**WYRWAŁ, Julia, NOWAK, Karolina, OLEJARZ, Zuzanna, DRYGAŁA, Zuzanna, ZIELIŃSKA, Zuzanna, SŁOWIK, Magdalena, NOWAK, Karolina, NIEĆ, Maria, GIERLACH, Katarzyna and KRASUSKA, Martyna. The Review of pharmacological treatment registered for obesity in Poland. Journal of Education, Health and Sport. 2024;56:54-67. eISSN 2391-8306.**
**https://dx.doi.org/10.12775/JEHS.2024.56.004**
**https://apcz.umk.pl/JEHS/article/view/47954**
**https://zenodo.org/records/10607745**

**The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).**
**Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;**

**The authors declare that there is no conflict of interests regarding the publication of this paper.**
**Received: 10.01.2024. Revised: 27.01.2024. Accepted: 30.01.2024. Published: 01.02.2024.**

# Review of pharmacological treatment registered for obesity in Poland

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**Summary**

**Introduction:** Obesity is a persistent chronic condition. It is associated with an increased risk of premature death and the development of accompanying diseases. According to statistical data, half of the population struggles with excessive body weight, with one in five Poles being obese. [2]

**Aim:** Our study aimed to evaluate the current literature on pharmacotherapy for obesity available in Poland using the PubMed database. We emphasize the crucial importance of an

individualized patient approach to attain therapeutic success, aligning with the latest guidelines and scientific research.

**A brief description of the state of knowledge:** In Poland, we have three registered medications intended for the treatment of obesity: naltrexone/bupropion, liraglutide, and orlistat. It's crucial that they assist in weight reduction, hence they should be used alongside a proper diet and physical activity, not as the sole form of treatment. Using them assists in achieving therapeutic targets determined in partnership with the patient, and lowers levels of particular indicators linked to chronic inflammation and arterial issues. Moreover, they diminish the chances of complications and early mortality due to the advancement of the condition.

**Summary:** Obesity is a serious condition, and there should be no fear in incorporating pharmacotherapy in patients with it. It is incredibly important to effectively treat this disease and take proactive health measures, even at the stage of overweight, considering it as a precursor to obesity.

KEYWORDS: Obesity; Orlistat; Bupropion; Naltrexone; Liraglutide

## Pathophysiology of obesity

The relationships among obesity, diabetes, and cancer are established through metabolic disruptions (like insulin resistance,following hyperinsulinemia, hyperglycemia, changes in hormone secretion related to lipids, biosynthesis of sex steroid hormones ), and persistent low-grade subclinical inflammation [3,4,5,6,7,8,9]

Obesity doesn't just lead to an increase in white adipose tissue but it also changes how the adipocytes function hormonally. They increase the production of leptin and reduce the production of adiponectin. These peptides have opposing effects on cancer development: leptin can function as a growth factor and encourage an inflammatory environment, whereas adiponectin suppresses the proliferation of cancer cells and reduces proinflammatory agents [4]

In cases of obesity, the white adipose tissue shows increased infiltration by immune cells like macrophages. These cells generate inflammatory proteins like tumor necrosis factor alpha, interleukins 1β and 6.These cells produce proinflammatory cytokines such as tumor necrosis factor alpha and interleukins 1β and 6.The production of these cytokines is additionally stimulated by the changes observed in the levels of adiponectin and leptin. These inflammatory mediators not only contribute to insulin resistance and lead to increased conversion of estrogen in the peripheral tissues but also trigger signaling pathways associated with tumor development such as the JAK/STAT pathway [3,4,7, 11]

Insulin resistance, a commonly observed condition in individuals with obesity and a crucial factor in the development of type 2 diabetes, encourages compensatory hyperinsulinemia at least when the functionality of the β-cells remains intact [4].Insulin is an anabolic hormone , working via tyrosine-kinase membrane receptors. This action results in mitogenic and anti-apoptotic effects, especially in cancer cells that no longer exhibit downregulation of the insulin receptor. [12] When pancreatic β-cells cannot produce more insulin in response to increasing insulin resistance, it results in high blood sugar levels. Elevated glucose in the bloodstream theoretically supports cancer development as cancerous cells alter their energy metabolism towards anaerobic glycolysis, a process demanding higher glucose amounts

to generate equivalent energy compared to oxidative phosphorylation. [12,13] Nevertheless, due to the fact that hyperglycemia indirectly encourages both hyperinsulinemia and increased IGF levels, its direct role in causing cancer is still a topic of debate [3,4]. It is important to remember that the blood glucose level is one of the factors and by itself may not be sufficient for carcinogenesis.

