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EVALUATION OF WEIGHT REDUCTION EFFICACY AND SAFETY OF SIBUTRAMIN-CONTAINING DRUGS IN PATIENTS WITH ALIMENTARY OBESITY

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The article presents clinical study results of the efficacy and safety of combination therapy with sibutramine and metformin (fixed combination) in comparison with sibutramine therapy with microcrystalline cellulose in patients with alimentary obesity.
The aim is to evaluate the efficacy and safety of using the sibutramine+metformin fixed dose combination (Reduxin® Forte) and compare it with the sibutramine + microcrystalline cellulose combination (Reduxin®) in patients with alimentary obesity in the course of the obesity therapy.
Materials and methods. Male and female patients (240 people) aged 18 to 65 years inclusive with alimentary obesity, meeting the inclusion criteria and not meeting the non-inclusion criteria, were randomized into 2 groups in a 1:1 ratio. One group (n=120) received sibutramine+ metformin p. o., 1 tablet (850 mg + 10 mg) once per day, the second group (n=120) received sibutramine+ microcrystalline cellulose (MCC) p. o., 1 capsule (10 mg + 158.5 mg) once per day in the morning. On day 30 ± 1, in the absence of a 2 kg weight loss compared to the first visit, the dose was increased in accordance with the medical instruction. The therapy period was 180 days. The randomization list was generated by the factory method of random numbers. The efficacy and safety were assessed by anthropometric, clinical and laboratory parameters and the SF-36 questionnaire. The proportion of patients who achieved a decrease in body weight by more than 5% in 6 months, the magnitude and dynamics of changes in body weight and body mass index, waist and hip measurements, their ratios, changes in lipid profile, blood pressure, as well as the total number of adverse events, their frequency and nature of occurrence were analyzed.
Results. The both drugs have demonstrated efficacy in all parameters of the obesity therapy. At the same time, in a comparative analysis, a statistically significant advantage of therapy with sibutramine + metformin was demonstrated in relation to the proportion of patients who had achieved more than 5% weight loss (body weight dynamics). Significant benefits were shown in terms of the magnitude of the change in body mass index (BMI); there was a statistically significant increase in the proportion of the patients who had switched from one category of BMI to another. By the end of the study, the vast majority of patients had no longer met the criteria for the diagnosis of “Obesity”. There was also a statistically significant benefit of

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sibutramine + metformin in terms of lowering triglycerides and low-density lipoprotein levels. The analysis of the safety parameters of sibutramine + metformin confirms a high safety profile of the drug, a comparative statistical analysis of adverse events in terms of their presence, severity, causal relationship with therapy and outcome have not revealed intergroup differences. Adverse events were transient and did not require discontinuation of therapy.

Conclusion. The results of the study showed that therapy with Reduxin® and Reduxin® Forte provides a pronounced decrease in body weight. However, the use of a fixed combination has a more effective positive effect on the lipid profile and patients' quality of life, which, combined with a high safety profile, proves the possibility and expediency of using Reduxin® Forte for the treatment of obesity and restoring metabolic health, even in patients without additional carbohydrate metabolism disorders.

Keywords: obesity; pharmacotherapy; sibutramine; metformin; Reduxin®; Reduxin® Forte

Abbreviations: AH – arterial hypertension; BP – blood pressure; BAS – biologically active supplement; WHO – World Health Organization; GLP-1 – glucagon-like peptide-1; BMI – body mass index; MS – metabolic syndrome; BW – body weight; MCC – microcrystalline cellulose; LDL – low density lipoproteins; HDL – high density lipoproteins; AE – adverse events; HW – hip width; WM – waist measurement; DM2 – type 2 diabetes mellitus; CVDs – cardiovascular diseases; NAFLD – non-alcoholic fatty liver disease; TGs – triglycerides; PhA – physical activity; CS – cholesterin; HR – heart rate.

ОЦЕНКА ЭФФЕКТИВНОСТИ СНИЖЕНИЯ ВЕСА И БЕЗОПАСНОСТИ ПРИМЕНЕНИЯ СИБУТРАМИНСОДЕРЖАЩИХ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ У ПАЦИЕНТОВ С АЛИМЕНТАРНЫМ ОЖИРЕНИЕМ

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В статье представлены результаты клинического исследования эффективности и безопасности фиксированной комбинации сибутрамином с метформином в сравнении с терапией сибутрамином с микрокристаллической целлюлозой у пациентов с алиментарным ожирением

Цель. Оценить эффективность и безопасность применения препарата сибутрамин в комбинации с метформином (Редуксин® Форте) в сравнении с терапией препаратом сибутрамин с микрокристаллической целлюлозой (Редуксин®) у пациентов с алиментарным ожирением.

Материалы и методы. Пациенты мужского и женского пола (240 человек) в возрасте от 18 до 65 лет включительно с алиментарным ожирением, соответствующие критериям включения и не соответствующие критериям невключения, рандомизировались в 2 группы в соотношении 1:1. Одна группа (n=120) получала препарат сибутрамин+метформин (фиксированная комбинация), перорально по 1 таблетке (850 мг + 10 мг) 1 раз в день, вторая группа (n=120) получала препарат сибутрамин+микрокристаллическая целлюлоза (МКЦ) перорально по 1 капсуле (10 мг + 158,5 мг) 1 раз в день утром. На 30±1 день при отсутствии снижения массы тела на 2 кг по сравнению с первым визитом, доза увеличивалась в соответствии с инструкцией по медицинскому применению. Период терапии составил 180 дней. Рандомизационный список был сгенерирован методом генерации случайных чисел. Эффективность и безопасность оценивались по антропометрическим, клинико-лабораторным показателям и опроснику SF-36. Анализировалась доля пациентов, достигших снижения массы тела более, чем на 5% за 6 месяцев терапии, величина и динамика изменения массы тела и индекса массы тела, окружности талии и бёдер, их соотношения, изменения показателей липидного профиля, артериального давления, а также общее количество нежелательных явлений, их частота и характер возникновения.

Результаты. Оба лекарственных препарата продемонстрировали эффективность в отношении всех параметров терапии ожирения. При этом, при сравнительном анализе было продемонстрировано статистически значимое преимущество терапии препаратом сибутрамин+метформин в форме фиксированной комбинации в отношении доли пациентов, достигших более 5% снижения массы тела, динамики массы тела. Значимые преимущества были показаны в отношении величины изменения индекса массы тела (ИМТ), отмечалось статистически значимое увеличение доли пациентов, перешедших из одной категории ИМТ в другую. К концу исследования абсолютное большинство пациентов перестали соответствовать критерию диагноза «Ожирение». Было также выявлено статистически значимое преимущество препарата сибутрамин+метформин в отношении снижения уровня триглицеридов и уровня липопротеидов низкой плотности. Анализ параметров оценки безопасности сибутрамин+метформин подтверждает высокий профиль безопасности препарата, сравнительный статистический анализ нежелательных явлений по их наличию, тяжести, причинно-следственной связи с терапией и исходу не выявил межгрупповых различий. Нежелательные явления носили транзиторный характер и не требовали отмены терапии.

Заключение. Результаты исследования показали, что терапия лекарственными препаратами Редуксин® и Редуксин® Форте обеспечивает выраженное снижение массы тела. Однако применение фиксированной комбинации оказывает более эффективное положительное влияние на показатели липидного профиля и качества жизни пациентов, что, в сочетании с высоким профилем безопасности, доказывает возможность и целесообразность применения лекарственного препарата Редуксин® Форте для лечения ожирения и восстановления метаболического здоровья даже у пациентов без дополнительных нарушений углеводного обмена.

Ключевые слова: ожирение; фармакотерапия; сибутрамин; метформин; Редуксин®; Редуксин® Форте

Список сокращений: АГ – артериальная гипертензия; АД – артериальное давление; БАД – биологически активная добавка; ВОЗ – Всемирная организация здравоохранения; ГПП-1 – глюкагоноподобный пептид-1; ИМТ – индекс массы тела; МС – метаболический синдром; МТ – масса тела; МКЦ – микрокристаллическая целлюлоза; ЛПНП – липопротеиды низкой плотности; ЛПВП – липопротеиды высокой плотности; НЯ – нежелательные явления; НАЖБП – неалкогольная жировая болезнь печени ОБ – окружность бёдер; ОТ – окружность талии; СД2 – сахарный диабет 2 типа; ССЗ – сердечно-сосудистые заболевания; ТГ – триглицериды; ФА – физическая активность; ХС – холестерин; ЧСС – частота сердечных сокращений.

INTRODUCTION

Obesity is a chronic disease characterized by an excessive accumulation of adipose tissue in the body, which poses a threat to health, and is also a major risk factor for several other chronic diseases, including type 2 diabetes mellitus (DM2) and cardiovascular diseases (CVDs) [1].

In May 2022, World Health Organization (WHO) experts compiled a report on a new pandemic of modern humanity, which states that 60% of citizens in Europe are either overweight or obese. The prevalence of obesity worldwide has nearly tripled since 1975, largely due to a gradual shift towards sedentary lifestyles and less healthy diets. According to WHO estimates, by 2025, one in five adults in the world will suffer from this pathology. The most depressing fact is the widespread increase in obesity among children and adolescents [2-4].

