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REVIEW ARTICLE

Naltrexone-bupropion for the treatment of binge eating disorder: a systematic review and meta-analysis

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Objective: This meta-analysis aimed to evaluate the efficacy of naltrexone-bupropion in binge eating disorder patients.
Methods: We searched MEDLINE, Embase, and Cochrane databases up to February 2025 for randomized controlled trials comparing naltrexone-bupropion to placebo. The primary outcome was binge eating frequency. Secondary outcomes included body mass index, body weight, depression, lipid profile, and glycated hemoglobin levels. Mean differences (MD) with 95%CI were pooled using appropriate methods.
Results: Three trials were included with a total of 177 patients, of whom 49% received the intervention. There was no significant difference between groups for binge eating (MD -1.25; 95%CI -5.61 to 3.11; 0 = 0.57), body mass index (MD -2.24; 95%CI -8.01 to 3.53; p = 0.45), depression (MD -0.81; 95%CI -3.48 to 1.87; p = 0.55), or total cholesterol (MD -9.98; 95%CI -21.31 to 3.34; p = 0.15). A potential benefit was observed in glycated hemoglobin levels (MD -0.10; 95%CI -0.28 to 0.08; p = 0.26).
Conclusion: This meta-analysis found that naltrexone-bupropion has no significant benefits over placebo in reducing binge eating episodes or in improving metabolic or psychological outcomes. The possible effect on glycated hemoglobin levels warrants further investigation.

Systematic review registration: PROSPERO CRD420250651559

Keywords: Bupropion; naltrexone; binge eating disorder; meta-analysis

Introduction

Binge eating disorder (BED) is characterized by recurrent episodes of excessive food intake in a short period of time, accompanied by the perception of loss of control over food intake.[1] The most prevalent eating disorder, it is often associated with psychiatric and clinical comorbidities, being responsible for significant functional impairments in the lives of affected individuals.[2] Its clinical relevance comes from its negative impact on the quality of life and overall health, in addition to its direct relationship with the increased incidence of obesity and its associated complications.[3]

Several therapeutic strategies are currently used for BED, especially psychological and pharmacological interventions. Cognitive behavioral therapy is the most studied psychotherapeutic approach, with demonstrated efficacy in reducing the frequency of binge episodes and increasing remission rates.[4] However, cognitive behavioral therapy has limitations regarding weight loss, a relevant aspect for many patients. Lisdexamfetamine is the only pharmacological treatment for BED approved by the U.S. Food and Drug Administration.[5] However, some patients are intolerant to the treatment or have contraindications, especially those with cardiovascular diseases. Thus it is essential to investigate new therapeutic approaches.

This study consolidates evidence on the efficacy of combined naltrexone and bupropion (NB) therapy for BED. In pilot studies and controlled clinical trials, NB has demonstrated safety and promising results.[6-8] Although most research focuses on humans, studies in animal models also point to significant therapeutic potential, highlighting the importance of further investigation. From a neurobiological point of view, this combination drugs acts on neural pathways related to the hypothalamus and the reward system, which are fundamental mechanisms in the pathophysiology of BED. This may explain its efficacy in controlling binge episodes.[9]

However, despite several studies, NB's efficacy for BED remains unclear. Due to small sample sizes, individual trials do not have sufficient statistical power to

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detect significant differences in outcome. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) on the efficacy of naltrexone/bupropion compared to placebo for clinical and laboratory-related outcomes in patients with ED.

Methods

Protocol and registration

This meta-analysis was conducted and reported following the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[10,11] It is also registered in PROS PERO (CRD420250651559).

Eligibility criteria

Inclusion in this meta-analysis was restricted to studies that met the following eligibility criteria: 1) RCTs; 2) comparing NB vs. placebo in BED; and 3) reporting at least one of the clinical outcomes of interest. We excluded studies that 1) involved overlapping patient populations, 2) lacked a placebo control group, 3) did not report relevant outcomes, or 4) were associated with psychotherapy. There were no restrictions concerning the date or language of publication.

Study selection and data extraction

We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials from inception to February 5, 2025. The detailed search strategies used are described in Supplementary Box S1. The reference lists of all included studies were also searched manually for relevant studies.

The data collection process commenced on March 11, 2025. Two researchers (JBCM and MVSS) independently screened all titles and abstracts to identify potentially eligible studies. The full texts of publications that passed the initial screening were independently assessed by the same researchers for eligibility. Data from the included studies were then extracted to a table in Google Sheets. Any disagreements were resolved through consensus.

