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The Role of Naltrexone-Bupropion in Obesity Management: Current State of Knowledge

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Abstract

Introduction: Obesity is a chronic disease characterized by excessive fat accumulation, leading to significant health risks and numerous comorbidities. Its rising global prevalence demands effective management strategies[1].

The aim of the study: This article examines the role of combined naltrexone-bupropion therapy in obesity treatment. It focuses on its indications, mechanism of action, efficacy in weight management, safety profile, and potential side effects.

Material and methods: A comprehensive literature review was performed using PubMed, Google Scholar, MedRxiv, and Scopus. The review included meta-analyses, randomized controlled trials, observational studies, and case reports assessing the pharmacotherapy of obesity with naltrexone-bupropion.

Summary of current knowledge: Pharmacotherapy is recommended alongside lifestyle modifications for obesity management. Naltrexone-bupropion works by targeting both hypothalamic appetite control and the mesolimbic reward system, leading to significant weight loss in clinical studies. However, its use is often accompanied by mild to moderate adverse effects, such as nausea and headaches.

Conclusions: Obesity requires a multifaceted treatment approach. Naltrexone-bupropion offers a promising adjunct to diet and exercise but long-term safety and individualized treatment strategies need further investigation.

Keywords: Naltrexone-Bupropion; Anti-obesity drugs; Weight loss medications; Obesity; Overweight;

1. Introduction and purpose

Obesity is a chronic disease and a growing global health issue, characterized by excessive fat accumulation that increases health risks. Its prevalence has risen sharply, affecting over 1.5 billion overweight adults and approximately 500 million obese individuals worldwide[1]. The World Health Organization (WHO) defines obesity as a body mass index (BMI) of 30 kg/m² or higher[2]

The development of obesity results from genetic predisposition, environmental influences, and lifestyle choices. Genetic factors affect appetite regulation and fat storage, but the dominant contributors are high-calorie diets and reduced physical activity[3]. Urbanization and socioeconomic factors further drive obesity rates.

Obesity arises from a chronic energy imbalance where calorie intake exceeds expenditure. Diets rich in processed foods and saturated fats promote visceral fat accumulation, leading to metabolic disorders[4]. Adipose tissue functions as an endocrine organ, releasing inflammatory mediators that contribute to insulin resistance and dyslipidemia[5]

Obesity is classified into three severity levels: class I (BMI 30-34.9 kg/m²), class II (BMI 35-39.9 kg/m²), and class III (BMI ≥40 kg/m²), with higher BMI levels correlating with increased health risks[6]. It is linked to type 2 diabetes, hypertension, cardiovascular disease, and non-alcoholic fatty liver disease[7]. Additionally, it raises the likelihood of cancers, fertility issues, osteoarthritis, and severe COVID-19 outcomes[8].

Beyond physical health, obesity affects mental well-being and social standing, leading to discrimination, reduced quality of life, and psychological distress. The economic burden includes healthcare costs and productivity losses.

Effective management requires lifestyle modifications, including diet, exercise, and behavioral interventions[9]. Pharmacotherapy and bariatric surgery may be necessary for severe cases[10]. While pharmacological treatments support weight management, long-term success depends on sustained lifestyle changes and multidisciplinary care[9].

Addressing obesity demands urgent public health measures and clinical strategies to mitigate its increasing prevalence and associated complications[11].

The aim of this article is to present the current role of the combined naltrexone-bupropion therapy in the treatment of obesity, including detailed indications for its use, its mechanism of action, potential benefits in weight management, as well as its safety profile and possible side effects.

2. Materials and methods

A comprehensive literature review was conducted using the PubMed, Google Scholar, and MedRxiv databases, as well as Scopus, to analyze the pharmacotherapy of obesity with the combination of naltrexone-bupropion. The following search terms were used: "naltrexone-bupropion", "obesity", "anti-obesity drugs", "weight loss medications" and "obesity treatment." We focused primarily on human studies but also considered relevant preclinical research. The review included meta-analyses, randomized controlled trials, crossover studies, case studies, and observational studies. Studies were categorized based on their findings related to efficacy, safety, metabolic effects, and impact on comorbidities associated with obesity.

3. Current state of knowledge

3.1. Pharmacological Approaches to Obesity: Indications and Available Treatments

Pharmacological treatment for obesity is recommended as an adjunct to lifestyle modifications, particularly for individuals with a BMI $\geq$30 kg/m^2 or $\geq$27 kg/m^2 if obesity-related comorbidities are present, such as type 2 diabetes, hypertension, or dyslipidemia[12,13,14]. These recommendations are based on guidelines from organizations such as the European Association for the Study of Obesity (EASO), the American Association of Clinical Endocrinology (AACE), and the Endocrine Society.