The relevance of obesity control is due not only to its high prevalence, but also to the negative impact on the quality of people's life and a particularly high risk of developing various diseases that lead to an early disability and a significant decrease in life expectancy. Overweight and obesity are major risk factors for cardiovascular diseases, diabetes mellitus and its complications, including blindness, limb amputation and a chronic kidney disease (CKD), a musculoskeletal disease (including osteoarthritis), gastrointestinal and respiratory diseases. Obesity is also associated with certain types of cancer, i. e. endometrial, breast, ovarian, prostate, liver, gallbladder, kidney and colon [5].

Many researchers emphasize the priority of fundamental changes in an obese patient's lifestyle, corrections of his diet and an increase in his physical activity (PhA). However, not all patients manage to achieve and/or maintain the target anthropometric parameters with the help of diet and PhA correction. Thus, according to the US National Institutes of Health, in 30-60% of patients treated with diets and exercises, body weight

(BW) returns to its baseline within one year, and after 5 years – in almost 100% patients. Thus, the feasibility and importance of developing additional approaches to weight loss is beyond doubt. To date, the main developments are carried out in two areas: pharmacotherapy and surgical treatment [6-8].

According to current guidelines, patients with body mass index (BMI) ≥ 27 kg/m^2 and 2 or more risk factors (smoking, AH > 140/90 mmHg, low density lipoproteins (LDLs) above 160 mg/dL, high density lipoproteins (HDLs) below 35 mg/dL, fasting hyperglycemia or impaired carbohydrate tolerance, a family history of an early cardiovascular disease (age < 45 years for men and < 55 years for women) or with a BMI ≥ 30 kg/m^2) require pharmacological intervention as an adjunct to the correction of the regime of physical activity and diet [9]. Based on this, the vast majority of patients with obesity and overweight who come to the attention of practitioners need medical treatment [10]. And taking into account the changes in metabolic processes related to age and an increased risk of developing diseases associated with weight gain (CVDs, T2DM, NAFLD, etc.), it is advisable to include the aid aimed at weight loss and its control in the program of preventive medical examination and medical recommendations, regardless of specialties.

For the treatment of obesity, pharmacological agents are divided into drugs of central (phentermine + topiromate, sibutramine, fluoxetine), peripheral (orlistat) and mixed (central and peripheral) actions (thermogenic sympathomimetics, a growth hormone, androgens, glucagon-like peptide-1 (GLP-1) agonists, the sibutramine + metformin combination [7, 8]. According to the National Clinical Guidelines, the following drugs for the treatment of obesity are currently registered in the Russian Federation (RF): orlistat, liraglutide, sibutramine + microcrystalline cellulose (MCC), sibutramine + metformin (fixed dose combination). At the same time, the broadest evidence base is currently available for the preparations containing sibutramine [8].

Sibutramine is a substance that has an anorexigenic effect by increasing satiety and reducing appetite. It inhibits the reuptake of neurotransmitters (serotonin and noradrenaline), and also increases thermogenesis, affecting brown adipose tissue [11, 12]. However, insulin resistance, as a key link in almost all pathogenetic "ways" of obesity with its metabolic, energy, hemodynamic and inflammatory links, further draws attention to metformin. Traditionally, one of the main mechanisms of a metformin action is its effect on the insulin resistance by suppressing gluconeogenesis in the liver (an endogenous glucose production). The drug also reduces the absorption of glucose in the intestine and possibly improves the absorption and utilization of glucose by peripheral tissues: skeletal muscle and adipose tissue. New evidence suggests that metformin-associated weight loss is due to the modulation of hypothalamic appetite control centers, changes in the gut microbiota, and effects on the aging process. In addition, metformin has a beneficial effect on lipid metabolism: it reduces the content of total cholesterol (CS), LDLs and triglycerides (TGs). Thus, metformin has a number of pleiotropic effects, which make it possible to use the drug in metabolic syndrome (MS), obesity, steatohepatosis, and a number of other diseases. It is important that many of the putative new targets are closely associated with obesity [13]. The prescription of metformin is clinically significant for metabolic health, but the minimal dynamics of weight loss against its background (1–5 kg per year) does not allow the use of the drug as a monotherapy for the obesity treatment [14]. In the medical correction of alimentary obesity, the sibutramine + metformin combination is mainly used [9]. Positive results of the fixed sibutramine + metformin combination in patients with obesity and other carbohydrate metabolism disorders (impaired glucose tolerance, type 2 diabetes) have been shown in numerous clinical studies [15–44]. It has been shown that the combined use of sibutramine with metformin increases the therapeutic efficacy of the combination used in patients with overweight and carbohydrate metabolism disorders.

It seems promising to study metformin protective effects and the action synergism of the sibutramine + metformin combination in a single dosage form, in relation to the restoration of metabolic health in obese patients without additional disorders of carbohydrate metabolism, as well as the assessment of such therapy safety.

THE AIM is to evaluate the efficacy and safety of using the sibutramine+metformin combination (Reduxin® Forte) and compare it with the sibutramine + microcrystalline cellulose combination (Reduxin®) in patients with alimentary obesity in the course of the obesity therapy.

MATERIALS AND METHODS

This "Open multicenter randomized study to evaluate the efficacy and safety of the drug Reduxin® Forte, film-coated tablets, in comparison with the drug Reduxin®, capsules, in patients with alimentary obesity", was conducted from 07/03/2020 to 05/21/2021 in 5 cities of the Russian Federation (St. Petersburg, Ivanovo, Kirov, Samara, Rostov-on-Don) on the basis of 8 research centers. The study was conducted in accordance with the principles of good clinical practice and was authorized by the Ministry of Health of the Russian Federation (No. 304 dated July 3, 2020), approved by the Ethics Council of the Ministry of Health of the Russian Federation, as well as by independent ethics committees of all clinical centers participating in the study.

Study Design

Male and female patients (240 people) aged 18 to 65 years inclusive with alimentary obesity with a body mass index of more than 30 kg/m^2, meeting the inclu-

ОРИГИНАЛЬНАЯ СТАТЬЯ
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sion criteria and not meeting the exclusion criteria, were randomized into 2 groups in a 1:1 ratio. The randomization list was generated by the factory method of random numbers.

Group 1 (n=120) received sibutramine + metformin, film-coated tablets, p. o., 1 tablet (850 mg + 10 mg) once per day in the morning, without chewing and followed with a glass of water, during meals, for 180 days.

Group 2 (n=120) received sibutramine + MCC capsules p. o., 1 capsule (10 mg + 158.5 mg) once per day in the morning, without chewing and followed with a glass of water, during meals for, 180 days.

A patient's condition was monitored at visits (V) at the research center in accordance with the Protocol. At V3 (Day 30 ± 1), in the absence of a 2 kg weight loss compared to V1 (Day 1), the zero dose was increased. Patients in the sibutramine+metformin group received 1 tablet (850 mg + 15 mg), and patients in the sibutramine + MCC group received 1 capsule (15 mg + 153.5 mg).

The total duration of the study for each patient was no more than 191 days: screening – no more than 10 days; randomization – no more than 1 day; therapy – no more than 180 days (6 months); the study completion – no more than 3 days. The graphic scheme of the study is shown in Figure 1.

Criteria for patients' inclusion in the study

Every patient had given written informed consent prior to the participation in the study. The study could include men and women aged 18 to 65 years with a diagnosis of "Alimentary obesity", BMI> 30 kg/m^2 and ineffective non-drug treatment at the time of screening (weight loss < 5% within 3 months of treatment). The consent from each patient was obtained for changes in diet, eating behavior, an increased physical activity, and adherence to the study physician's recommendations throughout the study participation. The patients were warned to use reliable methods of contraception throughout the study and for 3 weeks after its completion.

Main criteria for patients' non-inclusion in the study

These criteria are as follows: hypersensitivity to the components of the study / reference drug, secondary (symptomatic) obesity, type I or II diabetes mellitus in history and/or at the time of screening, a low-calorie (<1600 kcal/day) diet within 3 months before screening, a previous administration of sibutramine-based drugs, the use of drugs, herbal remedies or dietary supplements for the obesity treatment less than 3 months before screening, as well as a number of other criteria, including impaired liver and / or kidney function, uncontrolled arterial hypertension (AH), etc.

The decision to exclude a patient from the study was made by the investigator. The patient was withdrawn from the study in case of a treatment failure (weight loss <5% to V7 relative to V1); an increase in resting heart rate ≥10 bpm or systolic/diastolic pressure ≥10 mmHg at two visits in a row; an increase in blood pressure over 145/90 mmHg twice when remeasured; if any diseases or conditions appear during the study that worsen the patient's prognosis, and also make it impossible for the patient to continue participating in the clinical trial; if it is necessary to prescribe prohibited concomitant therapy (glucocorticoids, antidepressants, lipid-lowering, hypoglycemic drugs, macrolides, etc.) or if the study protocol is violated; if the patient refuses to participate in the study, and there can be a number of other reasons.