Outcomes

The primary efficacy outcome was binge eating, which was assessed using the Eating Disorder Examination Questionnaire. Secondary efficacy outcomes included depression (assessed using the Beck Depression Inventory), weight, body mass index (BMI), total cholesterol, HDL cholesterol, LDL cholesterol, and glycated hemoglobin levels.

Quality assessment

The quality of the included RCTs was assessed using the Cochrane tool for assessing risk of bias in randomized clinical trials.[12] Two authors independently conducted a bias risk assessment (JBCM and MVSS), and discrepancies were resolved through consensus.

Certainty of evidence

Two independent reviewers (JBCM and MVSS) evaluated the certainty of evidence for the primary outcome using the Grading of Recommendations, Assessment, Development and Evaluations framework.[13]

Statistical analysis

Treatment effects were compared using the mean difference (MD) with 95%CI for continuous outcomes. We used inverse variance for continuous endpoints. Heterogeneity was examined with Cochran's Q test, the I^2 statistic, and tau-square using the restricted maximum-likelihood estimator. Heterogeneity was reported as low (I^2 = 0-25%), moderate (I^2 = 26-50%), or high ($I^2 >$ 50%).[11] All statistical analyses were performed in RStudio (2023.12.1).

Results

Study selection and baseline characteristics

The initial search strategy identified 78 results (Figure 1). After duplicate records were removed and full-text screening was completed, three RCTs[6-8] met the eligibility requirements and were included in the meta-analysis.

The analysis included 177 patients, with 87 (49%) receiving naltrexone/bupropion. The follow-up period ranged from 12 to 16 weeks. The patients' mean age was 46.54 years, and 136 (77%) were female. Additional details about the included studies are presented in Table 1.

Pooled analysis of the studies

There were no significant differences between groups in terms of compulsion (MD -1.25; 95%CI -5.61 to 3.11; p = 0.57; I^2 = 30%) (Figure 2), BMI (MD -2.24; 95%CI -8.01 to 3.53; p = 0.45; I^2 = 78%) (Supplementary Figure S1), body weight (MD 0.50; 95%CI -5.92 to 6.91; p = 0.88; I^2 = 0%) (Figure 3), depression (MD -0.81; 95%CI -3.48 to 1.87; p = 0.55; I^2 = 0%) (Supplementary Figure S2), total cholesterol (MD -9.98; 95%CI -21.31 to 3.34; p = 0.15; I^2 = 0%) (Supplementary Figure S3), LDL cholesterol (MD -7.43; 95%CI -17.43 to 2.57; p = 0.15; I^2 = 0%) (Supplementary Figure S4), or HDL cholesterol (MD -0.15; 95%CI -5.25 to 4.97; p = 0.95; I^2 = 0%) (Supplementary Figure S5). NB therapy resulted in lower glycated hemoglobin levels than placebo (MD -0.10; 95%CI -0.28 to 0.08; p = 0.26; I^2 = 0%) (Supplementary Figure S6).

Risk of bias assessment

As shown in Supplementary Figure S7, all studies were classified as having a low risk of bias.

