citation: A.V. Safronenko, E.V. Gantsgorn, E.A. Sanina, M.A. Khachumova, S.O. Panenko, I.I. Kuznetsov, A.A. Kivva, V.I. Polyakova. Type 2 diabetes mellitus's decompensated form: on the problem of effective pharmacotherapy in real clinical practice. *Pharmacy & Pharmacology.* 2021;9(5): 377-386. **DOI:** 10.19163/2307-9266-2021-9-5-377-386

RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

Цель. Анализ схем фармакотерапии декомпенсированной формы сахарного диабета 2 типа (СД2) и оценка их соответствия клиническим рекомендациям.

Материалы и методы. Был выполнен фармакологический ретроспективный анализ 54 историй болезни пациентов с декомпенсированной формой СД2. В 1 группу (n=24; 44%) вошли пациенты, у которых по окончании 3-х месяцев гипогликемической терапии наблюдалось снижение уровня гликированного гемоглобина (HbA1) на 50% и более, а во 2 группу (n=30; 56%) – у которых уровень HbA1c снизился менее, чем на 50%.

Результаты. Уровень HbA1c в 1-й группе составил 10,4%, во 2-й группе 13,2% (p<0,001). Однако целевой уровень глюкозы плазмы венозной крови и HbA1c не были достигнуты ни в одной из групп пациентов. Общее количество назначаемых лекарственных средств составляло от 4 (в 25% (n=6) и 10% (n=3) случаев в 1 и 2 группах, соответственно) до 8 (в 12,5% (n=3) и 20% (n=6) случаев в 1 и 2 группах, соответственно), то есть полипрагмазия наблюдалась в абсолютном большинстве случаев. В ряде случаев были зафиксированы нарушения клинических рекомендаций: пациентам при наличии ожирения назначались препараты инсулина; при наличии в анамнезе сердечно-сосудистых заболеваний атеросклеротического генеза – производные сульфонилмочевины, но при этом редко назначались современные сахароснижающие лекарственные средства (ингибиторы натрий-глюкозного котранспортёра 2 типа, ингибиторы дипептидилпептидазы-4), обладающие доказанными преимуществами в отношении снижения сердечно-сосудистых рисков.

Заключение. Тактика лечения данной медико-социально значимой патологии в реальной клинической практике не в полной мере соответствует актуальным клиническим рекомендациям и требует дальнейшей оптимизации контроля эффективности.

Ключевые слова: гликированный гемоглобин; инсулин; полипрагмазия; сахарный диабет 2 типа; сахароснижающие лекарственные средства

Список сокращений: HbA1 – гликированный гемоглобин; СД – сахарный диабет; СД1 – сахарный диабет 1 типа; СД2 – сахарный диабет 2 типа; ЛС – лекарственное средство; ИМТ – индекс массы тела; иНГЛТ-2 – ингибитор натрий-глюкозного котранспортёра 2 типа; арГПП-1 – агонист рецепторов глюкагоноподобного пептида-1; иДПП-4 – ингибитор дипептидилпептидазы-4; БАБ – бета-адреноблокатор; иАПФ – ингибитор ангиотензинпревращающего фермента; АМР – антагонист минералокортикоидных рецепторов; БКК – блокатор кальциевых каналов; ЛПВП – липопротеины высокой плотности; ЛПНП – липопротеины низкой плотности; p – уровень статической значимости; ОШ – отношение шансов; ДИ – доверительный интервал; Q1–Q3 – интерквартильный размах; M – медиана; SD – стандартное отклонение.

INTRODUCTION

Diabetes mellitus (DM) is one of the most important medical and social problems of public health in the world, as it is a chronic, incurable disease, the therapeutic aspects of which require the patient to significantly change their lifestyle [1].

The total number of patients with DM in the Russian Federation (RF) as of January 2019 was 4 584 575 (3.12% of the population of the RF), including: type 1 diabetes mellitus (DM1) – 5.6% (256.2 thousand), type 2 diabetes mellitus (DM2) – 92.4% (4.24 million), other types of diabetes – 2% (89.9 thousand). Currently, the average prevalence of DM1 is 174.4 per 100 thousand population, DM2 – 2885.7 per 100 thousand, other types of DM – 61.2 per 100 thousand population[1]. Since 2000, the number of patients with DM in the RF has increased by 2.2 times: from 2.043 million to 4.58 million. As in many countries of the world, the RF continues to increase the prevalence of mainly DM2, with an annual increase of more than 250–300 thousand patients. During 2018, 10 805 new cases of DM1 and 298 628 of DM2 were identified [2]. However, these figures do not fully reflect the true scale of the non-communicable epidemic. The fact is that the register[2] records only officially registered the cases of the disease. At the same time, according to the national epidemiological study NATION [3], which included more than 26 thousand people in 63 subjects of the RF, the share of undiagnosed DM2 in the RF is 54% on average. Thus, the actual prevalence of DM2 with active screening for the level of glycated hemoglobin (HbA1c) is almost twice higher than officially registered, and can reach 8–9 million people [2].