The choice of dosage, dosing regimen, route of administration and duration of therapy for the study drugs, was based on these medical instructions for sibutramine + metformin[1], film-coated tablets, and sibutramine + MCC[2] capsules; on the standard of specialized medical care for obesity (Order of the Ministry of Health of the Russian Federation dated November 9, 2012 No. 850n "On approval of the standard for specialized medical care for obesity")[3], National guidelines for the diagnosis, treatment, prevention of obesity and associated diseases[4], as well as modern clinical studies to research the efficacy and safety of sibutramine, including its combination with metformin [14–30].

The use of the study / reference drug was carried out in combination with diet therapy, changes in eating behavior and an increase in PhA. The patients were recommended a diet with a deficit of 600 kcal per day of the total caloric content calculated for the patient or a diet with a restriction of fat intake. Recommendations were given on proper food intake (frequent and fractional meals in small portions; careful chewing of food; the last meal – not later than 3 hours before bedtime, etc.). It was also recommended to have 225-300 minutes of moderate intensity PhA per week or 150 minutes of high intensity aerobic PhA per week, which is equivalent to spending 1,800–2,500 kcal per week.

Estimated indicators of effectiveness and safety

The primary efficacy endpoint was the rate of achieving >5% weight loss at the last visit (V13, 6 months

[1] Instructions for the medical use of the drug Reduxin® Forte. Available from: https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=c-7cab986-bfca-49f5-8b22-61387351e80a. Russian

[2] Instructions for the medical use of the drug Reduxin®. Available from: https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=108c4981-0dbb-4bdc-a3fe-08395333313f. Russian

[3] Ministry of Health Order of the Russian Federation dated 2012 Nov 9, No. 850n "Ob utverzhdenii standarta specializirovannoj medicinskoj pomoshchi pri ozhirenii" [On approval of the standard for specialized medical care for obesity]. Available from: https://minzdrav.gov.ru. Russian

[4] Russian Society of Cardiology; Russian Scientific Medical Society of Therapists; Antihypertensive League; Organization to promote the development of prehospital medicine "Outpatient Doctor"; Association of Clinical Pharmacologists. Diagnostika, lechenie, profilaktika ozhireniya i associirovannyh s nim zabolevanij [Diagnosis, treatment, prevention of obesity and associated diseases] (National Clinical Guidelines) St. Petersburg; 2017: 164 p. Available from: https://scardio.ru/content/Guidelines/project/Ozhirenie_klin_rek_proekt.pdf. Russian

of therapy) compared with the first visit (V1, starting of therapy).

In addition, a few important factors were additionally assessed. They are: the proportion of the patients requiring an increase in the study / reference dose by V3; the magnitude of the change in body weight to V13 (6 months of therapy) relative to V1; change in BMI (%) to V13 relative to V1; dynamics of body weight (kg), BMI (kg/m^2), waist measurement, hip width, waist / hip measurements, dynamics of lipid profile indicators (TG, total cholesterol, LDL-cholesterol, HDL-cholesterol) and quality of life (according to the SF-36 questionnaire). The efficacy of treatment with the study drug was estimated at V1–7, 9, 11, 13. Anthropometric data (height, body weight, waist measurement, hip width) were collected by measurements. BMI was determined by the calculation method (body weight (kg) / height (m^2) based on the data obtained.

To determine the safety of the therapy, the dynamics of blood pressure, heart rate, ECG, as well as the total number and frequency of adverse events (AEs) and serious adverse events (SAEs) associated with the use of the study / reference drug, were estimated. The proportion of the patients with at least one AE and the proportion of the patients who had interrupted the treatment due to AEs, was taken into account. The changes in laboratory parameters were the AEs only if they were clinically significant and/or required therapeutic intervention.

Adverse events were assessed in all patients who received at least one dose of the drug.

Statistical processing of results

A statistical analysis was performed in accordance with the requirements of ICH9, the Rules of Good Clinical Practice approved by the Eurasian Economic Commission and other applicable requirements and laws. For the statistical analysis, certified statistical software with validated algorithms for performing statistical analyzes and proper documentation was used (StatSoft Statistica 10.0., IBM SPSS Statistics 22). Descriptive statistics was presented for all efficacy and safety measures collected during the study. Continuous (quantitative) data were presented using the number of observations, arithmetic mean, 95% confidence interval (CI) for the mean, standard deviation, median, interquartile range (25th and 75th percentiles), minimum and maximum. Ordinal, categorical, and qualitative data were presented as absolute frequencies (number of observations), relative frequencies (percentage), and 95% CI. The normality checking of the distribution was carried out by one of the generally accepted methods (Shapiro-Wilk test, Kolmogorov-Smirnov test). In the case of a non-Gaussian distribution, non-parametric evaluation methods could be used to compare the efficacy and safety performance. Significance levels and CIs were calculated as two-tailed: if the statistical significance of differences is two-tailed by default, then it was referred to a significance level of 0.05.

RESULTS

The study was completed by 228 patients (110 patients in the sibutramine + MCC group and 118 patients in the sibutramine + metformin group). The estimation of the study drugs effectiveness, based on the statistical analysis, showed that in the sibutramine + metformin group, the proportion of patients who had achieved more than 5% weight loss by the end of therapy (V13 or 6 months) was 99.15% (117/118), in the sibutramine + MCC group – 93.64% (103/110). As a result of a comparative frequency analysis of achieving more than 5% weight loss to V13, statistically significant differences were detected between the study groups. The difference in proportions was 0.0552 (5.52%), the 95% CI for the difference in proportions was [-0.0019; 0.1233] ([-0.19%; 12.33%]). Thus, it was demonstrated that both study drugs provide a clinically significant decrease in body weight, however, during the therapy with sibutramine + metformin, the effect was more pronounced.

As a result of the additional comparative analysis of the patients' frequency who had achieved a 5% decrease in body weight by V7 (90±1 days of therapy), statistically significant differences were found out between the study groups (p=0.0016). In the sibutramine + metformin group, the proportion of patients who had achieved a 5% decrease in body weight to V7 was 100.0%, in the sibutramine + MCC group – 91.67%, which indicates a high effectiveness of the therapy in terms of achieving an early response to it. Moreover, against the background of taking a fixed combination, the proportion of early responders was higher.

Moreover, the additional analysis showed that in the sibutramine + metformin group, the proportion of the patients who had achieved a weight loss of 10% or more by V13 (180±1 days), was 93.22% (110/118), in the sibutramine group + MCC – 80.00% (88/110). The differences between the study groups were statistically significant (p=0.0032).

According to the protocol, the frequency of patients who required an increase in the dose of the study / reference drug by V3 (30±1 days), was also assessed. In the absence of a decrease in body weight of 2 kg compared with V1, the patients in the sibutramine + metformin group received 1 tablet (850 mg + 15 mg), and the patients in the sibutramine + MCC group received 1 capsule (15 mg + 153.5 mg) per day. In the sibutramine + metformin group, the proportion of patients who required an increase in the dose of the study / reference drug was 10.17% (12/118), for the sibutramine+metformine, in the sibutramine + MCC group – 14.55% (16/110) (p=0 ,2416). Thus, the absolute majority of patients showed a response to therapy when taking drugs at a minimum dose, which reduces the risk of developing AEs and preserves the possibility of increasing the dose in case of phisiological the plateau effect occurs.

Body weight significantly decreased in both groups, while statistically significant differences confirming the benefits of using the combination of sibutramine + met-

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2022-10-3-289-304

formin, were found out (Fig. 2). The average value of the change in patients' body weight by V13 (180±1 days) relative to V1 for the entire population was (-14.29±4.97 kg), for the sibutramine + metformin group – (-14.99±4.64 kg), for the sibutramine + MCC group – (-13.54±5.22 kg). The difference in the average values of changes in patients' BW to V13 relative to V1 between the groups was 1.45 kg, 95% CI was [0.17;2.74] (p=0.0272).

Additionally, a comparative analysis of the decrease in patients' body weight by V7 (90±1 days) relative to V1 and to V13 (180±1 days) relative to V7 (90±1 days), was carried out. The average value of the changes in patients' body weight by V7 relative to V1 for the entire population was (–8.94±2.69 kg), for the sibutramine + metformin group – (–9.28±2.67 kg), for the sibutramine group + MCC – (–8.59±2.68 kg).

The average value of the changes in the patients' BW by V13 (180±1 days) relative to V7 (90±1 days) for the sibutramine + metformin group was (–5.62±3.12 kg), for the sibutramine + MCC group – (–4.54±3.70 kg) (Fig. 4).

Thus, a decrease in body weight was observed during the entire period of therapy without the occurrence of a plateau effect.

The difference in the mean values of changes in patients' BW by V7 relative to V1 between the groups was 0.99 kg, 95% CI [0.28; 1.70] and 1.09 kg, 95% CI for the difference in mean [0.21; 1.96] values of changes in the patients' BW by V13 relative to V7 (p=0.0148), respectively.