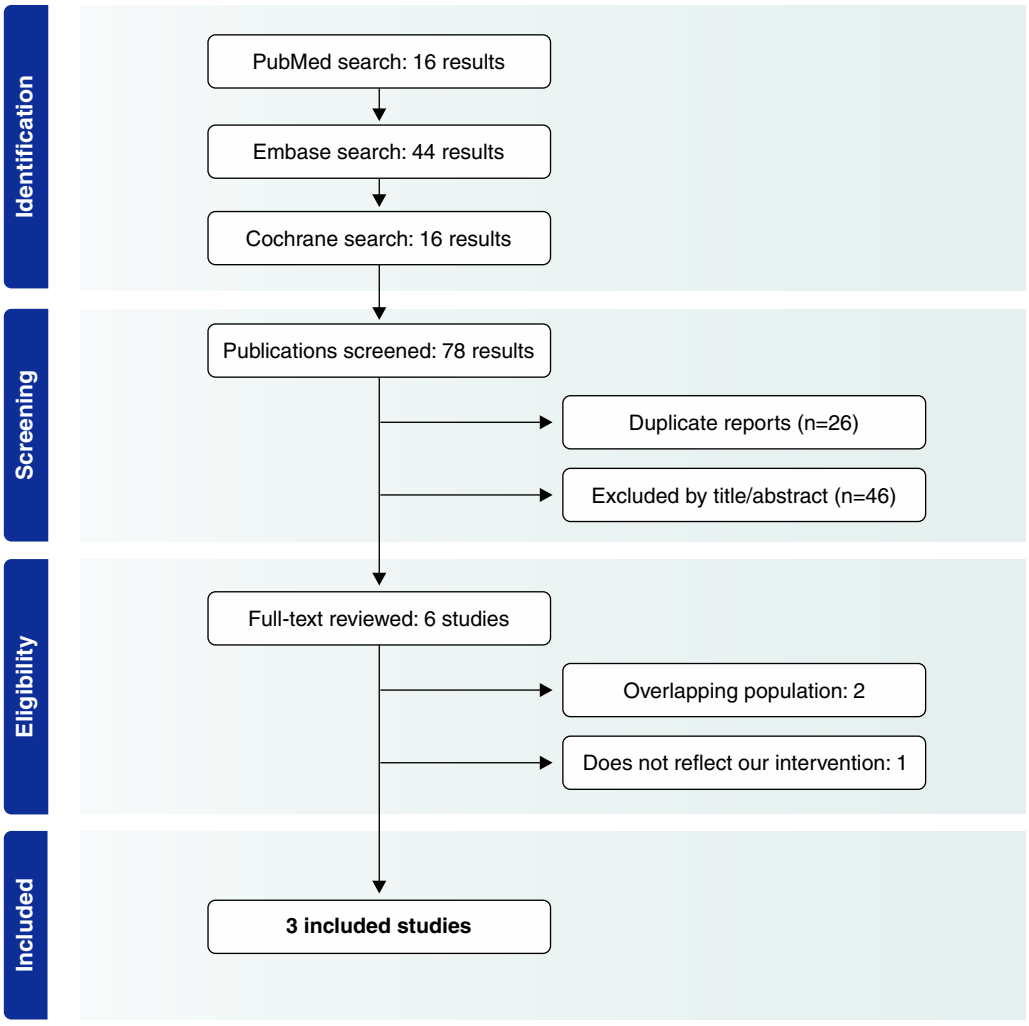

Figure 1 PRISMA flow diagram of study screening and selection.

Certainty of evidence

According to the Grading of Recommendations, Assessment, Development and Evaluations assessment, the quality of evidence for the BE outcome was moderate. This level of certainty indicates that, although the results are relatively reliable, some uncertainty remains that could influence the interpretation of the findings. There was no significant difference between the groups regarding compulsive behavior. The relatively wide confidence interval suggests that the intervention's effects may vary, introducing a degree of imprecision. However, the heterogeneity was moderate, indicating a reasonable level of consistency among the included studies. Therefore, while these findings are based on moderate-quality evidence, further research could refine this estimate and potentially alter current conclusions regarding the intervention's effect. A detailed assessment of the certainty of evidence can be found in Supplementary Table S1.

Discussion

This meta-analysis is the first comprehensive examination of NB compared to placebo, based on a cohort of 177 patients diagnosed with BED across three RCTs. The main findings from the combined analysis were: 1) NB therapy was not associated with a significant reduction in binge eating episodes; 2) NB did not lead to an improved lipid profile compared to placebo; 3) BMI and body weight remained equivalent between the groups; 4) NB therapy did not result in significant reductions in depression scale scores; and 5) compared to placebo, NB therapy contributed to improved glycated hemoglobin levels.

Given these findings, it is essential to contextualize NB in relation to existing pharmacological treatments. Currently, lisdexamfetamine dimesylate is the only Food and Drug Administration-approved medication for BED.[14] However, despite its efficacy, approximately 50% of patients fail to achieve full remission, continuing to experience binge eating episodes, and most do not attain