A high medical and social significance of DM is due, among other things, to the high risk of associated micro- (nephropathy, retinopathy) and macroangiopathies (an ischemic heart disease, cerebrovascular diseases, and diseases of the arteries of the lower extremities). For example, DM is one of the leading risk factors for the development of acute cerebral circulatory disorders, leading to the so-called "vascular catastrophes" 3–4 times more often than in patients without carbohydrate metabolism disorders [4–6].

The level of glycated hemoglobin (HbA1c) is an integral indicator of glycemia, which serves as an indispensable diagnostic criterion in monitoring carbohydrate metabolism, evaluating the effectiveness of hypoglycemic therapy and predicting the course of diabetes, so its determination is currently mandatory [7, 8]. Thus, a 1% reduction in HbA1c in patients with DM2 reduces the risk of death by 21%, of an acute myocardial infarction – by 14%, and microvascular complications – by 37% [9, 10]. According to the World Health Orga-

[1] The Federal Register of Diabetes Mellitus of the Russian Federation. Available from: http://sd.diaregistry.ru/content/epidemiologiya.html
[2] Ibid.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2021-9-5-377-386

nization criteria, there are compensated diabetes (6.0–6.5% HbA1c), subcompensated diabetes (6.6–7.0% HbA1c) and decompensated diabetes (>7.0% HbA1c) [9].

Treatment of DM is one of the most expensive items of the health budget in many countries of the world. Thus, in 2017, the market volume of sugar-lowering drugs in the RF amounted to approximately 11612.5 million rubles. In the United States in 2012, 245 billion dollars were spent on the treatment of diabetes, in Italy in 2014 – about 20.3 billion euros [6, 11]. With effective therapy at an early stage of the disease, complications of the disease, disability and mortality are reduced. At the same time, there is an increase in costs at the initial stage, and then their reduction due to the prevention of hospitalizations associated with complications [12].

Patients with DM2, especially older age groups, often have concomitant chronic diseases, such as hypertension, dyslipidemia, a coronary heart disease, depressive disorders, a chronic kidney disease. They requires a simultaneous administration of several, usually more than 5–7 drugs; that exposes patients of this profile to a high risk of polypragmasia [13, 14].

From the standpoint of fundamental and clinical pharmacology, polypragmasia is the main cause of the undesirable side effects development in elderly and senile people [15, 16]. Polypragmasia bates the problems of drug interactions, reduces patients' adherence to antidiabetic therapy, and often causes suboptimal glycemic control. The presence of polypragmasia is also associated with a cascade of drug administrations, in which their side effects are misinterpreted as new pathological conditions, which can lead to the prescroption of new drugs. Polypharmacy has other negative health consequences, such as an increased risk of hospitalization, deterioration of a clinical status, poor quality of life (QoL) at patients, and significant economic consequences [13, 14].

THE AIM of this retrospective study was to analyze the pharmacotherapy regimens of the decompensated form of type 2 diabetes mellitus in settings of an endocrinological hospital, and to evaluate its effectiveness, as well as its compliance with clinical recommendations.

MATERIALS AND METHODS

The retrospective study was based on the analysis of medical cards of 54 patients with DM2 who were routinely hospitalized in a patient endocrinological facility in 2019. In the present study, only official documents (hospital history sheets) were studied, their analysis did not include direct identification of the patient's identity, therefore, the confidentiality of personal data was in no way violated. Thus, the planning and conduct of the study fully complied with the provisions on the ethical correctness of performing biomedical works[3] [17, 18].

The criteria for including patients in the study are: DM2 in the decompensation stage, the duration of the disease more than 10 years, a long-term and regular intake of hypoglycemic drugs. The criteria for excluding patients from the study are: DM1 and other disorders of carbohydrate metabolism, taking hypoglycemic drugs for less than 3 months, an inorganic and/or functional brain damage, a senile asthenia syndrome (according to the Fried criteria), a positive family history, thyroid diseases, liver diseases, abdominal cavity organs diseases, the age of patients up to 45 years.

A life history, modifiable, non-modifiable risk factors, biochemical parameters, therapeutic regimens and their modifications for the treatment of hyperglycemia and concomitant pathology were subjected to the pharmacological evaluation, including compliance with existing clinical recommendations, in order to choose the most optimal from the position of the attending physician and the patient. HbA1c was selected as a criterion for the therapy effectiveness.

Based on the assessment of the HbA1c level (the target levels ranged from 6.5% to 8%, the baseline – from 13% to 17.2%) in dynamics 3 months after hospitalization, two groups of patients were identified: the 1st group (n=24) included the patients who had a decrease in the HbA1c level by 50% or more, the 2nd group (n=30) – the patients whose HbA1c level decreased by less than 50%.

The patient groups were comparable in terms of gender, age, and the baseline clinical status ($p>0.05$). The general clinical characteristics of patients in the 1st and 2nd groups are presented in Tables 1 and 2.

