psychiatry international

MDPI

Systematic Review

Efficacy of Naltrexone/Bupropion in Treatment of Binge Eating: A Systematic Review and Meta-Analysis

Mostafa Hossam-Eldin Moawad [1,2], Mohammed Ahmed Sadeq [3], Abdallah Abbas [4], Reem Mohamed Farouk Ghorab [3], Ibrahim Serag [5], Mohamed Hendawy [6] and Muhammad Alkasaby [7,*]

1 Clinical Department, Faculty of Pharmacy, Alexandria University, Alexandria 21521, Egypt; mh3912214@gmail.com
2 Faculty of Medicine, Suez Canal University, Ismailia 41522, Egypt
3 Emergency Medicine Department, Elsheikh Zayed Specialized Hospital, Elsheikh Zayed City 12588, Egypt
4 Faculty of Medicine, Al-Azhar University, Damietta 34517, Egypt
5 Faculty of Medicine, Mansoura University, Mansoura 35516, Egypt
6 Faculty of Pharmacy, Alexandria University, Alexandria 21521, Egypt; hendawym335@gmail.com
7 Centre for Global Mental Health, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK
* Correspondence: muhammad.alkasaby@lshtm.ac.uk

Abstract: Background: As the most widespread eating disorder in the world now, binge eating disorder (BED) is a mental condition characterized by recurrent periods of excessive food consumption and an inability to regulate one's portion sizes. The utilization of a bupropion–naltrexone (NB) combination has been suggested as a potential therapeutic approach for BED. Assessing the effectiveness of NB in the treatment of BED and its accompanying obesity is the purpose of this research. **Methods:** A comprehensive search was conducted in order to obtain any pertinent articles. PubMed, Scopus, Web of Science, and Cochrane Clinical Trials were consulted against in the databases that were searched. In our final meta-analysis, we incorporated interventional or observational studies that documented the effects of NB therapy for binge eating in adults. We also examined the difference in the mean change between the NB and placebo groups, as well as the disparity in outcomes before and after treatment. **Results:** This study shows that the use of an NB combination is associated with a statistically significant reduction in the weight, BMI, and Binge Eating Scale (BES) of the patients compared to their weight before treatment with MD: −8.52 (95% CI: −10.01–−6.94, $p < 0.00001$), MD: −4.95 (95%CI: −9.72–−0.17, $p = 0.04$), and MD: −7.66 (95%CI: −14.36–0.96, $p = 0.02$), respectively. The absolute mean change was statistically significantly higher in the drug combination group compared to the placebo group. **Conclusions:** NB showed efficacy in the improvement of the weight and psychiatric symptoms associated with BED and this provides a promising treatment option.

Keywords: bupropion; naltrexone; binge eating; weight

Citation: Moawad, M.H.-E.; Sadeq, M.A.; Abbas, A.; Ghorab, R.M.F.; Serag, I.; Hendawy, M.; Alkasaby, M. Efficacy of Naltrexone/Bupropion in Treatment of Binge Eating: A Systematic Review and Meta-Analysis. *Psychiatry Int.* **2024**, *5*, 323–337. https://doi.org/10.3390/psychiatryint5030022

Academic Editors: Antonios E. Koutelidakis and Fragiskos Gonidakis

Received: 18 August 2023
Revised: 16 January 2024
Accepted: 23 April 2024
Published: 2 July 2024

1. Introduction

Binge eating disorder (BED), currently the most prevalent eating disorder globally [1], is a psychiatric disorder defined by recurring episodes of binge eating, associated with a loss of control over the amount of food consumed. This lack of control is a main distinguisher between BED and overeating [2]. Another characteristic of BED is that while the consumption of food occurs with distress, inappropriate weight-compensatory behaviors are absent, such as excessive exercise or vomiting found in patients with bulimia nervosa [3]. While BED is strongly associated with obesity, it remains a separate entity with different psychopathological, behavioral, and neurobiological features than that of obesity [4].

BED and other eating disorders are associated with significant morbidity, including other psychiatric disorders such as substance use, anxiety, and major depressive disorders. They are also correlated with a lower quality of life and a higher economic burden. Despite this, numerous patients with BED remain undiagnosed and untreated [5].

Cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT) are often used for the treatment of BED, and while being effective in reducing binge eating in the short and long term, they have not resulted in any significant weight loss [6]. In a systematic review done in 2008, it was concluded that antidepressants produced higher remission rates than placebos; however, no substantial change in the BMI was noted [7]. When used, topiramate, an antiseizure medication, led to significantly reduced binging and a higher weight loss than placebos [8], particularly when added to CBT [9]; however, due to its adverse effects, it has a very high rate of discontinuity [10]. Lisdexamfetamine, a D-amphetamine prodrug, which is originally indicated for the treatment of attention deficit/hyperactivity disorder, has been the only FDA-approved drug for the treatment of BED. When compared to placebo, it showed a great reduction in binge eating as well as reported weight loss [11]. Unfortunately, its labeling includes a "Limitation of Use" specifying that it is not indicated for weight loss and that drugs of a similar class have been associated with cardiovascular events. In addition, it is considered a Drug Enforcement Agency (DEA)-controlled drug with a label indicating a high potential for dependence or abuse [12]. Thus, a pressing need remains for a safe and effective pharmacologic approach to treating BED and its associated obesity.

Bupropion, which is a dopamine and norepinephrine reuptake inhibitor, and Naltrexone, an opioid antagonist, were approved by the FDA to be used together in the treatment of obesity in 2014 [13]. Their combined usage reduces appetite and food cravings by working on two distinct areas of the brain, namely, the arcuate nucleus of the hypothalamus, which is involved with the regulation of appetite, as well as the mesolimbic dopamine reward circuit. By regulating the mesolimbic reward system and sustaining the activation of hypothalamic pro-opiomelanocortin (POMC) neurons, naltrexone–bupropione (NB) can accomplish this while lowering urges [13]. In a study published in 2013, the effect of NB on obese patients with major depressive disorder was explored over the course of 24 weeks, and the results showed that not only did this combination significantly reduce their body weight from the baseline, but it also reduced their depressive symptoms. Furthermore, the research investigated self-reported binge eating behaviors using the Binge Eating Scale (BES) both before and after NB as a secondary endpoint. Significantly, the BES values decreased throughout the course of the trial [14].

This study aims to assess the efficacy of NB for the treatment of BED and its associated obesity.

2. Materials and Methods

Our study was conducted following the PRISMA guidelines and our protocol was registered in OSF registries [15].

2.1. Search Strategy

We carried out a systematic search to retrieve any relevant articles. The following databases were searched: PubMed, Scopus, Web of Science, and Cochrane Clinical Trials. We performed the computer-based search on the databases using the following search terms: Bupropion AND Naltrexone AND binge eating with no filters. We manually searched the reference list of included papers to find any relevant paper that was missed during the systematic search.

2.2. Inclusion and Exclusion Criteria

We developed the following inclusion criteria for article selection: interventional randomized controlled trials (RCTs) or observational studies reporting the outcomes of using NB in the treatment of binge eating in adults. We excluded case reports, case series, reviews, and meta-analyses. Articles were screened by title and abstract first by two independent authors in a blinded manner. Any article that did not meet the previously agreed-upon inclusion criteria was excluded, and a third author settled any conflict. Included articles from this stage were retrieved in a PDF format to proceed to full-text screening. Full-text screening was performed by two independent authors in a blinded fashion and any conflict was settled by a third author.

2.3. Risk of Bias Assessment

A risk of bias evaluation was carried out by two separate writers; any discrepancies were forwarded to a third author. Several assessment instruments were used, depending on the study design. We employed the Cochrane risk-of-bias instrument (RoB 2.0) [16] for RCTs, which has five domains with a series of questions in each. These inquiries have the following responses: "yes", "no", "possibly yes", "possibly no", and "no information". After that, a graphic was used to aggregate the data and identify one of three bias levels: low risk, moderate concerns, or high risk. If each of the five domains is judged to have a low risk of bias, then the study as a whole has a low risk of bias. The study is said to contain some bias concerns if there are concerns in at least one domain. The study is considered to have a high risk of bias if there is a high risk of bias in at least one domain or if there are concerns in multiple domains.

2.4. Data Extraction and Statistical Analysis

Two independent authors performed data extraction on included articles from the full-text screening stage. Any conflict was settled via an online meeting. Extracted data included: study design, intervention name, and control drug name. Moreover, we extracted data pertaining to the sample size, gender, age for both intervention and control groups, inclusion and exclusion criteria, aim of the study, and main findings (Tables 1 and 2). We also extracted data on patient comorbidities, weight, Body Mass Index (BMI), BES, and Eating Disorder Examination Questionnaire (EDE-Q) pre- and post-treatment. A meta-analysis was conducted using Review Manager. The mean difference was used to calculate the effect size with the random effect model. Furthermore, we assessed heterogeneity between studies using an I^2 statistical test. A p-value < 0.05 was considered statistically significant.