Table 1 Baseline patient characteristics in the included studies

Study	Protocol	Follow-up (weeks)	Dose	Patients	Female/%	Age†	BMI†	Inclusion criteria
Grilo et al.[6]	NCT02317744	12	Naltrexone 32 mg/day + bupropion 360 mg/day; the titration schedule was progressive: starting with 8 mg of naltrexone/90 mg of bupropion once a day, with weekly dose increases until reaching 16 mg/180 mg twice a day.	12/10	92.0/80.0	51.2/ 49.4	37.1/ 37.0	Eligibility criteria included: 1) DSM-5 criteria for binge eating disorder; 2) age 18 to 65 years; 3) BMI between 30 and 50 kg/m^2.
Grilo et al.[7]	NCT03045341	16	Naltrexone 32 mg/day + bupropion 360 mg/day in two daily doses of 8 mg/90 mg each.	32/34	81.3/82.4	46.0/ 46.9	37.2/ 37.0	Eligibility criteria included: 1) DSM-5 criteria for binge eating disorder; 2) age 18 to 70 years; 3) BMI between 30.0 and 50.0 (or $\geqslant$ 27 with obesity-related comorbidity).
Grilo et al.[8]	NCT03539900	12	Naltrexone 32 mg/day + bupropion 360 mg/day; the titration schedule was progressive: starting with 8 mg of naltrexone/90 mg of bupropion once a day, with weekly dose increases until reaching of 16 mg/180 mg twice a day.	43/46	69.8/71.7	45.3/ 46.0	35.4/ 35.8	Eligibility criteria included: 1) DSM-5 criteria for binge eating disorder; 2) age 18 to 70 years; 3) BMI $\geqslant$ 21.5 and $\leqslant$ 50.0 kg/m^2.

BMI = body mass index.
† Median.

clinically meaningful weight loss.[15] These limitations underscore the need for additional therapeutic strategies to improve clinical outcomes in this population.

NB has been explored as a potential therapeutic alternative, particularly among individuals with comorbid obesity, given its approval for chronic weight management.[16,17] This combination exerts its effects by stimulating pro-opiomelanocortin neurons, increasing the release of α-melanocyte-stimulating hormone, a neuropeptide involved in appetite suppression.[18-20] Naltrexone enhances this effect by blocking opioid-mediated autoinhibition, further reducing food intake.[21] The combination also modulates mesolimbic dopaminergic reward pathways, thereby attenuating compulsive eating behaviors and diminishing the hedonic response to food.

In contrast, lisdexamfetamine primarily enhances dopaminergic and noradrenergic neurotransmission, leading to improved impulse control and a reduction in binge eating episodes.[14,22] However, its stimulant profile is associated with an increased risk of cardiovascular side effects and potential for misuse, which may limit its applicability in certain patient populations.[23]

Although our meta-analysis identified a trend toward reduced binge-eating episodes, BMI, body weight, depressive symptoms, total cholesterol, LDL cholesterol, and HDL cholesterol, these findings did not reach statistical significance, likely due to the insufficient sample size. This highlights the need for high-quality RCTs to further evaluate the efficacy of NB in BED.

In Grilo et al.,[6] adverse events were more frequent in the NB group than the placebo group (57 vs. 21 events, respectively), with a progressive reduction in both groups. In the first month, there was no significant difference between the conditions, while in the second month adverse events were significantly higher in the NB group. In the third month, the difference between the groups was no longer significant. The most common adverse effects in the NB group were nausea, dizziness, insomnia, headache, dry mouth, vomiting, diarrhea, and constipation, with symptoms decreasing over time, which suggests adaptation to treatment. However, these side effects were considered tolerable and, thus, did not have a significant effect on study withdrawal. In the other two studies by Grilo et al.,[7,8] the incidence of adverse events was not analyzed, thus preventing a meta-analysis for safety outcomes.

The cardiovascular safety of NB therapy is another critical aspect to consider, particularly in populations with increased cardiovascular risk. Although previous studies have evaluated this combination in patients with obesity and smoking cessation, data specific to individuals with BED remain limited. A comprehensive meta-analysis[24] of 12 RCTs with a total of 19,176 patients found no association between therapy with naltrexone, bupropion, or their combination and an increased risk of major adverse cardiovascular events. However, caution is needed when applying these findings to patients with BED, since most of the studies were conducted in populations with distinct characteristics, primarily focused on weight loss or smoking cessation. However, despite these discrepancies, NB may represent a viable

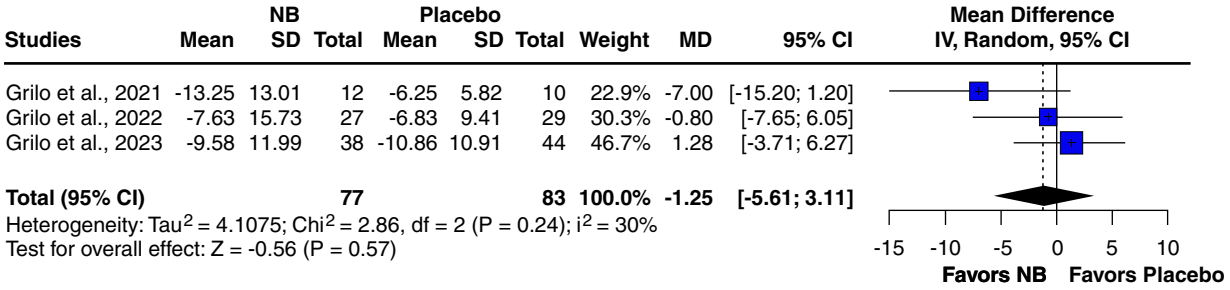

Figure 2 Forest plot of the meta-analysis for compulsion. df = degrees of freedom; MD = mean difference; NB = naltrexone-bupropion.