The accumulation, correction, systematization of the initial information and visualization of the results were carried out in Microsoft Office Excel 2019 spreadsheets. The statistical analysis was performed using the IBM SPSS Statistics v. 26 program (IBM Corporation). The study materials were subjected to the statistical analysis using parametric and nonparametric analyses: Shapiro-Wilk test, Student t-test, Wilcoxon's rank sum test, F-test, Cramer's V, Spearman's rank correlation (the coefficient of the correlation was interpreted in accordance with the Cheddock scale), F-ratio test, Scheffe's test. The differences were considered statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

First of all, the status of patients with the primary disease – DM2 in the stage of decompensation – at the

[3] The Federal Law "On the Fundamentals of Health Protection of Citizens in the Russian Federation" dated 21.11.2011 N 323-FZ. Russian

end of 3 months of hypoglycemic treatment was evaluated. It was discovered that the target level of venous blood plasma glucose and HbA1c had not been achieved in any of the patient groups. When comparing the average values of the HbA1c level using the Student t-test in the 1st and 2nd groups, statistically significant differences were found ($p<0.001$): the level of HbA1c (%) in the 1st group was 10.4% and in the 2nd group – 13.2%. By comparison of glucose values in the groups, statistically insignificant data were obtained ($p=0.264$): the level of venous blood plasma glucose was 8.5 mmol/L in the 1st group and 9.2 mmol/L in the 2nd group, respectively.

Subsequently, the details of the pharmacotherapeutic schemes of hypoglycemic therapy were analyzed. Table 3 shows the registered regimens and the frequency of their administration to the patients in 1st and 2nd groups.

Thus, 18 hypoglycemic therapy's regimens used were found. In both groups, the hypoglycemic drugs incompatible with each other were not prescribed. The recommendations regarding the prescription of a biguanide group representative – metformin, as the initiation of therapy in patients with DM2 and its use as the basis for further therapy in most patients which corresponds to both Russian and international recommendations, were followed [21, 22]. However, a detailed evaluation of these regimens (Table 4) revealed violations of current clinical guidelines in a number of cases [21].

Table 1 – General clinical characteristics (quantitative indicators) of patients in 1st and 2nd groups

Indicator	1st group (n=24)				2nd group (n=30)				p
	Men (n=10)		Women (n=14)		Men (n=14)		Women (n=16)		
	Me	Q1–Q3	Me	Q1–Q3	Me	Q1–Q3	Me	Q1–Q3	
Age	61.0	60.5–62.5	62	58.0–66.0	62.0	61.0–68.0	68.0	67.0–68.5	0.15
Glucose level in blood plasma before	12.8	10.9–14.0	12.5	12.0–13.6	16.0	14.0–16.0	15.0	14.0–16.6	0.10
Initial HbA1c level	17.0	16.2–17.1	13.7	13.6–15.3	16.6	13.2–16.7	14.4	13.9–14.8	0.40
Target HbA1c level (%)	7.0	6.8–7.3	7.0	6.8–7.5	7.0	7.0–7.5	7.0	6.8–7.5	0.80
BMI	M±SD	95% CI	M±SD	95% CI	M±SD	95% CI	M±SD	95% CI	p
	32.0±2.4	30.4–30.7	34.3±0.8	31.9–36.7	38.7±4.4	35.3–42.1	34.9±0.7	33.9–39.9	0.61

Note: 1st group (n=24) – patients with a decrease in HbA1c level by 50% or more; 2nd group (n=30) – patients with a decrease in HbA1c level by less than 50%; HbA1c – glycated hemoglobin; BMI – body mass index; Me – median; Q1–Q3 – interquartile range; SD – standard deviation; p – level of statistical significance (Shapiro-Wilk test).

Table 2 – General clinical characteristics (qualitative indicators) of patients in 1st and 2nd groups

Indicator	Patient groups								p*	V**	OR; 95% CI
	1st group(n=24)				2nd group (n=30)						
	n	%	n	%	n	%	n	%			
Gender	Male		Female		Male		Female		0.417	0.125	0.60; 0.20–1.8
	9	37.5	15	62.5	15	50	15	50			
Social status	Employed		Unemployed		Employed		Unemployed		0.692	0.178	–
	0	0	24	100	2	6.7	28	93.3			
Obesity	Present		Absent		Present		Absent		0.097	0.309	2.4; 1.6–3.4
	20	83.3	4	16.7	15	50	15	50			
Arterial hypertension	Present		Absent		Present		Absent		–	–	–
	24	100	0	0	30	100	0	0			
Coronary heart disease	Present		Absent		Present		Present		1.00	<0.001	1.0; 0.33–3.0
	12	50	12	50	15	50	15	50			
Hereditary predisposition to DM	Present		Absent		Present		Absent		0.558	0.098	0.67; 0.21–2.2
	18	75	6	25	21	70	9	30			
School of patients with DM	Attended		Did not attend		Attended		Did not attend		0.637	0.158	0.45; 0.07–2.7
	18	75	6	25	26	86.7	4	13.3			

Note: 1st group (n=24) – patients with a decrease in HbA1c level by 50% or more; 2nd group (n=30) – patients with a decrease in HbA1c level by less than 50%; n – absolute value; p-value – the level of static significance (statistically significant at $p<0.05$*; F-test); **V – Cramer's V-test; OR – odds ratio; 95% CI – 95% confidence interval (important when going beyond the border 1)