Significant dynamics of BMI was shown in the both study groups. The average value of the change in BMI (%) by V13 for the sibutramine + metformin group was (–15.67±4.31%), for the sibutramine + MCC group – (–12.90±5.36%), the difference in the average values change in BMI (%) between the groups was 1.99%, 95% CI [0.76; 3.23] and was statistically significant (p=0.0017). The changes in BMI by V7 (90±1 days) relative to V1 were also statistically significant (p=0.0052) and amounted to 0.94%, 95% CI [0.28;1.60]; the significant differences (p = 0.0129) were present at V13 relative to V7: the difference in the average values of changes in BMI (%) by V13 between the groups was 1.18%, 95% CI [0.25; 2.1

Thus, the results demonstrate a decrease in BW and BMI both in absolute terms and in percentage terms in both groups, while in the group of patients receiving a fixed combination of sibutramine + metformin, the results were more significant.

Additionally, the distribution of patients into categories in accordance with the BMI index was calculated and the frequency of patients who had moved from one category to another (i.e., reduced the degree of obesity) by V7 (90 ± 1 day) and V13 (180 ± 1 day) compared to V1, was assessed. For the distribution of patients, the following categories of BMI were distinguished (Table 1).

A frequency assessment of the patients who had moved from one BMI category to another after 3 and 6 months of therapy, was made in the both groups. At V1, the proportion of patients with category 3 in the sibutramine + metformin group was 54.24% (64/118), in the sibutramine + MCC group – 52.73% (58/110); the proportion of patients with category 4 in the sibutramine + metformin group was 32.20% (38/118), in the sibutramine + MCC group – 34.55% (38/110). The proportion of patients with category 5 at V1 in the sibutramine + metformin group was 13.56% (16/118), in the sibutramine + MCC group – 12.73% (14/110). At V7 (90±1 days), the proportion of patients with category 2 in the sibutramine + metformin group was 33.90% (40/120), in the sibutramine + MCC group it was 31.82% (35/110). Therefore, we can say that after 3 months of therapy, every third patient moved into the category of "overweight", and more than 50% of patients reduced the severity of obesity. At V13, the proportion of patients with category 1 (with normalized body weight), was notified. In the sibutramine + metformin group it was 1.69% (2/118), and in the sibutramine + MCC group it was 0.91% (1/ 110). Herewith, after 6 months of therapy, the absolute majority of patients in the sibutramine + metformin group moved from the "obesity" category to the "overweight" category. Thus, at V13, the proportion of patients with category 2 in the sibutramine + metformin group was 60.17% (71/118), in the sibutramine + MCC group – 49.09% (54/110). The distribution of the patients' proportion who took the sibutramine + metformin drug, depending on the severity of obesity according to BMI, is shown in Figure 3.

A comparative analysis of the frequency of patients who had switched from one BMI category to another, at V13 revealed statistically significant differences between the study groups (p=0.0065).

A frequency assessment of the patients who had achieved a BMI value of less than 30 kg/m^2 at V7 and V13 showed that after 3 months of therapy, the proportion of patients who had reached a BMI value of less than 30 kg/m^2 in the sibutramine + metformin group was 34.17%, and in the sibutramine + MCC group it was 30.00%. The proportion of patients who had reached a BMI value of less than 30 kg/m^2 in the sibutramine + metformin group after 6 months of therapy, was 61.67%, in the sibutramine + MCC group it was 46.67%. The difference between the groups was statistically significant, p = 0.0197 (Fig. 4).

Thus, the proportion of patients who had reduced the degree of obesity and even moved into the category of overweight patients was significantly higher in the sibutramine + metformin group.

When assessing the dynamics of body weight, it was shown that the change in body weight by each visit differed statistically significantly between the groups of drugs sibutramine + metformin and sibutramine + MCC (p<0.05), and in the group of the drug sibutramine + metformin, the dynamics of the decrease in BW was more pronounced.

Table 1 – Categories of BMI for patients' distribution

Category No.	Description
1	Patients with BMI less than 25 kg/m^2
2	Patients with BMI of 25 or less than 30 kg/m^2
3	Patients with BMI of 30 or less than 35 kg/m^2
4	Patients with BMI of 35 or less than 40 kg/m^2
5	Patients with BMI of 40 kg/m^2 or more

Table 2 – Indicators of triglycerides amount in sibutramine + metformin group and in sibutramine + MCC group

Visit	Average value of TG, mmol/l	
	Sibutramine + metformin group	Sibutramine + MCC group
V0	1.71±0.76	1.62±0.65
V7	1.54±0.40	1.50±0.44
V13	1.47±0.40	1.50±0.45

Table 3 – Indicators of lipid metabolism to V13 relative to V1 in sibutramine + metformin group and in sibutramine + MCC group

Lipid fractions, mmol/l		Sibutramine + metformin group	Sibutramine + MCC group
Total cholesterol	V0	5.12±0.94	5.29±1.03
	V13	4.51±0.91	4.73±0.94
LDL	V0	2.44±1.42	2.71±1.46
	V13	1.8±1.01	2.15±1.11
TG	V0	1.71±0.76	1.62±0.65
	V13	1.47±0.40	1.50±0.45
HDL	V0	1.41±0.51	1.47±0.61
	V13	1.48±0.74	1.6±0.78

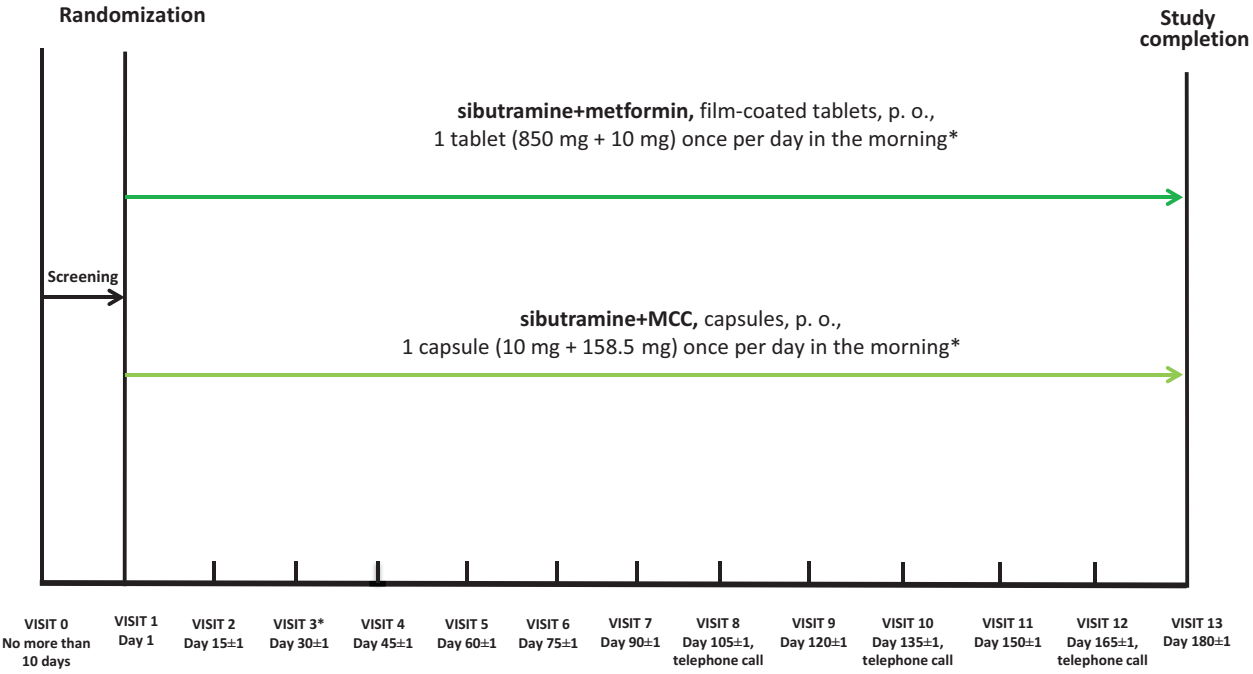

Figure 1 – Graphic study scheme

Note: * – at Visit 3 if there is no weight loss of 2 kg compared to Visit 1, the dose will be increased. Patients in the sibutramine+metformin group will receive 1 tablet (850 mg + 15 mg) and patients in the sibutramine+MCC group would received 1 capsule (15 mg + 158.3 mg).