Before initiating pharmacotherapy, secondary causes of obesity, such as endocrine disorders (Cushing's syndrome, hypothyroidism, hypothalamus damage, brain tumors, adiposogenital dystrophy, insulinoma) or medication-induced weight gain (glucocortykosteroids, beta-blokers), should be excluded[15].

The duration of pharmacological treatment should be at least 12 months and adjusted based on the patient's individual needs and therapeutic goals. Short-term therapy (3-6 months) is not recommended as it does not provide long-term effects and health benefits[12]. As obesity is a chronic disease, pharmacotherapy should be continued as long as it remains effective and well tolerated. Premature discontinuation of medication may result in weight regain[12]. These principles align with long-term obesity management strategies recommended by the Obesity Society (TOS) and the World Obesity Federation (WOF).

The effectiveness and safety of pharmacotherapy must be monitored regularly, especially in the initial months of treatment, to assess its impact on weight reduction and metabolic health[16]. If weight loss is less than 5% after three months of pharmacotherapy, discontinuation should be considered[17].

Currently, several medications are approved for obesity treatment, including orlistat, liraglutide, semaglutide, tirzepatide, and the combination of naltrexone and bupropion[314]. These medications have been evaluated according to the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) criteria for obesity pharmacotherapy, which require demonstrated weight loss efficacy of at least 5% over a year, along with favorable safety profiles. Orlistat acts peripherally by inhibiting gastric and pancreatic lipases, reducing fat absorption from the diet[18]. Liraglutide and semaglutide, both GLP-1 receptor agonists, regulate appetite centrally and delay gastric emptying, leading to reduced caloric intake[19]. Naltrexone/bupropion affects brain pathways related to food intake and reward mechanisms, thereby reducing cravings and increasing satiety[20]. Tirzepatide, a dual GLP-1 and GIP receptor agonist, enhances weight loss by improving insulin sensitivity and appetite control[21]. The choice of medication should be individualized based on patient characteristics, contraindications, cost, and potential side effects.

Long-term pharmacotherapy should be considered similarly to treatments for other chronic diseases, aiming to maintain weight loss and prevent obesity-related complications[22]. Proper monitoring ensures timely adjustments in treatment and helps mitigate any potential adverse effects, maximizing therapeutic benefits.

3.2. The Pharmacological Action of Naltrexone-Bupropion

The combination of naltrexone and bupropion exerts its anti-obesity effects by targeting both hypothalamic appetite regulation and the mesolimbic reward system [2324]. Bupropion, a selective norepinephrine–dopamine reuptake inhibitor with additional non-competitive antagonism at nicotinic receptors, stimulates pro-opiomelanocortin (POMC) neurons in the arcuate nucleus, leading to the release of anorectic peptides such as α-melanocyte-stimulating hormone (α-MSH) and endorphins that promote satiety[2526]. Concurrently, naltrexone, acting predominantly as a μ-opioid receptor antagonist, blocks the autoinhibitory feedback of β-endorphin on POMC neurons, thereby prolonging their activation and enhancing the appetite-suppressing effect initiated by bupropion [2526]. This synergistic interaction, often described as hyperadditive synergy, modulates both homeostatic and hedonic pathways, ultimately leading to a reduction in food intake and significant weight loss as demonstrated in clinical studies[272417] . Although the complete molecular mechanism remains to be fully elucidated, the combined modulation of the hypothalamic and mesolimbic circuits underpins the therapeutic efficacy of this dual-agent strategy[17]. Additionally, the gradual dose escalation employed in clinical settings helps mitigate common side effects, such as nausea and headache, thereby supporting patient adherence to the treatment regimen.

3.3 Effectiveness of Naltrexone-Bupropion in Obesity Management

The efficacy of naltrexone–bupropion in the treatment of obesity has been evaluated in several robust clinical studies and meta-analyses. In the Contrave Obesity Research trials (COR-1, COR-II, and COR-BMOD) involving a total of over 4,900 participants, the fixed-dose combination of naltrexone-SR 32 mg and bupropion-SR 360 mg produced an additional weight loss of approximately 4–5 kg at 1 year compared to placebo, with 48–66% of patients achieving at least a 5% reduction in initial body weight and 25–42% attaining at least a 10% reduction-contrasted with 16–42% and 6–20%, respectively, in the placebo groups[28,26,29]. A meta-analysis of 28 randomized clinical trials further confirmed these findings by reporting an average weight reduction of 5 kg relative to placebo, with 55% of patients reaching a ≥5% weight loss and 30% achieving a ≥10% loss, compared to 23% and 9% in placebo-treated subjects[23]. Additional research has demonstrated that the combination yields a placebo-subtracted weight loss of around 4%[30] and other studies have shown weight loss percentages ranging from −5.0% to −6.1% in the treatment groups versus −1.2% to −1.3% with placebo, culminating in an overall mean loss of −6.8% (or −7.3 kg) at one year[31]. In a 12-week randomized controlled trial, naltrexone–bupropion was associated with a mean weight loss of approximately 3.4% versus 0.1% in the placebo group, and logistic regression analyses revealed that 27.9% of patients on the combination achieved greater than 5% weight loss compared to only 6.5% of placebo recipients, with another analysis showing rates of 24.2% versus 2.8%[32]. When compared with other FDA-approved anti-obesity medications, naltrexone-bupropion has shown greater efficacy than lorcaserin and orlistat, which typically achieve about a 3% placebo-subtracted weight loss, although its effect is somewhat lower than that observed with phentermine–topiramate, which reaches an approximate 8.9% weight reduction; however, the safety profile of naltrexone-bupropion is notably more favorable[30,31]. Moreover, the extended-release formulation (Contrave, Mysimba) has been approved as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in obese adults or overweight individuals with weight-related comorbidities such as hypertension, type 2 diabetes, or dyslipidemia[33]. Collectively, these data underscore that naltrexone–bupropion produces statistically significant and clinically meaningful weight loss, positioning it as a valuable option in the therapeutic management of obesity[34,32,31,23].