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2021-9-5-377-386

Table 3 – Hypoglycemic therapy's regimens used in 1st and 2nd groups

	Hypoglycemic therapy's regimen	Number of patients receiving/not receiving treatment according to this regimen								p*	V**
		1st group (n=24)				2nd group (n=30)					
		Using		Not using		Using		Not using			
		n	%	n	%	n	%	n	%		
1	Insulin aspart – biphasic	0	0	24	100	3	10	27	90		
2	Insulin detemir + Insulin lispro	3	12.5	21	87.5	0	0	30	100		
3	Insulin-isophan [human biosynthetic] + Insulin soluble [human biosynthetic]	3	12.5	21	87.5	0	0	30	100		
4	Insulin detemir + Metformin	0	0	24	100	2	6.7	28	93.3		
5	Metformin + Glibenclamide	2	8.4	22	91.6	1	3.4	29	96.6		
6	Metformin + Gliclazide	0	0	24	100	7	23.4	23	76.6		
7	(Dapagliflozin + Metformin) + Glibenclamide	3	12.5	21	87.5	0	0	30	100		
8	(Dapagliflozin + Metformin) + Gosogliptine + Glibenclamide	1	4.2	23	95.8	0	0	30	100		
9	Insulin detemir + Insulin aspart + Metformin	1	4.2	23	95.8	3	10	27	90		
10	Insulin glargine + Insulin aspart + Metformin	1	4.2	23	95.8	0	0	30	100		
11	Insulin detemir + Metformin + (Antibodies to the C-terminal fragment of the β-subunit of the insulin receptor + antibodies to endothelial NO-synthase) affinity purified	0	0	24	100	3	10	27	90	<0.001	0.884
12	Insulin glargine + Metformin + Gosogliptine	3	12.5	21	87.5	1	3.4	29	96.6		
13	Insulin-isophan [human biosynthetic]+ Metformin + Glibenclamide	0	0	24	100	2	6.7	28	93.3		
14	Insulin-isophan [human biosynthetic] + Metformin + (Antibodies to the C-terminal fragment of the β-subunit of the insulin receptor + antibodies to endothelial NO-synthase) affinity purified	3	12.5	21	87.5	0	0	30	100		
15	Metformin + Glibenclamide + Alogliptin	3	12.5	21	87.5	0	0	30	100		
16	Insulin glargine + (Dapagliflozin + Metformin) + Metformin	1	4.2	23	95.8	3	10	27	90		
17	Insulin detemir + Metformin + Glibenclamide	0	0	24	100	3	10	27	90		
18	Metformin + Gosogliptine	0	0	24	100	2	6.7	28	93.3		

Note: 1st group (n=24) – patients with a decrease in HbA1c level by 50% or more; 2nd group (n=30) – patients with a decrease in HbA1c level by less than 50%; n – absolute value; p-value – the level of static significance (statistically significant at p<0.05*; Fischer's criterion); **V – Cramer's V-test

Table 4 – Groups of hypoglycemic drugs used in 1st and 2nd groups

Hypoglycemic drugs's groups	Number of patients with/no drugs as a component of therapy								p*	V**	OR; 95% CI
	1st group (n=24)				2nd group (n=30)						
	Presence		Absence		Presence		Absence				
	n	%	n	%	n	%	n	%			
Biguanides	14	58.4	10	66.7	26	86.7	4	13.3	0.028	0.321	0.215; 0.06–0.82
Insulin's drugs	19	79.2	5	20.8	19	63.4	11	36.6	0.243	0.172	2.2; 0.64–7.6
Sulfonylureas's drugs	15	62.5	9	37.5	17	56.7	13	43.3	0.783	0.059	0.78; 0.26–2.35
GLPra-1	3	12.5	21	87.5	1	3.3	29	96.7	0.312	0.174	4.14 0.4–42.66
iSGLT-2	0	0	24	100	3	10	27	90	0.245	0.217	0.59 0.41–0.69
iDPP-4	4	16.7	20	83.3	2	6.7	28	93.3	0.389	0.158	2.8; 0.47–16.8

Note: 1st group (n=24) – patients with a decrease in HbA1c level by 50% or more; 2nd group (n=30) – patients with a decrease in HbA1c level by less than 50%; n – absolute value; p-value – level of static significance (statistically significant at p<0.05*; Fischer's test); OR – odds ratio; 95% CI – 95% confidence interval (important when going beyond border 1); **V – Cramer's V-test; GLPra-1 – glucagon-like peptide receptor agonists 1; iSGLT-2 – sodium-glucose cotransporter inhibitor 2; iDPP-4 – inhibitors of dipeptidyl peptidase 4