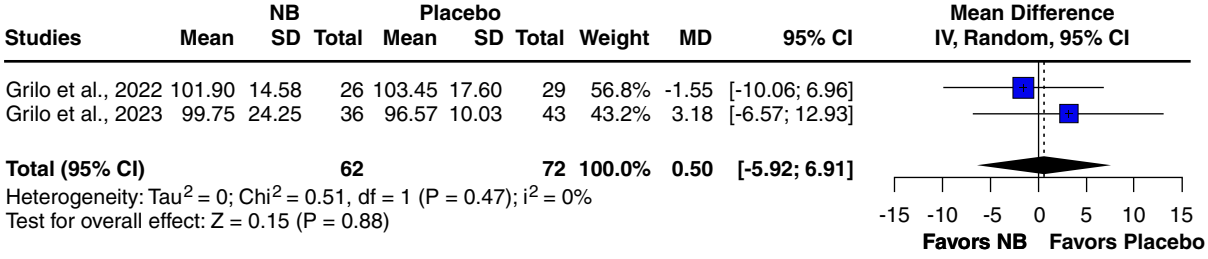

Figure 3 Forest plot of the meta-analysis for body weight. df = degrees of freedom; MD = mean difference; NB = naltrexone/bupropion.

alternative for patients who fail to achieve an adequate response with lisdexamfetamine, particularly those with comorbid obesity, given its approval for chronic weight management. However, its use should be carefully considered in patients with contraindications, such as a history of epilepsy or active suicidal ideation, due to the seizure risk associated with bupropion and the potential neuropsychiatric effects of its combination with naltrexone. Further research is warranted to clarify its role as a personalized treatment strategy for BED.

This study has several limitations. First, the relatively small number of included RCTs (n=3) and the modest overall sample size (n=177) limit the statistical power and generalizability of the findings. Second, the trials' short follow-up duration (ranging from 12 to 16 weeks) may be insufficient to fully assess the long-term effects of NB on BED and metabolic outcomes. Third, a safety analysis was not feasible due to the lack of comprehensive adverse event reporting in most trials; however, the findings of Grilo et al.[6] provided data on adverse events, which we discussed. Finally, although heterogeneity was generally low for most outcomes, there was substantial heterogeneity for BMI (I^2 = 78%), suggesting variability in treatment response across studies, which may have influenced the pooled results.

Despite these limitations, this meta-analysis is the most comprehensive synthesis of evidence available on the efficacy of NB for BED. Given the paucity of RCTs on this topic, our findings provide valuable insights into the potential therapeutic role of this pharmacological combination. However, the above mentioned limitations highlight the need for additional high-quality RCTs with larger sample sizes and longer follow-up periods to better evaluate the long-term efficacy and safety of NB in this population. Future studies should also include standardized assessments of adverse events to enable a more robust analysis of the treatment's risk-benefit profile.

In conclusion, this meta-analysis synthesized the available evidence on NB therapy for BED. The findings suggest that it has no significant effect on binge eating episodes, body weight, BMI, depressive symptoms, or lipid profile, although there was a potential benefit in glycated hemoglobin levels. However, the moderate certainty of evidence and small sample size limit the strength of these conclusions. In this regard, further high-quality trials with longer follow-up are needed. Until stronger evidence is available, NB remains a potential but unproven option, particularly for patients with comorbid obesity or contraindications to stimulant-based treatments.

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The authors used ChatGPT to improve the text's clarity and readability, subsequently reviewing and editing the content to ensure accuracy. The authors assume full responsibility for the final publication.

Data availability statement

The data that support this study are available from the authors upon request.

Disclosure

The authors report no conflicts of interest.

Author contributions

JBCM: Conceptualization, Investigation, Writing – original draft, Writing – review and editing.
MVSS: Methodology, Investigation, Writing – review and editing.
MPE: Formal analysis, Statistical support, Investigation.
GPR: Supervision, Writing – review and editing.
All authors have read and approved of the final version to be published.

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