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2022-10-3-289-304

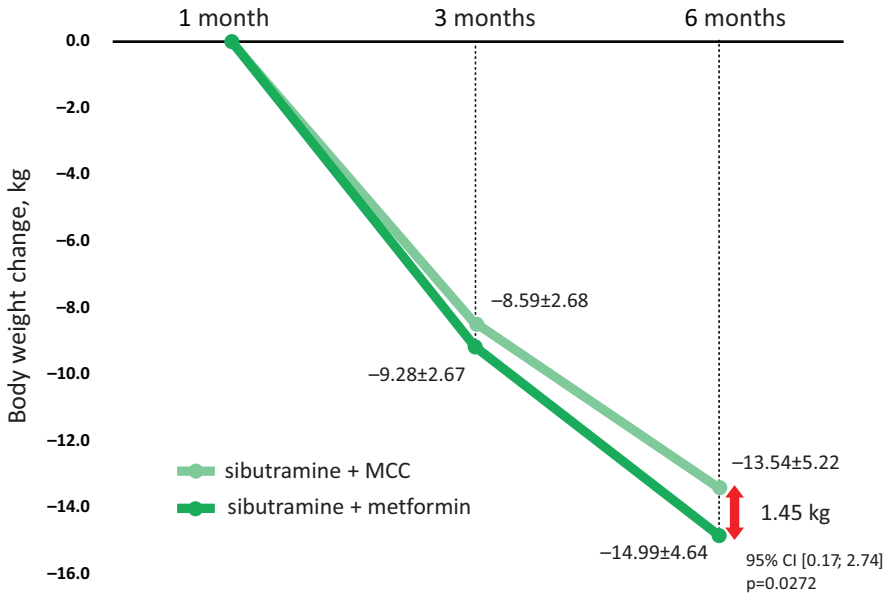

Figure 2 – Dynamics of mean values in patients' body weight changes at V1 (1 month), V7 (3 months) and V13 (6 months) in sibutramine + MCC and sibutramine + metformin groups

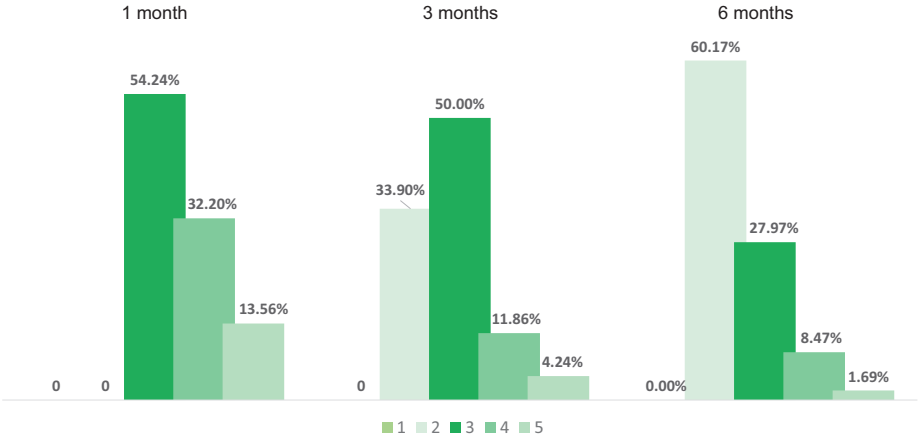

Figure 3 – Proportion of patients who switched from one category to another after 3 and 6 months of treatment in sibutramine + metformin group

Note: 1–5 – BMI categories in accordance with Table 1.

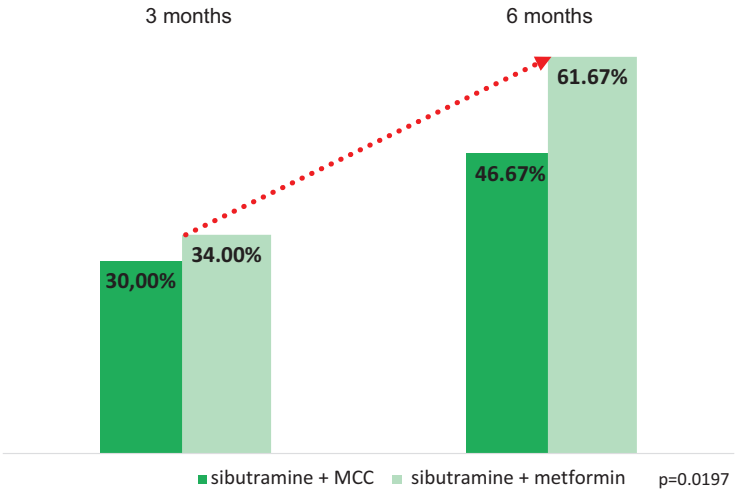

Figure 4 – Proportion of patients who reached BMI less than 30 kg/m2 by V13 relative to V7, in sibutramine + MCC group and in sibutramine + metformin group

The mean body weight in the sibutramine + metformin group at V0 was 99.53±13.53 kg, at V7 it was 90.37±12.77 kg, and at V13 this value was 84.74±12.23 kg. The average value of BW in the sibutramine + MCC group at V0 was 99.10±13.62 kg, at V7it was 90.83±13.04 kg, and at V13 – 86.29±13.44 kg.

Waist measurement dynamics is an important marker of a decrease in the amount of visceral fat, and hence a decrease in the risk of associated complications. The study detected that waist measurement was statistically significantly different at each visit relative to V0 ($p<0.05$) in the both sibutramine+metformin and sibutramine+MCC groups. At V0, the average waist measurement in the sibutramine + metformin group was 101.61±12.85 cm, at V7 it was 94.76±12.02 cm, at V13 – 89.24±11.51 cm. At V0, the sibutramine + MCC group showed an average waist measurement of 100.34±13.76 cm, at V7 – 93.28±12.78 cm, at V13 – 88.21±12.36 cm, respectively.

Thus, in waist measurement, the both drugs showed a reduction of about 12 cm in 6 months, which indicates their effectiveness in relation to decrease visceral obesity.

The results of the waist / hip measurements ratio were statistically significantly different for each visit relative to V0 ($p<0.05$) in the both sibutramine + metformin and sibutramine + MCC groups, which also indicates effectiveness in reducing the amount of visceral fat.

The lipid profile is an important predictor of the developing cardiovascular disease risk, atherosclerosis, and other conditions associated with obesity.

The analysis revealed a significant difference between visits in terms of lipid profile parameters in the both groups, with more pronounced dynamics observed in the group of patients taking sibutramine + metformin ($p<0.00062$), which is associated with the additional action of metformin. So, as a result of the comparative analysis of the magnitude change in TG (%) to V13 relative to V7, statistically significant differences were revealed between the studied groups ($p = 0.0240$). The difference in the mean values of the change in TG (%) between the groups was 6.44%, 95% CI for the difference in the means was [0.86; 12.02] (Table 2).

When assessing the total cholesterol in the group of patients taking sibutramine + metformin, a significant difference between visits was also found out ($p<0.00001$).

The mean value of the total cholesterol in the sibutramine + metformin group significantly decreased: at V0 it was 5.12±0.94 mmol/L; at V7 it was 4.80±0.76 mmol/L; at V13 – 4.51±0.91 mmol/L. There was also a decrease in the sibutramine + MCC group: at V0 it was 5.29±1.03 mmol/L; at V7 it was 4.90±0.95 mmol/L; at V13 – 4.73±0.94 mmol/L.

The estimation and comparative analysis of the LDL-cholesterol amount showed positive dynamics in both groups, while significant differences were established between the sibutramine + metformin and sibutramine + MCC groups at V11 ($p=0.0274$) and V13 ($p=0.0231$). This shows a more pronounced effect of the drug sibutramine + metformin on this indicator.

According to the results of the intragroup analysis, a significant difference was found out between visits in terms of the HDL cholesterol dynamics in the sibutramine + metformin group ($p<0.0088$) and in the sibutramine + MCC group ($p<0.00001$). The dynamics of lipid profile indicators is presented in Table 3. Thus, a long-term use, more than 3 months, of the drug sibutramine + metformin provides a signifikant improvent in lipid profile parameters.

According to the data obtained using the SF-36 Quality of life questionnaire, there is a pronounced positive dynamic of psychological and physical health indicators in both groups, while in the sibutramine + metformin group, the dynamics was more pronounced.

The dynamics of the average score of the physical health component in the sibutramine + metformin group was more than 10 points (from 60.99±9.27 points at V1 to 71.68±8.76 points at V13), and in the sibutramine + MCC group – from 60.74±8.58 points at V1 to 71.09±8.83 points at V13, respectively. The physical health component was also shown to be statistically significantly different at each visit relative to V1 ($p<0.05$) in both the sibutramine+metformin and sibutramine+MCC groups.

The average score of the psychological health component has also improved by 10 points: in the sibutramine + metformin group – by 58.46±8.98 points at V1 and by 68.15±10.98 points at V13. The average score dynamics of the psychological health component in the sibutramine + MCC group was 57.22±10.80 points at V1 and 67.95±10.25 points at V13, respectively. It was found out that the psychological component of health differed statistically significantly for each visit relative to V1 ($p<0.05$) in both groups.

Safety assessment

Safety assessment was performed using a statistical analysis of safety endpoints. The condition of the study participants was assessed with respect to AEs, the data on blood pressure, heart rate throughout the study ECG and laboratory tests.

In the sibutramine + metformin group, the frequency of patients with reported cases of AEs was 33.33% (40/120), and the sibutramine + MCC group – 30.00% (36/120). In both groups, the most common AEs were dry mouth, headache, and sweating.

Among the reported AEs, 89.88% (151/168) were of mild severity, 10.12% (17/168) were of moderate severity. According to the investigators, the causal relationship with therapy based on the study / reference drug was assessed as “not related” in 41.07% (69/168) of cases, as “possible” – in 22.02% (37/168) cases, as “probable” – in 29.76% (50/168) of cases, as “certain” – in 2.38% (4/168) of cases, as “doubtful” – in 4.76% (8/168) cases. The analysis of the frequency of patients’ AEs outcomes showed that “recovery without consequences” was observed in 79.76% (134/168) of cases, “improvement” in 19.05% (32/168) of cases, the outcome “unknown” – in 1.19% (2/168) of cases.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2022-10-3-289-304

Thus, the majority of reported AEs were not related to the study drugs. It is important to note that the AEs were transient in nature and did not require discontinuation of therapy.