Table 5 – Antihypertensive therapy's regimens used in 1st and 2nd groups

	Antihypertensive therapy's regimen	Number of patients receiving/not receiving treatment according to this regimen								p*	V**
		1st group (n=24)				2nd group (n=30)					
		Using		Not using		Using		Not using			
		n	%	n	%	n	%	n	%		
1	Bisoprolol + Indapamide + Perindopril	0	0	24	100	9	30	21	70	<0.001	0.942
2	Bisoprolol + Indapamide + Losartan	0	0	24	100	3	10	27	90		
3	Bisoprolol + Amlodipin + Perindopril	0	0	24	100	3	10	27	90		
4	Bisoprolol + Indapamide	0	0	24	100	3	10	27	90		
5	Perindopril + Indapamide	3	12.5	21	87.5	3	10	27	90		
6	Indapamide + Losartan	0	0	24	100	3	10	27	90		
7	Bisoprolol	0	0	24	100	3	10	27	90		
8	Bisoprolol + Indapamide + Amlodipine + Candesartan	0	0	24	100	3	10	27	90		
9	Bisoprolol + Moxonidine + Nifedipin	3	12.5	21	87.5	0	0	30	100		
10	Indapamide	3	12.5	21	87.5	0	0	30	100		
11	Bisoprolol + Moxonidine + Losartan + Spironolactone	3	12.5	21	87.5	0	0	30	100		
12	Metoprolol + Indapamide + Candesartan	3	12.5	21	87.5	0	0	30	100		
13	Amlodipine + Losartan	3	12.5	21	87.5	0	0	30	100		
14	Indapamide + Perindopril + Moxonidine + Bisoprolol	3	12.5	21	87.5	0	0	30	100		
15	Indapamide + Lisinopril + Amlodipine + Bisoprolol	3	12.5	21	87.5	0	0	30	100		

Note: 1st group (n=24) – patients with a decrease in HbA1c level by 50% or more; 2nd group (n=30) – patients with a decrease in HbA1c level by less than 50%; n – absolute value; p-value – level of static significance (statistically significant at p<0.05*; Fischer's criterion); **V – Cramer's V-test

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2021-9-5-377-386

Table 6 – Groups of antihypertensive drugs used in 1st and 2nd groups

Antihypertensive drugs groups	Number of patients with drugs as a component of therapy								p*	V**	OR; 95% CI
	1st group (n=24)				2nd group (n=30)						
	Presence		Absence		Presence		Absence				
	n	%	n	%	n	%	n	%			
BABs	15	62.5	9	37.5	24	80	6	20	0.223	0.194	0.417; 0.12–1,4
ACEi	15	62.5	9	37.5	15	50	15	50	0.417	0.125	0.60; 0.2–1.8
Diuretics	18	75	6	35	24	80	6	20	0.748	0.06	0.75; 0.2–2.7
Sartans	9	37.5	15	62.5	9	30	21	70	0.577	0.079	1.4; 0.45–4.4
Statins	12	50	12	50	18	60	12	40	0.584	0.100	0.67; 0.23–1.9
MRAs	9	37.5	15	62.5	0	0	30	100	<0.001	0.50	0.34; 0.22–0.51
CCBs	9	37.5	15	62.5	6	20	24	80	0.223	0.194	2.4; 0.71–8.1

Note: 1st group (n=24) – patients with a decrease in HbA1c level by 50% or more; 2nd group (n=30) – patients with a decrease in HbA1c level by less than 50%; n – absolute value; p-value – level of static significance (statistically significant at p<0.05*; Fisher's test); OR – odds ratio; 95% CI – 95% confidence interval (important when going beyond the limit of 1); **V – Cramer's V-test; BABs – beta-adrenoblockers; ACEi – angiotensin converting enzyme inhibitors; MRAs – mineralocorticoid receptor antagonists; CCBs – calcium channel blockers

In the 1st group, 62.5% (n=15) of patients with a history of cardiovascular diseases of the atherosclerotic origin were prescribed drugs from the group of sulfonylurea derivatives. At the same time, there is some evidence that older representatives of sulfonylurea derivatives – glibenclamide, gliclazide, tolbutamide – violate the ischemic preconditioning, i.e., the process of adaptation of the myocardium to ischemia after a number of repeated episodes of transient ischemia of moderate severity. This may cause an increased risk of myocardial infarction and a worse prognosis after a myocardial infarction [19]. The administration of insulin's drugs to obese patients, which aggravates the course of this disease because insulin increases the expression of the Glut4 transporter and the activity of acetyl-CoA-carboxylase in adipocytes, as well as fatty acid synthase and lipoprotein lipase, which leads to rapid clearance from the circulation and deposition of glucose and lipids [19], also raises questions: out of 20 obese people, they were prescribed to 17 patients (85%). The fact that in a number of clinical trials in European countries (Germany, France, Spain) patients with an HbA1c level of more than 7% could not reach the target level of venous blood plasma glucose and HbA1c during a course of basal insulin therapy, was considered [21]. In addition, none of the 1st group patients received a sodium-glucose cotransporter inhibitor type 2 (iSGLT-2) and in a lower ratio compared to other drugs from the groups of glucagon-like peptide-1 receptor agonists (GLPra-1) (12.5% (n=3)) and dipeptidyl peptidase-4 inhibitors (iDPP-4) (16.7% (n=4)). That has proven benefits in patients with DM2 with associated cardiovascular diseases in terms of reducing cardiovascular and renal risks [19, 22]. In the process of a meta-analysis, it was found that, compared with the control group, the incidence of adverse cardiovascular events in the iSGLT-2 group (OR=0.86, 95% CI 0.80-0.93, p <0.0001), such as myocardial infarction (OR=0.86, 95% CI 0.79–0.94, p=0.001), as well as mortality from this pathology (OR=0.74, 95% CI 0.67-0.81, p<0.0001) was statistically lower [23]. As far as iDPP-4 group is concerned, in one of clinical stadies, the role of this group in the prevention of cardiovascular diseases was not so pronounced in comparison to iSGLT-2 [24].

