

Golacki Jakub, Marczak Aleksandra, Hordejuk Michalina, Sapula Klaudia, Iwaszko-Sochal Klaudyna. Polypharmacotherapy with anti-obesity drugs – case report. Journal of Education, Health and Sport. 2022;12(7):233-237. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2022.12.07.023>  
<https://apcz.umk.pl/JEHS/article/view/JEHS.2022.12.07.023>  
<https://zenodo.org/record/6790807>

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).

Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przynależność dyscypliny naukowej: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 20.06.2022. Revised: 20.06.2022. Accepted: 02.07.2022.

## **Polypharmacotherapy with anti-obesity drugs – case report**

**Jakub Gołacki, Aleksandra Marczak, Michalina Hordejuk, Klaudia Sapula,  
Klaudyna Iwaszko-Sochal**

### **Jakub Gołacki**

[jakub.golacki@gmail.com](mailto:jakub.golacki@gmail.com), <https://orcid.org/0000-0001-8502-3030>

Samodzielny Publiczny Szpital Kliniczny nr 4 w Lublinie

### **Aleksandra Marczak**

[aleksandramarczak26@gmail.com](mailto:aleksandramarczak26@gmail.com), <https://orcid.org/0000-0002-3025-5907>

Samodzielny Publiczny Szpital Kliniczny nr 1 w Lublinie

### **Michalina Hordejuk**

[michalina.hordejuk@gmail.com](mailto:michalina.hordejuk@gmail.com), <https://orcid.org/0000-0003-2473-1062>

Wojewódzki Szpital Specjalistyczny w Lublinie

### **Klaudia Sapula**

[klaudiaa.em@gmail.com](mailto:klaudiaa.em@gmail.com), <https://orcid.org/0000-0003-2436-0150>

Samodzielny Publiczny Szpital Kliniczny nr 4 w Lublinie

### **Klaudyna Iwaszko-Sochal**

[klaudyna.iwaszko92@gmail.com](mailto:klaudyna.iwaszko92@gmail.com), <https://orcid.org/0000-0001-9228-6138>

Samodzielny Publiczny Szpital Kliniczny nr 4 w Lublinie

## **Abstract**

Obesity is a chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse health consequences. It is diagnosed based on body mass index and waist circumference. In case of severe obesity, bariatric surgery or pharmacotherapy is recommended. We present a case report of a 28 years old man with class III obesity ( $77,6 \text{ kg/m}^2$ ). In order to qualify the patient for bariatric surgery, a decision to combine two anti-obesity medications has been made. This kind of obesity management is neither recommended, not contraindicated, but has shown good effects on body mass reduction. This case report should initiate the discussion about recommendations modification towards combining anti-obesity medications of different mechanisms of action.

**Keywords:** obesity; treatment; anti-obesity drugs; combination obesity pharmacotherapy

## **Introduction**

Obesity, according to Obesity Medicine Association, is a chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences.

The etiology of obesity is believed to be multifactorial. It consists of genetic predisposition, poor eating habits, low physical activity and unhealthy lifestyle, chronic stress, and hormonal disorders. It is assumed that phenotypically, two basic types of fat deposition can be distinguished in the human body: central and peripheral fat deposition [1]. Central obesity (known as an apple or android-shaped body) contributes to worse metabolic complications. Peripheral obesity (known as a pear-shaped body or gynecoid phenotype) correlates with a reduced risk of metabolic complications.

Body Mass Index (BMI) is assumed to be an objective indicator that defines obesity. It is expressed as the quotient of body weight and body surface area, using units of  $\text{kg/m}^2$ . According to the World Health Organisation (WHO), a BMI above or equal 25 is classified as overweight, while above or equal 30 is classified as obesity. Obesity is a growing health problem, including in Poland [2]. It is estimated that more than 1,9 billion adults are overweight and 650 million of whom are obese.

The U.S. has seen an increase in health care financial expenditures for obesity. It is estimated that by 2030, the total cost of Health Care for people with obesity could consume as much as 16-18 % of the US Health Care budget [3].

## **Case report**

### **Diagnostic process**

In December 2021, a 28 year old patient was admitted to the Clinical Department of Endocrinology, Diabetology and Metabolic Disorders within obesity treatment program. At height of 183 cm and body mass of 260 kg, a body mass index (BMI) of  $77,6 \text{ kg/m}^2$  was calculated. Waist circumference (WC) of 177 cm was measured. A diagnosis of class III obesity and abdominal obesity have been made.

The patient has been obese since childhood. Family history for obesity is positive (parents and grandparents). He lives a sedentary lifestyle, both in free time and at work (IT specialist). He does not have any sport activity because of joints pain. The patient eats breakfast at 6:00 am, second breakfast at 9:00 am, lunch at 1:00 pm and dinner at 4 pm, after which he begins intermittent fasting, which unfortunately tends to be stopped by snacks and sweetened beverages.

He smokes one pack of cigarettes per week and drinks excessive amount of alcohol once per weekend. In 2009 he was diagnosed with fatty liver disease, but he did not get any treatment. In 2013 the patient was diagnosed with hypertension and got treatment but stopped it on his own.