According to the results of the intragroup analysis, a significant difference between the visits was found. It indicates the presence of positive dynamics in relation to the decrease in systolic blood pressure in the sibutramine + metformin group ($p<0.00001$) and in the sibutramine + MCC group ($p<0.2623$). It also shows the presence of positive changes in diastolic blood pressure in the sibutramine + metformin group ($p<0.0138$) and in the sibutramine + MCC group ($p<0.0135$). As a result of the comparative analysis, no significant differences between the groups of the study drugs have been identified. During the study, the patients did not experience an increase in resting heart rate ≥10 bpm or systolic/diastolic pressure ≥10 mmHg at two consecutive visits, no exclusion or discontinuation of therapy was required for these criteria. There was also no need to exclude patients due to increased blood pressure.

There was no negative effect of the studied therapy on ECG parameters, as well as indicators of clinical and biochemical blood tests.

As a result of a comparative statistical analysis of AEs in terms of their presence, severity, causal relationship with therapy and its outcomes, there were no intergroup differences ($p\geq0.05$). There were no reported cases of SAEs during the study, including deaths and other significant adverse events. None of the patients required discontinuation of therapy due to the development of AEs.

Thus, the study proved a high safety profile and good tolerability of sibutramine + MCC and sibutramine + metformin, which also speaks in favor of the hypothesis of the advisability of taking sibutramine + metformin in obese patients without additional disorders of carbohydrate metabolism.

DISCUSSION

The present study was conducted to investigate the efficacy and safety of the sibutramine+metformin fixes dose combination, as well as to evaluate the additional benefits in the treatment of overweight patients.

Sibutramine has been successfully used in clinical practice for more than 15 years and is included in all clinical guidelines and standards for the treatment of obesity.

In recent years, it has been shown that metformin, which is the drug of the first choice for the treatment of patients with carbohydrate metabolism disorders, has the potential for a wider therapeutic use, demonstrating pleiotropic effects in relation to the pathogenetic links of the metabolic syndrome and obesity, which seems to be clinically significant for metabolic health. However, the weight loss dynamics against its background has been minimal. Therefore, it is optimal to include metformin in the treatment of obesity and overweight in combinations with other drugs registered for the treatment of this pathology. The previous studies have already demonstrated the benefit of using a unique fixed metformin+sibutramine combination in patients with obesity and carbohydrate metabolism disorders [45, 46]. The combination of central and peripheral actions, the impact on the main pathogenetic links in the development of obesity and associated comorbid conditions, the effects associated with facilitating the observance and consolidation of rational eating habits in the patient and, consequently, the consolidation of the result, as well as a high safety profile, determine the place of the drug containing a fixed metformin+sibutramine combination (Reduxin® Forte), in clinical guidelines and standards [1, 8]. That makes it a kind of benchmark in the treatment of obesity.

The evaluation of this drug use in relation to weight loss and restoration of metabolic health in patients with alimentary obesity, including those without impaired carbohydrate metabolism, is of great interest.

According to the National Clinical Guidelines for the Diagnosis, Treatment, and Prevention of Obesity and Associated Diseases [8], weight loss by 5% or more is one of the main criteria for assessing response to therapy. It provides a possible reduction in health risk and improvement in the course of diseases associated with obesity; maintaining the achieved result; improving the quality of patients' life. Thus, a decrease in body weight by 5% or more improves multi-organ insulin sensitivity and the function of pancreatic β-cells, it provides a protective effect against the risks of type 2 diabetes. Further weight loss provides additional benefits in terms of predicting cardiometabolic outcomes and reducing the risks of not only T2DM, but also other obesity-associated diseases, such as cardiovascular diseases, diseases of the musculoskeletal system and the reproductive system, oncological diseases, etc. [38].

The data of the study showed that the proportion of patients who had achieved more than 5% weight loss by 6 months of therapy in the sibutramine + metformin group, was 99.15%, in the sibutramine + MCC group – 93.64%, the differences were statistically significant. This confirms the effectiveness of the complementary action of the metformin+sibutramine combination in comparison with sibutramine+MCC combination. Moreover, it is important to notify that such a high response to treatment is currently one of the most effective in comparison with the use of other pharmacotherapy options [46, 47].

Over 6 months of therapy, more than 93% of patients treated with the fixed metformin+sibutramine combination, achieved 10% or more weight loss, which confirms a high effectiveness of this therapy type in achieving the true aim of obesity therapy – reducing the risk of complications associated with obesity and improving the forecast.

Quite an important indicator for both the practitioner and the patient is the rate of weight loss in kg. Moreover, the absence of the plateau effect onset is an important motivating factor and helps to eliminate food breakdowns. Here, it is necessary to notify more pronounced values against the background of the combination ther-

apy with sibutramine + metformin, where by the 3rd month, this figure was about 9 kg, and at the end of the study, the average weight loss was almost 15 kg, which was significantly more than in the comparison group.

Achieving a clinically significant effect of therapy when using the minimum dose of the drug, is a very important point. More than 90% of patients did not require an increase in study drug/comparator dose. This makes it possible to talk about a high frequency of an early response to therapy even when taking the minimum dose of sibutramine preparations. This may be especially important for patients in whom the use of a lower dose is preferable against the background of concomitant diseases, and is also relevant from the point of view of the possibility of increasing the dose with prolonged (more than 6 months) treatment, as this may allow to overcome the plateau effect if it occurs.

BMI is the main criterion for diagnosing obesity worldwide and the change in this indicator also reflects the effectiveness of the treatment. The results of the study confirm the advantage of the fixed metformin+sibutramine combination in terms of reducing BMI both after 3 and 6 months of therapy. As a result, BMI for six months of therapy decreased by 15.67%, which was 2% more than during the therapy with the sibutramine+MCC combination. In both groups, a decrease in the degree of obesity from visit to visit was proven, and at the end of the study in the sibutramine + metformin group, more than 60% of patients reached the BMI less than 30 kg/m2 and no longer met the criteria for the diagnosis of "Obesity".

In addition to BMI, an important anthropometric indicator is waist measurement and the ratio of waist to hip measurements. A decrease in waist measurement is a marker of a decrease in the amount of visceral fat and a decrease in the risk of complications. A decrease in this indicator of about 12 cm has been demonstrated during the treatment with sibutramine preparations, along with a decrease in the ratio of waist to hip measurements.

It should be notified that an increase in the duration of the course up to 6 months increases the effectiveness of the treatment, which indicates the feasibility of obesity long-term therapy using the fixed metformin+sibutramine combination to reduce body weight and reduce the risk of complications associated with obesity. These data are consistent with Russian and international clinical guidelines [1, 8, 48].

Of course, along with anthropometric indicators, it is important to assess the effect of therapy on metabolic parameters, in particular, indicators of atherogenic blood fractions, since the normalization of the lipid profile of an obese patient improves the prognosis for cardiometabolic risks and indicates the restoration of metabolic health in general. The results of the lipid profile analysis in patients showed a decrease in cholesterol, TG, LDL and an increase in HDL, and in the group of therapy with the metformin+sibutramine combination, the dynamics of the parameters under consideration was more pronounced.

Improving the overweight patients' quality of life is an important parameter for achieving surrogate endpoints of therapy. During the study, it was found out that treatment with sibutramine preparations was accompanied by a statistically significant improvement under the condition of all assessed scales; the psychological and physical components of health differed statistically significantly by each visit.

The most important component of the algorithm for monitoring the safe pharmacotherapy of obesity is the control of the cardiovascular system state. During the study, ECG parameters, systolic and diastolic kinds of blood pressure and heart rate remained stable in both groups.

The study demonstrated good tolerability of sibutramine therapy. During the study, there were no reported cases of SAEs, including deaths and other significant adverse events. AEs were transient and did not require discontinuation of treatment.

Thus, the composition of the metformin+sibutramine fixes dose combination makes it an optimal and safe choice for achieving therapeutic goals in the treatment of obesity and the restoration of metabolic health.

CONCLUSION

The feasibility and importance of weight loss, especially through effective and safe pharmacotherapy, is an indisputable fact. At the same time, the goals of obesity therapy include not only weight loss, but also the improvement of metabolic health parameters, as well as reducing the risk of developing comorbid diseases and complications associated with excess visceral fat.