In 2nd group, the number of patients receiving iSGLT-2, GLPra-1, and iDPP-4 was also insignificant: 10% (n=3), 3.3% (n=1), and 6.7% (n=2), respectively. The prescribed therapeutic regimen for the patients with concomitant risk-associated pathology also raises questions: 56.7% (n=17) of the patients with atherosclerotic cardiovascular pathology were prescribed sulfonylurea derivatives; 66.7% (n=10) of obese patients were prescribed insulin preparations. Thus, according to the results of the meta-analysis conducted in 2016 [25], it was found that metformin monotherapy was accompanied by a lower (≥2 years) mortality from complications of cardiovascular diseases compared with sulfonylurea monotherapy. The frequency of deaths from myocardial infarction was lower in the group where metformin alone was used (2 of 1454 participants (0.1%); the median follow-up was 4 years) than in the glibutide group (3 of 1441 participants (0.2%); the median follow-up was 3.3 years).

When assessing the contribution of a particular drugs group of achieving the target HbA1c level using the exact Fisher test and the Cramer's V, a statistically

significant level (p=0.028) with a relatively strong binding force was obtained for a representative of the biguanide group – metformin. In order to determine the role of this drug, a single-factor analysis (ANOVA) was performed, during which a statistically significant effect of metformin's usage (p=0.018) on the outcome of treatment in both groups was established. The contribution to the dispersion of metformin as a component of therapy was 10.3%.

When comparing the levels of venous blood plasma glucose and HbA1c with the number of prescribed hypoglycemic drugs, a statistically significant direct correlation of weak crowding was established and no correlation was found, respectively, on the Cheddock scale. Thus, the expediency of appointing more than 2 representatives of hypoglycemic drugs was absent.

The comorbidity of the patients presented in this study, also required an assessment of polypragmasia, which causes significant harm to human healths, leads to economic losses, and negatively affects the reputation of the doctor. In addition, a large number of prescribed drugs negatively affect the patient's compliance. The problem of polypragmasia is largely due to the lack of awareness of doctors about the drugs taken by the patient, which are prescribed by other specialists.

Arterial hypertension was considered as comorbid pathology present in 100% of patients in the 1st and 2nd groups. The particular pharmacotherapy regimens used and the groups of antihypertensive agents prescribed to patients, are shown in Tables 5 and 6, respectively.

When analyzing the pharmacotherapy of arterial hypertension, the following data were obtained. The patients from the 1st group received a selective beta-adrenoblocker (BAB) – bisoprolol in 62.5% (n=15) of cases. According to the literature data [26, 27] the usage of highly selective beta-blockers does not significantly change the metabolism of lipids (total cholesterol, HDL, LDL, triglycerides) in comparison with non-selective (BABs), which violate carbohydrate tolerance, increase insulin resistance, and have a hyperlipidemic effect. In 37.5% (n=9) of cases, 4 drugs were prescribed as a treatment for a high blood pressure and its complications. In 50% of cases (n=15), the 2nd group patients were prescribed 3 drugs for the treatment of a high blood pressure. In 30% (n=9) of cases, a two-component scheme was prescribed (BABs were not included in these schemes).

When comparing the levels of venous blood plasma glucose and HbA1c with the number of prescribed antihypertensive drugs, a negative correlation of weak crowding was established and no correlation was found, respectively, on the Cheddock scale.

When comparing the levels of venous blood plasma glucose and HbA1c with the number of prescribed hypoglycemic and hypotensive drugs, there was no correlation revealed and a negative correlation of weak crowding was established, respectively, according to the Cheddock scale.

The total number of drugs prescribed to patients of the 1st group (hypoglycemic drugs + antihypertensive drugs + statins) was: 4 drugs in 25% (n=6) of cases; 5 drugs 12.5% (n=3); 6 drugs 12.5% (n=3); 7 drugs 37.5% (n=9); 8 drugs 12.5% (n=3). The total number of the drugs prescribed to patients of the 2nd group (hypoglycemic drugs + antihypertensive drugs + statins) was: 4 drugs 10% (n=3); 5 drugs 30% (n=9); 6 drugs 20% (n=6); 7 drugs 20% (n=6); 8 drugs 20% (n=6). Thus, the phenomenon of polypragmasia was observed in the absolute majority of cases. At the same time, it should be noted once again that the target level of venous blood plasma glucose and HbA1c were are not achieved in any of the patient groups, so the existing polypragmasia was not justified from the point of view of the effectiveness of the pharmacotherapy.

However, it should be noted that this study, due to its retrospective nature, had some limitations, which must be taken into account when interpreting the results obtained.

CONCLUSION

According to the results obtained in the course of this retrospective analysis, we concluded that the tactics of pharmacotherapy in the patients with a type DM2 decompensated form, often does not fully comply with the approved clinical recommendations. In particular, patients are prescribed potentially non-recommended medications that significantly reduce the QoL and increase the risk of developing undesirable adverse reactions, and/or, conversely, the treatment regimen does not use potentially recommended medications necessary to improve the prognosis, reduce the risk of complications, and reduce the number of hospitalizations.

To solve the current situation, it can be necessary to consider the following theses.