The diagnostic process of obesity causes and complications has been conducted. The most common obesity causes (hypothyroidism, Cushing's syndrome, drug-induced mechanisms) have been excluded. Considering patient's lifestyle and habits, his obesity type has been determined as primary, caused by excess calories intake accompanied with insufficient calories loss due to low physical activity. Obesity complications screening included blood pressure measurement, serum concentration of glucose, HbA1c, lipids, uric acid, creatinin, sodium, potassium, calcium, liver function parameters, D3 vitamin and imaging studies. Hypertension, type 2 diabetes, hyperuricemia and vitamin D3 deficiency were diagnosed.

Because of enormous level of obesity and potential need for bariatric (metabolic) surgery qualification, a chest and abdomen CT-scan has been made. Result showed steatosis hepatis, probably due to metabolic associated fatty liver disease (MAFLD), a new name for non-alcoholic fatty liver disease (NAFLD); splenomegaly, and Schmorl nodes – a symptom typical for Scheuermann's disease, that can also be present due to obesity and vitamin D deficiency [4].

## **Treatment**

So far the patient has tried normalising his body weight six times, each time with lifestyle changes only. The disease has been relapsing after ca. three months. He tried joining a sports team, but due to knee trauma he stopped working out. He did not look for professional medical help concerning obesity until his friend with obesity died at similar age.

According to obesity treatment guidelines, pharmacotherapy for weight loss can be used for individuals with  $BMI \geq 30 \text{ kg/m}^2$  or  $BMI \geq 27 \text{ kg/m}^2$  with adiposity-related complications, in conjunction with medical nutrition therapy, physical activity and psychological interventions [5].

Because of particularly high body mass index and waist circumference, a decision to use two anti-obesity medications was made: bupropion/naltrexone and semaglutide.

Bupropione-naltrexone is administered orally twice per day and acts centrally on hunger and satiety centers in hypothalamus. Semaglutide, an injection medication administered subcutaneously once per week, is a glucagon-like peptide 1 (GLP-1) analogue that acts both centrally on hypothalamus and peripherally on pancreas, stomach and many other organs. Although semaglutide's registration for obesity treatment in European Union is still pending, it is already registered as an antidiabetic medication in EU and as an antidiabetic and anti-obesity medication in the USA.

The topic of polypharmacotherapy with two or more anti-obesity drugs registered in the EU is not covered by current obesity treatment guidelines. It is not neither recommended, nor contraindicated. So far, to the best of our knowledge, scientific papers or case reports have not covered this topic as well. Considering that neither of these two medications have caused pharmacological interactions with each other, a decision to implement both has been made.

Moreover, the patient has started treatment with metformin for type 2 diabetes mellitus. Because of high blood pressure, he has been prescribed with nebivolol, amlodipine, candesartan, indapamide and spironolactone. Additionally, the patient got allopurinol for hyperuricemia and cholecalcyferole for vitamin D deficiency.

Another important part of obesity treatment are lifestyle changes. A reduction diet of 3000 kcal has been recommended. The patient has been educated about the need to eat less sugars and high glycemic index foods, as well as eat more fiber and poly-unsaturated fatty acids. The patient has also been instructed about physical activity adequate to his health condition and has been referred to rehabilitation course.

## **Follow-up**

After a month, the patient came for a follow-up. Anthropometric parameters were measured and cardio-metabolic risk was estimated again. The patient met a set goal of body mass reduction of 0,5–1 kg per week: he went down by 3,5 kg from 260 kg (BMI 77,6 kg/m<sup>2</sup>) to 256,5 kg (BMI 76,6 kg/m<sup>2</sup>). Additionally, the patient reduced his waist circumference by 3 cm, from 177 cm to 174 cm. He also made changes to his lifestyle – started walking 5 thousand steps per day, eating and sleeping regularly. He joined swimming classes. Most importantly, he tolerated his double pharmacological anti-obesity treatment very well, with no side effects.

## **Discussion**

This case report raises some questions about how patients with obesity should be diagnosed and treated.

First of all, even though this patient has been obese since childhood, the diagnosis of obesity has never before appeared in his medical record. Since obesity is a well known risk factor for developing certain metabolic and non-metabolic consequences, in case of this patient it should be coded as “Class III Obesity complicated by Type 2 Diabetes, Hypertension, Hyperuricemia and Osteoarthritis”.

Although there are no clear guidelines and recommendations concerning combination anti-obesity pharmacotherapy, this kind of treatment is not contraindicated both by medical societies and medication manufacturers. A weight loss of 2 to 4 kilograms per month is typically expected during anti-obesity pharmacotherapy. A bigger loss should be expected when combining multiple medications but this requires strict life style changes. At this level of obesity typical physical activity tends to not be possible because of potential trauma risk and coexistent osteoarthritis. Every patient requires personal assessment for recommended physical activity level.

The matter of cost of this kind of therapy must be thoroughly discussed with the patient. The patient needs to be informed that pharmacotherapy would be long, with at least 12 months in lower level obesity. Dosage should be increased slowly and the patient should be checked up regularly on possible side effects, due to medications combination in particular.

Another important aspect is the difficulty of the radiologic diagnostic process. In case a patient with obesity will not fit into a typical CT-scanner, a polytrauma or veterinarian diagnostic facility should be taken into consideration. Even then, the interpretation of a CT-scan is not easy due to excess fat tissue.

Finally, in case of Class III Obesity, a bariatric operation is advised. Most bariatric centers recommend pre-operative pharmacotherapy with anti-obesity medications. Moreover, obesity complications and coexistent diseases should be kept in a controlled state.

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