The conducted "Open multicenter randomized study to evaluate the efficacy and safety of the use of the drug Reduxin® Forte, film-coated tablets, in comparison with the drug Reduxin®, capsules, in patients with alimentary obesity", showed a significant improvement in body weight, waist measurement and BMI, as well as the main metabolic parameters and patients' quality of life against the background of the fixed metformin+sibutramine combination. The data obtained prove the effectiveness of this therapy type in terms of normalizing metabolic health, reducing the risk of developing comorbid diseases and improving the prognosis in obese patients even without additional carbohydrate metabolism disorders. This fact was reflected in the medical instructions' changes concerning the use of the drug in question and the official approval of its use in patients with alimentary obesity without even without additional disorders of carbohydrate metabolism (impaired glucose tolerance, T2DM)[5]. It is worth considering the inclusion of weight loss aid, comprising the subscription of this type of ther-

[5] Russian State Register of Medicines. Reduxin® Forte. Available from: https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=108c4981-0dbb-4bdc-a3fe-08395333313f. Russian

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2022-10-3-289-304

apy, in clinical examination programs and clinical recommendations for the treatment of non-communicable diseases allied with metabolic disorders (CVD, T2DM, NAFLD, etc.) in order to prevent the development of the latter or their complications.

Taking into account the contribution of obesity to the pathogenesis of a wide range of non-communicable and even infectious diseases, and the proven positive effect of weight loss on improving the prognosis of patients, it is advisable to conduct further clinical studies to identify new possible niches for the use of this type of therapy.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

DTYu – developing the concept of a clinical trial, analysis of the results, correction of the text; IMYa – data collection and processing, the article writing; USE – data collection and processing, the article writing; ZKYa – developing the design and concept of the study, the article writing; OAA – data collection and processing, the article writing; PVV – data collection and processing, the article writing, NME – the article writing and proofreading, VAF – data collection and processing, the article writing; BPA – text correction, consolidation of results, organization of statistical processing.

REFERENCES

1. Dedov II, Mokrysheva NG, Mel'nichenko GA, Troshina EA, Mazurina NV, Ershova EV, Komshilova KA, Andreeva EN, Antsiferov MB, Biriukova EV, Bordan NS, Vagapova GR, Volkova AR, Volkova NI, Volynkina AP, Dzgoeva FKh, Kiseleva TP, Neimark AE, Romantsova TI, Ruiatkina LA, Suplotova LA, Khalimov IuSh, Yashkov IuI. Ozhirenie. Klinicheskie rekomendacii [Obesity. Clinical guidelines]. Consilium Medicum. 2021; 23 (4): 311–25. DOI: 10.26442/20751753.2021.4.200832. Russian
2. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism. 2022 Aug;133:155217. DOI: 10.1016/j.metabol.2022.155217.
3. Mohammed MS, Sendra S, Lloret J, Bosch I. Systems and WBANs for Controlling Obesity. J Healthc Eng. 2018 Feb 1;2018:1564748. DOI: 10.1155/2018/1564748.
4. Antwi F, Fazylova N, Garcon MC, Lopez L, Rubiano R, Slyer JT. The effectiveness of web-based programs on the reduction of childhood obesity in school-aged children: A systematic review. JBI Libr Syst Rev. 2012;10(42 Suppl):114. DOI: 10.11124/jbisrir-2012-248.
5. Al Kibria GM. Prevalence and factors affecting underweight, overweight and obesity using Asian and World Health Organization cutoffs among adults in Nepal: Analysis of the Demographic and Health Survey 2016. Obes Res Clin Pract. 2019 Mar–Apr;13(2):129–36. DOI: 10.1016/j.orcp.2019.01.006. Epub 2019 Feb 1. Erratum in: Obes Res Clin Pract. 2019 May–Jun;13(3):328.
6. Shi Q, Wang Y, Hao Q, Vandvik PO, Guyatt G, Li J, Chen Z, Xu S, Shen Y, Ge L, Sun F, Li L, Yu J, Nong K, Zou X, Zhu S, Wang C, Zhang S, Qiao Z, Jian Z, Li Y, Zhang X, Chen K, Qu F, Wu Y, He Y, Tian H, Li S. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. Lancet. 2022 Jan 15;399(10321):259–69. DOI: 10.1016/S0140-6736(21)01640-8.
7. Drapkina OM, Samorodskaya IV, Starinskaya MA, Kim OT, Neimark AE. Ozhirenie: ocenka i taktika vedeniya pacientov [Obesity: assessment and management of patients], Monograph, National Medical Research Center for Therapy and Preventive Medicine, Publishing house LLC "Silicea-Polygraph"; 2021: 180 p. Russian
8. Dedov II, Shestakova MV, Melnichenko GA, Mazurina NV, Andreeva EN, Bondarenko IZ, Gusova ZR, Dzgoeva FK, Eliseev MS, Ershova EV, Zhuravleva MV, Zakharchuk TA, Isakov VA, Klepikova MV, Komshilova KA, Krysanova VS, Nedogoda SV, Novikova AM, Ostroumova OD, Pereverzev AP, Rozhivanov RV, Romantsova TI, Ruyatkina LA, Salasyuk AS, Sasunova AN, Smetanina SA, Starodubova AV, Suplotova LA, Tkacheva ON, Troshina EA, Khamoshina MV, Chechelnitskaya SM, Shestakova EA, Sheremet'eva EV. Mezhdisciplinarnye klinicheskie rekomendacii «Lechenie ozhireniya i komorbidnyh zabolevanij» [Interdisciplinary clinical practice guidelines «Management of obesity and its comorbidities»]. Obesity and metabolism. 2021;18(1):5–99. DOI:10.14341/omet12714. Russian
9. Batrak GA. Effektivnost' kombinirovannoj terapii sibutraminom i metforminom u pacientov s abdominal'nym tipom ozhireniya [The efficacy of combined therapy by sibutramin and metformine in patients with abdominal obesity type]. BULLETIN of the Ivanovo Medical Academy. 2015; 20(3): 59–60. Russian
10. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res. 1998 Sep;6 Suppl 2:51S–209S. Erratum in: Obes Res 1998 Nov;6(6):464.

11. Romantsova TI. Sibutramine: efficacy and safety of prescribing in routine clinical practice. Obesity and metabolism. 2015;12(3):18–24. DOI: 10.14341/omet2015318-24. Russian

12. Hansen DL, Toubro S, Stock MJ, Macdonald IA, Astrup A. Thermogenic effects of sibutramine in humans. Am J Clin Nutr. 1998 Dec;68(6):1180–6. DOI: 10.1093/ajcn/68.6.1180.

13. Ruyatkina LA, Ruyatkin DS. Ozhirenie: «perekrestki» mnenij, znanij i vozmozhnostej [Obesity: The Crossroads of Opinion, Knowledge, and Opportunity]. Medical Council. 2020;(7):108–20. DOI:10.21518/2079-701X-2020-7-108-120. Russian

14. Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. Curr Opin Endocrinol Diabetes Obes. 2014;21(5):323–9. DOI: 10.1097/MED.0000000000000095/

15. Fantino M, Souquet AM. Effects of Metabolites 1 and 2 of Sibutramine on the Short-Term Control of Food Intake in the Rat. Int. J. Obes. 1995;1 (Suppl. 2): 145.

16. Connoley IP, Liu YL, Frost I, Reckless IP, Heal DJ, Stock MJ. Thermogenic effects of sibutramine and its metabolites. Br J Pharmacol. 1999 Mar;126(6):1487–95. DOI: 10.1038/sj.bjp.0702446.

17. Cheetham SC, Viggers JA, Butler SA, Prow MR, Heal DJ. [3H]nisoxetine--a radioligand for noradrenaline reuptake sites: correlation with inhibition of [3H]noradrenaline uptake and effect of DSP-4 lesioning and antidepressant treatments. Neuropharmacology. 1996 Jan;35(1):63–70. DOI: 10.1016/0028-3908(95)00134-4.

18. Shupenina EY, Yushchuk EN, Vasyuk YuA, Yureneva SV, Dubrovina AV. The experience of sibutramine administration in patients with obesity and controlled arterial hypertension. *Obesity and metabolism*. 2019;16(2):42–8. Russian

19. Luscombe GP, Hopcroft RH, Thomas PC, Buckett WR. The contribution of metabolites to the rapid and potent down-regulation of rat cortical beta-adrenoceptors by the putative antidepressant sibutramine hydrochloride. Neuropharmacology. 1989 Feb;28(2):129–34. DOI: 10.1016/0028-3908(89)90048-8.

20. Janssen PJ, Gardiner SM, Compton AM, Bennett T. Mechanisms contributing to the differential haemodynamic effects of bombesin and cholecystokinin in conscious, Long Evans rats. Br J Pharmacol. 1991 Jan;102(1):123–34. DOI: 10.1111/j.1476-5381.1991.tb12143.x.

21. de Souza BP, da Silva ED Jr, Jurkiewicz A, Jurkiewicz NH. Influence of acute treatment with sibutramine on the sympathetic neurotransmission of the young rat vas deferens. Eur J Pharmacol. 2014 Sep 5;738:118–24. DOI: 10.1016/j.ejphar.2014.05.035.

22. Brown M, Bing C, King P, Pickavance L, Heal D, Wilding J. Sibutramine reduces feeding, body fat and improves insulin resistance in dietary-obese male Wistar rats independently of hypothalamic neuropeptide Y. Br J Pharmacol. 2001 Apr;132(8):1898–904. DOI: 10.1038/sj.bjp.0704030.