1. For the treatment of DM2, the prescribed pharmacotherapy should be based on the current clinical recommendations.

2. To improve the prognosis of the DM2 course, to improve patient QoL, is possible only with a comprehensive approach, including, first, the prescription of adequate pathogenetic and personalized therapy, especially in the case of comorbid risk-associated pathologies's presence.

3. Each case of polypragmasia should be justified in the aspect of the "effectiveness-safety" ratio, and the choice of specific drugs for a joint use is based on considering the issues of their interaction from the point of view of fundamental pharmacology.

4. When following-up patients with DM2, it is extremely important to have a high professional level and a close cooperation of specialists of various profiles: endocrinologists, cardiologists, neurologists, nephrologists, ophthalmologists, and clinical pharmacologists.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2021-9-5-377-386

FUNDING

This study did not receive any financial support from outside organizations.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR'S CONTRIBUTION

Andrey V. Safronenko, Elena V. Gantsgorn – working out the concept and study design, results interpretation and the final article edition; Ekaterina A. Sanina, Marina A. Khachumova – collection and primary processing of clinical materials, a draft article preparation; Stanislav O. Panenko – participation in the interpretation of the results obtained, translation of the article into English; Igor I. Kuznetsov – statistical processing of primary data, results interpretation; Anastasia A. Kivva, Viktoria I. Polyakova – participation in the literary references search and a draft article preparation.

REFERENCES

1. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, Song X, Ren J, Shan PF. Global, regional and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep. 2020;10(1):14790. DOI: 10.1038/s41598-020-71908-9.
2. Shestakova MV, Vikulova OK, Zheleznyakova AV, Isakov MA, Dedov II. Diabetes epidemiology in russia: what has changed over the decade? Therapeutic archive. 2019;91(10):4–13. DOI: 10.26442/00403660.2019.10.000364. Russian
3. Dedov II, Shestakova MV, Galstyan GR. The prevalence of type 2 diabetes mellitus in the adult population of Russia (NATION study). Diabetes mellitus. 2016;19(2):104–12. DOI: 10.14341/DM2004116-17. Russian
4. Gantsgorn EV, Alekseev AN. Case report: «difficult patient» and the problem of polymorbidity and polypragmasy. Medicine. 2018;6(4):99–108. DOI: 10.29234/2308-9113-2018-6-4-99-108. Russian
5. Gantsgorn EV, Nasyrova VA, Shahbanov ASh, Alekseev AN. Cardiovascular comorbidity and diabetes mellitus (clinical case). Medicine. 2020;8(1):34–50. DOI: 10.29234/2308-9113-2020-8-1-34-50. Russian
6. Tkacheva ON, Ostroumova OD, Kotovskaya YuV, Krasnov GS, Kochetkov AI, Pereverzev AP. Deprescribing of glucose-lowering medications in the elderly. Clinical pharmacology and therapy. 2019;28(3):62–7. DOI: 10.32756/0869-5490-2019-3-62-67. Russian
7. Biryukova EV. The role of glycated hemoglobin in the diagnosis and improved prognosis of diabetes mellitus. Medical Council. 2017;(3):48–53. DOI: 10.21518/2079-701X-2017-3-48-53. Russian
8. Kassahun T, Eshetie T, Gesesew H. Factors associated with glycemic control among adult patients with type 2 diabetes mellitus: a cross-sectional survey in Ethiopia. BMC research notes. 2016;9:78. DOI: 10.1186/s13104-016-1896-7.
9. Zubova AV, Poteryaeva ON, Russkikh GS, Gevorgyan MM. Content of pro-insulin and glycosylated hemoglobin depending on the stage of diabetes mellitus compensations. Siberian Journal of Medical Sciences. 2015;3:93. Russian
10. Mamo Y, Bekele F, Nigussie T, Zewudie A. Determinants of poor glycemic control among adult patients with type 2 diabetes mellitus in Jimma University Medical Center, Jimma zone, south west Ethiopia: a case control study. BMC endocrine disorders. 2019;19(1):91. DOI: 10.1186/s12902-019-0421-0.
11. Keresztes P, Peacock-Johnson A. CE: type 2 diabetes: a pharmacologic update. The American journal of nursing. 2019;119(3):32–40. DOI: 10.1097/01.NAJ.0000554008.77013.cf.
12. Breuker C, Abraham O, di Trapanie L, Mura T, Macioce V, Boegner C, Jalabert A, Villiet M, Castet-Nicolas A, Avignon A, Sultan A. Patients with diabetes are at high risk of serious medication errors at hospital: Interest of clinical pharmacist intervention to improve healthcare. Eur J Int Med. 2017;38:38–45. DOI: 10.1016/j.ejim.2016.12.003.
13. Alwhaibi M, Balkhi B, Alhawassi TM, Alkofide H, Alduhaim N, Alabdulali R, Drweesh H, Sambamoorthi U. Polypharmacy among patients with diabetes: a cross-sectional retrospective study in a tertiary hospital in Saudi Arabia. BMJ Open. 2018;8(5):e020852.
14. Artasensi A, Pedretti A, Vistoli G, Fumagalli L. Type 2 Diabetes Mellitus: A Review of Multi-Target Drugs. Molecules. 2020;25(8): 1987. DOI: 10.3390/molecules25081987.
15. Rodrigues MC, Oliveira C. Drug-drug interactions and adverse drug reactions in polypharmacy among older adults: an integrative review. Revista latino-americana de enfermagem 24. 2016;e2800. DOI: 10.1590/1518-8345.1316.2800.
16. Kochetkov AI, De VA, Voevodina NYu, Chachiashvili MV, Grishina AV, Vikentiev DV, Ostroumova OD. Analysis of drug prescription appropriateness according to the STOPP/START criteria of the elderly patients with type 2 diabetes mellitus in the endocrinology department of a multi-speciality hospital. Russian Journal of Geriatric Medicine. 2020;1:47–56. DOI: 10.37586/2686-8636-1-2020-47-56. Russian
17. Belousov YuB. Ethical review of biomedical research. Practical recommendations. M.: Publishing House of the Society of Clinical Researchers. 2005, 156 p.
18. Declaration of Helsinki, World Medical Association, Department of Health and Social Security. Great Britain. Committee of Inquiry into Human Fertilization and Embryology. Mary Warnock, Chair. A Question of Life: The Warnock Report on Human Fertilization and Embryology New York: Basil Blackwell, 1985. Text of 1984 Report, with added introduction and conclusion by Mary Warnock. – 2001.
19. Dedov II, Shestakova MV, Mayorov AYu. Standards of specialized diabetes care. 9th edition. Diabetes Mellitus. 2019;22(1S1):1–144. DOI: 10.14341/DM20171S8. Russian
20. Qaseem A, Barry MJ, Humphrey LL, Forciea MA. Clinical Guidelines Committee of the American College of Physicians. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med. 2017;166(4):279–90. DOI: 10.7326/M16-1860.