**Individual comprehensive obesity treatment plan**

Obesity should be treated as a serious illness, and its therapy should begin at the stage of overweight. It is important to firstly exclude secondary obesity. Take into account cause, stage of the disease, overall health, presence of complications, establish treatment goals, and consider the patient's willingness to cooperate. It is also necessary to consider the coexistence of obesity-related conditions such as prediabetes, diabetes, or hypertension, as well as eating disorders leading to overeating, as this is crucial. A holistic approach is the key to success,

encompassing both non-pharmacological methods and registered medications for adjunctive obesity treatment.

**Pharmacological methods of treating obesity**

The aim of pharmacological treatment for obesity is primarily to help individuals in adhering more effectively to dietary recommendations and to establish healthier lifestyle changes**.** Properly conducted pharmacological treatment enables greater weight reduction compared to behavioral interventions alone and facilitates achieving therapeutic goals**.** Weight reduction is associated with a decrease in metabolic risk, improvement in overall health, and the course of coexisting diseases.

The selection of medication should be tailored individually to the patient. It is essential to consider the mechanism leading to obesity in a particular individual, contraindications and warnings provided in the medication's characteristics to avoid drug interactions and potential side effects. Factors such as the method of administration, costs, and the risk of treatment discontinuation should also be taken into account.

It's important to note that these medications are contraindicated in women planning pregnancy. For women of reproductive age, the use of effective contraception is required. Pharmacological treatment for obesity is supplementary to non-pharmacological treatment and will not be effective on its own if the patient does not adhere to the diet, maintain an adequate level of physical activity, and implement other health-promoting lifestyle modifications.

In Poland, there are currently three registered medications for treating obesity: 1) a combination product containing two active substances: naltrexone hydrochloride and bupropion hydrochloride, 2) liraglutide, and 3) orlistat.

Irrespective of the chosen pharmacological treatment, it's crucial to evaluate its effectiveness and safety at least once a month during the initial 3 months of therapy. This assessment is vital to promptly discontinue the medication in case of significant adverse effects or serious safety concerns. Each of the discussed drugs specifies a treatment duration in their registration documents. Following this period, the effectiveness in reducing body weight should be assessed, guiding the decision to either continue or discontinue the treatment:

- Treatment with a medication containing naltrexone and bupropion should be discontinued if after 16 weeks of use, the patient's body weight has not decreased by ≥5% compared to the initial weight.[17]
- If there is no reduction of ≥5% in the initial body weight after 12 weeks of using liraglutide at a dose of 3 mg/day, the medication should be stopped.[28]
- Treatment with orlistat should be halted after 12 weeks if patients have not managed to reduce their body weight by ≥5% from the initial weight at the start of the treatment.[30]

Indications for pharmacotherapy in obesity treatment in adults, as a supplement to a low-calorie diet and increased physical activity, are similar and include an initial Body Mass Index of: ≥30 kg/m² or ≥27 to <30 kg/m², if accompanied by at least one comorbidity (e.g., dyslipidemia, type 2 diabetes, hypertension).

**Naltrexone-bupropion in weight loss management**

Naltrexone/bupropion is a medication combining two different mechanisms, and is employed for prolonged obesity management. Both constituents of this drug have been utilized to treat other medical conditions since the 1980s [14]. It obtained approval from the FDA and EMA (Mysimba®) in 2014 and 2015, respectively. As there is no evidence of any drug abuse resulting from this medication, it is not classified as a controlled substance.