23. Shishkova VN. Obesity as a reflection of psycho-emotional disorders: focus on pharmacotherapy. *Pharmacy & Pharmacology*. 2022;10(1):19–30. DOI:10.19163/2307-9266-2022-10-1-19-30.

24. Paul D, Allakonda L, Satheeshkumar N. A validated UH-PLC-QTOF-MS method for quantification of metformin and teneligliptin in rat plasma: Application to pharmacokinetic interaction study. J Pharm Biomed Anal. 2017 Sep 5;143:1–8. DOI: 10.1016/j.jpba.2017.05.026.

25. Li X, Chen Y, Zhao Z, Lu W, Zhou T. Pharmacokinetic/Pharmacodynamic Analysis of Metformin using Different Models in Diabetic Rats. Drug Res (Stuttg). 2016 Oct;66(10):547–54. DOI: 10.1055/s-0042-111514.

26. Ford MD, Delaney KA, Ling LJ, Erickson T. Clinical toxicology WB Saunders, 2000.

27. Stepensky D, Friedman M, Raz I, Hoffman A. Pharmacokinetic-pharmacodynamic analysis of the glucose-lowering effect of metformin in diabetic rats reveals first-pass pharmacodynamic effect. Drug Metab Dispos. 2002 Aug;30(8):861–8. DOI: 10.1124/dmd.30.8.861.

28. Kappe C, Patrone C, Holst JJ, Zhang Q, Sjöholm A. Metformin protects against lipoapoptosis and enhances GLP-1 secretion from GLP-1-producing cells. J Gastroenterol. 2013 Mar;48(3):322-32. DOI: 10.1007/s00535-012-0637-5.

29. Murai Y, Ohta T, Tadaki H, Miyajima K, Shinohara M, Fatchiyah F, Yamada T. Assessment of Pharmacological Responses to an Anti-diabetic Drug in a New Obese Type 2 Diabetic Rat Model. Med Arch. 2017 Dec;71(6):380-384. DOI: 10.5455/medarh.2017.71.380–4.

30. Spasov AA, Vorohkova MP, Snegur GL, Cheplyaeva NI, Chepurnova MV. Eksperimental'naya model' saharnogo diabeta tipa 2 [Experimental model of a type 2 diabetes]. Journal Biomed. 2011; 1(3): 12–8. Russian

31. Dedov II, Troshina EA, Mazurina NV, Galieva MO, Logvinova OV. Rol' nejrotransmitterov v regulyacii energeticheskogo gomeostaza i vozmozhnosti medikamentoznoj korrekcii ego narushenij pri ozhirenii [The role of neurotransmitters in regulation of energy homeostasis and possibility of drug correction of its disturbances in obesity]. Obesity and metabolism. 2016;13(1):9-15. DOI:10.14341/omet201619-15. Russian

32. Bouchoucha M, Uzzan B, Cohen R. Metformin and digestive disorders. Diabetes Metab. 2011 Apr;37(2):90–6. DOI: 10.1016/j.diabet.2010.11.002.

33. Vettor R, Serra R, Fabris R, Pagano C, Federspil G. Effect of sibutramine on weight management and metabolic control in type 2 diabetes: a meta-analysis of clinical studies. Diabetes Care. 2005 Apr;28(4):942–9. DOI: 10.2337/diacare.28.4.942.

34. Fujioka K, Seaton TB, Rowe E, Jelinek CA, Raskin P, Lebovitz HE, Weinstein SP; Sibutramine/Diabetes Clinical Study Group. Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2000 Jun;2(3):175-87. DOI: 10.1046/j.1463-1326.2000.00081.x.

35. Dedov II, Mel'nichenko GA, Romantsova TI. The strategy of obesity management: the results of All-Russian observational program "Primavera". Obesity and metabolism.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2022-10-3-289-304

2016;13(1):36–44. DOI: 10.14341/omet2016136-44. Russian

36. Mahmood K, Naeem M, Rahimnajjad NA. Metformin: the hidden chronicles of a magic drug. Eur J Intern Med. 2013 Jan;24(1):20–6. DOI: 10.1016/j.ejim.2012.10.011.
37. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond). 2012 Mar;122(6):253–70. DOI: 10.1042/CS20110386.
38. Dedov II, Romantsova TI, Shestakova MV. Racional'nyj podhod k terapii pacientov s SD2 i ozhireniem: itogi Vserossijskoj nablyudatel'noj programmy «AVRORA» [Rational approach to patients treatment with type 2 diabetes and obesity: results of the All-Russian observational program «AURORA»]. *Obesity and metabolism*. 2018;15(4):48-58. DOI: 10.14341/omet10076. Russian
39. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Pediatrics. 2001 Apr;107(4):E55. DOI: 10.1542/peds.107.4.e55.
40. Foster GD, Wadden TA, Vogt RA, Brewer G. What is a reasonable weight loss? Patients' expectations and evaluations of obesity treatment outcomes. J Consult Clin Psychol. 1997 Feb;65(1):79–85. DOI: 10.1037//0022-006x.65.1.79.
41. Sari R, Eray E, Ozdem S, Akbas H, Coban E. Comparison of the effects of sibutramine versus sibutramine plus metformin in obese women. Clin Exp Med. 2010 Sep;10(3):179–84. DOI: 10.1007/s10238-009-0080-y.
42. Gokcel A, Gumurdulu Y, Karakose H, Melek Ertorer E, Tanaci N, BascilTutuncu N, Guvener N. Evaluation of the safety and efficacy of sibutramine, orlistat and metformin in the treatment of obesity. Diabetes Obes Metab. 2002 Jan;4(1):49–55. DOI: 10.1046/j.1463-1326.2002.00181.x.
43. Baptista T, Uzcátegui E, Rangel N, El Fakih Y, Galeazzi T, Beaulieu S, de Baptista EA. Metformin plus sibutramine for olanzapine-associated weight gain and metabolic dysfunction in schizophrenia: a 12-week double-blind, placebo-controlled pilot study. Psychiatry Res. 2008 May 30;159(1–2):250–3. DOI: 10.1016/j.psychres.2008.01.011.
44. Guerrero-Romero F, Rodríguez-Morán M, Pérez-Fuentes R, Sánchez-Guillén MC, González-Ortiz M, Martínez-Abundis E, Brito-Zurita O, Madero A, Figueroa B, Revilla-Monsalve C, Flores-Martínez SE, Islas-Andrade S, Rascón-Pacheco RA, Cruz M, Sánchez-Corona J. Prediabetes and its relationship with obesity in Mexican adults: The Mexican Diabetes Prevention (MexDiab) Study. Metab Syndr Relat Disord. 2008 Mar;6(1):15–23. DOI: 10.1089/met.2007.0020.
45. Ametov AS, P'yanykh OP, Nevol'nikova AO. Sovremennye vozmozhnosti upravleniya metabolicheskim zdorov'em u pacientov s ozhireniem i narusheniyami uglevodnogo obmena [Modern opportunities of metabolic health management in patients with obesity and carbohydrate metabolism disorders]. Endokrinologiya: novosti, mneniya, obuchenie [Endocrinology: News, Opinions, Training]. 2020; 9 (1): 17–26. DOI: 10.33029/2304-9529-2020-9-1-17-26. Russian
46. P'yanykh OP, Gusenbekova DG, Ametov AS. Preimushchestva dolgosrochnogo upravleniya metabolicheskim zdorov'em u pacientov s ozhireniem i rannimi narusheniyami uglevodnogo obmena [Advantages of long-term management the metabolic health in patients with obesity and early disorders of carbohydrate metabolism]. Endokrinologiya: novosti, mneniya, obuchenie [Endocrinology: News, Opinions, Training]. 2020; 9 (2): 40–8. DOI: 10.33029/2304-9529-2020-9-2-40-48. Russian
47. Mehta A, Marso SP, Neeland IJ. Liraglutide for weight management: a critical review of the evidence. Obes Sci Pract. 2017 Mar;3(1):3–14. DOI: 10.1002/osp4.84.
48. Wharton S, Lau DCW, Vallis M, Sharma AM, Biertho L, Campbell-Scherer D, Adamo K, Alberga A, Bell R, Boulé N, Boyling E, Brown J, Calam B, Clarke C, Crowshoe L, Divalentino D, Forhan M, Freedhoff Y, Gagner M, Glazer S, Grand C, Green M, Hahn M, Hawa R, Henderson R, Hong D, Hung P, Janssen I, Jacklin K, Johnson-Stoklossa C, Kemp A, Kirk S, Kuk J, Langlois MF, Lear S, McInnes A, Macklin D, Naji L, Manjoo P, Morin MP, Nerenberg K, Patton I, Pedersen S, Pereira L, Piccinini-Vallis H, Poddar M, Poirier P, Prud'homme D, Salas XR, Rueda-Clausen C, Russell-Mayhew S, Shiau J, Sherifali D, Sievenpiper J, Sockalingam S, Taylor V, Toth E, Twells L, Tytus R, Walji S, Walker L, Wicklum S. Obesity in adults: a clinical practice guideline. CMAJ. 2020 Aug 4;192(31):E875-E891. DOI: 10.1503/cmaj.191707.

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