3.4. Common Side Effects of Naltrexone-Bupropion in Obesity Treatment

Naltrexone-bupropion treatment for obesity has been associated with a range of adverse effects that are generally mild to moderate and tend to be transient during the initial dose adjustment phase[26,35]. The most frequently reported side effects include nausea, headache, and constipation; for instance in one study, nausea has been observed in 29.2-42.3% of patients compared to 5.3-10.5% in placebo groups[30] and in another study at 31.8% versus 6.7% with placebo[31]. Other commonly reported adverse events include dizziness, insomnia, vomiting, and gastrointestinal discomfort-with headache occurring in 17.6% versus 10.4% and constipation in 18.1% versus 7.2% of patients, respectively[23]. Additionally, transient cardiovascular changes have been noted, such as a 1.5 mmHg rise in systolic blood pressure during the first 8 weeks (declining by approximately 1 mmHg by week 12) and an increase in heart rate by around 1 bpm[30].

Notably, discontinuation rates due to adverse events were significant, with up to 45% of patients ceasing treatment-primarily within the first 8 weeks (25–34% discontinuation rate)[36]. Finally, while meta-analytic data indicate that the overall risk of major adverse cardiovascular events (MACE) is comparable to placebo (approximately 2.7–2.8%), a higher incidence of non-MACE events such as hypertension and tachycardia has been observed[33].

In terms of contraindications, naltrexone-bupropion should not be used in patients with uncontrolled arterial hypertension, severe hepatic or renal impairment, a history of seizures, or eating disorders such as anorexia nervosa or bulimia nervosa[3723].

3.5. Position of Naltrexone-Bupropion in Polish and International Obesity Guidelines

The 2024 guidelines of the Polish Obesity Treatment Society provide a detailed algorithm for selecting obesity pharmacotherapy[12]. They recommend that treatment decisions should be based on a comprehensive evaluation of contraindications, the etiology of obesity, and accompanying comorbidities. In patients whose obesity is primarily driven by emotional hunger, naltrexone–bupropion is recommended as the first-line treatment, and this combination is also preferred for individuals who are dependent on tobacco or planning to quit smoking. For patients with metabolic complications-such as prediabetes, type 2 diabetes, hypertension, hyperlipidemia, obstructive sleep apnea, polycystic ovary syndrome, or MASLD-the guidelines recommend first-line use of GLP-1 receptor agonists (liraglutide, semaglutide, or tirzepatide), while in patients without significant comorbidities, any approved anti-obesity drug available in Poland may be considered based on patient preference. These recommendations are complemented by additional international guidelines provided by a panel of experts involved in the registration of the combination product Mysimba®[23]. Finally, it is noteworthy that in the United Kingdom, the National Institute for Health and Care Excellence (NICE) did not recommend naltrexone–bupropion in July 2017 due to uncertainties about its clinical and cost effectiveness, particularly in patients with a BMI under 30 kg/m²[34]

Conclusions

Obesity is a severe, chronic disease that demands serious attention due to its extensive health implications. Although pharmacological approaches have shown considerable promise in facilitating weight loss, they should be viewed as complementary to fundamental lifestyle modifications-including a balanced diet, regular physical activity, and appropriate therapeutic interventions. Naltrexone–bupropion is particularly noteworthy because it targets both the hypothalamic centers that regulate appetite and the mesolimbic reward system responsible for food cravings, thereby promoting satiety and reducing excessive intake. Nevertheless, while its clinical benefits are compelling, issues like gastrointestinal discomfort, headaches, and minor cardiovascular changes may pose challenges for some patients. These observations highlight the need for ongoing research to better characterize the long-term safety and efficacy of this treatment, ultimately paving the way for more individualized and effective obesity management strategies.

Disclousure

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