Bupropion is recommended to address severe episodes of depression (major depression as per DSM-5) and is supportive in managing nicotine addiction. It functions as a non-selective inhibitor of dopamine and norepinephrine reuptake, alongside being an antagonist of acetylcholinergic nicotinic receptors [15]. Whereas naltrexone is an opioid receptor antagonist utilized in the treatment of alcohol and opioid addictions [16]. The combination of naltrexone and bupropion is thought to induce an anorectic effect. The reason behind this may be that the endogenous opioids inhibit POMC, leading to a potential decrease in the appetite-suppressing effects of bupropion. However, the addition of naltrexone, functioning as an opioid antagonist, can maintain the activation of POMC initially triggered by bupropion, thereby enhancing its capability to reduce appetite [18]. This product is the only appetite-suppressing medication available in Poland.

Meta-analysis from 2020 confirms that a substantially higher number of individuals within the N-B group accomplished a minimum 5% decrease in body weight in comparison to the placebo. The total weight loss achieved translates to 2.5 kg more weight loss compared to the placebo during a 12-month period. Furthermore, a notably higher proportion of participants using N-B attained at least a 10% reduction in body weight compared to those using the placebo. Additionally, N-B showed positive effects on various cardiovascular risk markers, although the full extent of these effects remains unclear due to incomplete outcome data. [20].

The most frequently reported side effects associated with taking the medication are nausea, which in most cases are transient and diminish within several weeks. Also commonly occurring are headaches, dizziness, insomnia, and vomiting, which may result in discontinuing the therapy.

In the Summary of Product Characteristics (SmPC) for the combined naltrexone with bupropion preparation, an increased risk of suicidal behavior, seizures, allergic reactions, elevated blood pressure, serotonin-noradrenaline syndrome, neuropsychiatric symptoms, manic activation, and hepatotoxicity are listed. It should not be used in elderly individuals or those with kidney or liver function impairment. Additionally, it may affect the ability to operate vehicles. As a standard practice, the dosage is commonly escalated gradually to prevent these side effects [17].

Among the contraindications for using the medication, we can include uncontrolled arterial hypertension, period immediately after sudden cessation of alcohol, benzodiazepines or opioids in a person with addiction, epilepsy, bipolar affective disorder, anorexia or bulimia in the medical history, tumors within the central nervous system, taking naltrexone or bupropion for other reasons, taking monoamine oxidase inhibitors within ≥14 days, severe liver or renal failure, pregnancy.

Every patient, besides dietary recommendations and health education, should be supported by pharmacotherapy, and if needed, psychotherapy. This combination drug is relatively safe, effective, and should be considered as a first-line treatment in obesity pharmacotherapy.

**Liraglutide in obesity management**

The mechanism of action of Glucagon-like peptide-1 (GLP-1) involves its secretion from the intestines following the digestion of carbohydrates and fats consumed during a meal. It functions by diminishing caloric intake through the enhancement of satiety, resulting in individuals to feel fuller and more satisfied after consuming food. [22]. Liraglutide, although 97% similar to human GLP-1, has an extended duration of action.[23] Liraglutide interacts with the GLP-1 receptor in the hypothalamus, stimulating neurons such as POMC, amphetamine-and cocaine-, regulated transcript neurons. This stimulation helps suppress appetite and indirectly hinders neuropeptide-Y/agouti-related protein neurons, which otherwise trigger appetite, thereby reducing the urge to eat and facilitating weight loss [21,24].

Additionally, in the peripheral system, liraglutide slows down the emptying of the stomach post-meal and regulates the balance between insulin and glucagon secretion to control blood sugar levels.