21. Ceriello A, deValk HW, Guerci B, Haak T, Owens D, Canonobio M, Fritzen K, Stauther C, Schnell O. The burden of type 2 diabetes in Europe: Current and future aspects of insulin treatment from patient and healthcare spending perspectives. Diabetes Res Clin Pract. 2020;161:108053. DOI: 10.1016/j.diabres.2020.108053.

22. Ismail-Beigi F, Moghissi E, Kosiborod M, Inzucchi SE. Shifting Paradigms in the Medical Management of Type 2 Diabetes: Reflections on Recent Cardiovascular Outcome Trials. J Gen Intern Med. 2017;32:1044–51. DOI: 10.1007/s11606-017-4061-7.

23. Zou CY, Liu XK, Sang YQ, Wang B, Liang J. Effects of SGLT2 inhibitors on cardiovascular outcomes and mortality in type 2 diabetes: A meta-analysis. Medicine. 2019;98(49):e18245. DOI: 10.1097/MD.0000000000018245.

24. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler DJ, Buse JB. Management of Hyperglycemia in Type 2 Diabetes. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669–701. DOI: 10.2337/dci18-0033.

25. Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, Chu Y, Iyoha E, Segal JB, Bolen S. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. Ann Intern Med. 2016;164(11):740–51. DOI: 10.7326/M15-2650.

26. Radchenko GD. The place of beta-blockers in the treatment of arterial hypertension in 2017: is all so bad? Arterial hypertension. 2017;2(52):9–34. DOI: 10.22141/2224–1485.2.52.2017.101292. Russian

27. Standl E, Schnell O, McGuire DK. Heart Failure Considerations of Antihyperglycemic Medications for Type 2 Diabetes. Circulation research. 2016;118(11):1830–43. DOI: 10.1161/CIRCRESAHA.116.306924.

AUTHORS

Andrey V. Safronenko – Doctor of Sciences (Medicine), Head of the Department of Pharmacology and Clinical Pharmacology, Rostov State Medical University. ORCID ID: 0000-0003-4625-6186. E-mail: andrejsaf@mail.ru

Elena V. Gantsgorn – Candidate of Sciences (Medicine), Associate Professor at the Department of Pharmacology and Clinical Pharmacology, Rostov State Medical University. ORCID ID: 0000-0003-0627-8372. E-mail: gantsgorn@inbox.ru

Ekaterina A. Sanina – 6th year student of Faculty of General Medicine, Rostov State Medical University. ORCID ID: 0000-0002-9154-0154. E-mail: katyameskhi17@mail.ru

Marina A. Khachumova – 6th year student of Faculty of General Medicine, Rostov State Medical University. ORCID ID: 0000-0002-9334-9062. E-mail: khachumovamarina@gmail.com

Stanislav O. Panenko – postgraduate student of the Department of Internal Medicine No.3, Rostov State Medical University. ORCID ID: 0000-0002-7794-7134. E-mail: stasrostov555@gmail.com

Igor I. Kuznetsov – 6th year student of Faculty of General Medicine, Rostov State Medical University. ORCID ID: 0000-0003-3678-0427. E-mail: igork1997@yandex.ru

Anastasia A. Kivva – 5th year student of Faculty of General Medicine, Rostov State Medival University. ORCID ID: 0000-0002-6938-4677. E-mail: kivvaanastasia@yandex.ru

Viktoria I. Polyakova – 4th year student of Pediatric Faculty, Rostov State Medical University. ORCID ID: 0000-0002-8886-8984. E-mail: polyakowa.vi@yandex.ru