The liraglutide group demonstrated notably greater mean weight reduction compared to the placebo group, as noted in the Satiety and Clinical Adiposity-Liraglutide (SCALE) studies. These studies were structured to assess the efficacy and safety of liraglutide 3.0 mg in conjunction with a reduced-calorie diet and enhanced physical activity for managing weight in overweight and obese patients, whether or not they had other health conditions. Furthermore, a significantly larger proportion of individuals in the liraglutide group achieved a minimum 5% reduction in weight from their initial measures, indicating that the impact of liraglutide satisfies both the average and categorical weight loss standards. In all the SCALE trials, liraglutide showed superior improvement compared to the placebo concerning glycemic control, blood pressure, lipid levels, and the quality of life related to health in overweight or obese individuals. The FDA suggested discontinuing liraglutide if a weight reduction of more than 4% is not attained within 16 weeks of administration. [17].

The primary side effects associated with liraglutide include gastrointestinal symptoms like nausea, vomiting, diarrhea, and constipation. The gradual escalation of the drug dosage is recommended [17]. The patients frequently report headaches as an adverse effect. Other commonly occurring side effects include hypoglycemia, insomnia, dyspepsia, gastritis,

gastroesophageal reflux, upper abdominal pain, abdominal bloating or rash [28]. Furthermore, the administration of liraglutide may lead to the development of gallstones and, to a lesser extent, acute pancreatitis [2,10]. Cases of anaphylactic reaction, acute kidney failure, or impairment of their function have also been recorded. The contraindications for taking the medication include a history of pancreatitis, severe liver dysfunction, advanced kidney failure, and pregnancy [28].

Liraglutide does not affect appetite [25], so it should be considered as a second-line treatment when emotional eating (reaching for food in response to both positive and negative emotions, boredom, and eating disorders like compulsive eating, binge eating disorder, and night eating syndrome) depression, or persistent contraindications for the use of first-line medication have been excluded.

**Orlistat**

Orlistat is a strong and selective inhibitor of pancreatic lipase, the inhibition of which reduces fat absorption in the intestine. It is the only anti-obesity medication acting locally in the gastrointestinal tract — It operates without affecting appetite-regulating mechanisms.[17, 19] It is the oldest among currently used drugs registered for the management of obesity, holding limited importance in pharmacological treatment. Orlistat is used concurrently with a moderately low-calorie diet.

An analysis of 30 studies showed that a greater percentage of individuals, specifically 21% more, using orlistat for a duration of one year accomplished a weight loss of at least 5% or more, and 12% more participants achieved a weight reduction of 10% or higher in comparison to those using a placebo.[2] The effect, however, is not as spectacular as the drugs mentioned above.

An increased fat content in stool leads to significant gastrointestinal discomfort, especially after meals containing fat. The troublesome side effects of treatment, primarily affecting the digestive tract, including fatty anal leakage, abdominal pain, abdominal discomfort, gas with discharge, urge to pass stools, fatty or oily stools, bloating with gas passage, loose stools, increased frequency of bowel movements, largely contribute to discontinuation of therapy and significantly limit the use of this medication in practice. [17]

Orlistat should not be used in cases of chronic malabsorption syndrome, cholestasis, during breastfeeding, and for the over-the-counter version: during pregnancy or when using cyclosporine, warfarin, or other oral anticoagulants simultaneously to enhance safety during independent use. Long-term use of the medication may lead to reduced absorption of fat-soluble vitamins, requiring additional supplementation.[30]

## Conclusion

The issue of obesity is a growing global concern. A crucial aspect in improving the treatment's effectiveness lies in comprehending its development mechanisms and embracing a holistic approach. The ideal scenario involves collaboration among physicians from different medical disciplines, psychologists, and dietitians. Obesity should not be treated as a cosmetic defect. This is a serious, progressive disease that shortens lifespan. Therefore, pharmacotherapy should be incorporated in line with recommendations.

The order of weight loss effectiveness among these three anti-obesity medications is as follows: liraglutide > naltrexone-bupropion > orlistat. [17] When choosing a medication, it's important to consider its mechanism of action and provide comprehensive support with an empathetic approach to the patient.

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All authors have read and agreed with the published version of the manuscript. Funding: This research received no external funding. Institutional Review Board Statement: Not applicable. Informed Consent Statement: Not applicable. Data Availability Statement: Not applicable.

Acknowledgments: Not applicable. Conflicts of Interest: The authors declare no conflict of interest.

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