Table 1. Baseline characteristics of the patients in the included studies.

Study ID	Study Design	Intervention	Control	Sample Size		Gender (m/f)		Age	
				Intervention	Control	Intervention	Control	Intervention	Control
Carbone et al., 2020 [17]	RCT	Naltrexone–Bupropion	Placebo	23	20	4/15	7/8	41	44.4
Dalton et al., 2017 [18]	RCT	Naltrexone–Bupropion	Placebo	1310	763	275/1035	160/603	47.0 (10.8)	47.4 (11.1)
Grilo et al., 2022 [19]	RCT	Naltrexone–Bupropion	Placebo	32	34	5/26	6/28	46.03	46.94
Grilo et al., 2020 [20]	RCT	Naltrexone–Bupropion	Placebo	12	10	1/11	2/8	51.17 (7.95)	49.40 (10.13)
Guerdjikova et al., 2017 [21]	Open-label, uncontrolled study	Naltrexone–Bupropion	Uncontrolled study	23	-	0/23	-	NA	-
Halseth et al., 2018 [22]	RCT	Naltrexone–Bupropion	Placebo	71	82	14/57	11/71	48 (9)	48 (10)

Table 2. Aims and summary of findings of the included studies.

Study ID	Aim of the Study	Comorbidities of Patients	Main Findings	Inclusion Criteria	Exclusion Criteria
Carbone et al., 2020 [17]	Evaluate the efficacy of NB in improving pathological eating behavior and losing weight in BED patients.	Obesity	• Similar weight loss was evident for both groups. • Pathological eating behavior, BES score, and YFAS severity significantly improved, especially among BED.	• Male and female patients; • Age 18–65 years; • Diagnosis of BED according to DSM-5; • Obesity (BMI $\geq$ 30 kg/m^2); • Having undergone at least five weight-loss programs without success; • Able to respond autonomously to self-administered questionnaires.	• Age out of the range 18–65 years; • Incapable of expressing valid consent; • Psychotic disorders; • Suicidal risk; • Alcohol or substance abuse; • Pregnant women or women within 12 months of childbirth and/or breastfeeding.

Table 2. *Cont.*

Study ID	Aim of the Study	Comorbidities of Patients	Main Findings	Inclusion Criteria	Exclusion Criteria
Dalton et al., 2017 [18]	To determine whether early changes improve self-reported control over food craving.	DM	• Craving Control, Positive Mood, Craving for Sweet, and Craving for Savory with good internal consistency (Cronbach's α = 0.72–0.92). Subjects with the greatest improvement in Craving Control.	• Had complete weight and CoEQ measurements at baseline and week 56.	NR
Grilo et al., 2022 [19]	Test the effectiveness of naltrexone–bupropion and behavioral weight loss therapy.	Obesity	• BWL and naltrexone–bupropion were associated with significant improvements in binge-eating disorder, with a consistent pattern of BWL being superior to no BW.	• Meeting DSM-5 criteria for binge-eating disorder; • Age between 18 and 70 years; • Body mass index (BMI) between 30.0 and 50.0.	• Concurrent treatment for eating or weight disorders.
Grilo et al., 2020 [20]	Show efficacy of Naltrexone + Bupropion Combination for the Treatment of Binge-eating Disorder with Obesity.	Obesity	• Completion rates (NB, 83.3%; placebo, 70.0%) and adverse events did not differ significantly between NB and placebo's significant reductions from the baseline. • In binge eating, eating-disorder psychopathology, depression, and weight during treatment.	• Age 18–65 years; • Body mass index (BMI) C27 to B43 kg/m^2; • MDD, without psychotic features; • IDS-SR score [26 at screening].	• The receipt of any concurrent.
Guerdjikova et al., 2017 [21]	Evaluation of NB in BED in randomized controlled trials appears warranted.	Major Depressive Disorder	• Binge eating, at least when accompanied by MDD and overweight/obesity, may respond to NB plus behavioral treatment. • Evaluation of NB in BED in randomized controlled trials appears warranted.	• Adult male and female participants; • Aged 18–60 years; • Had an initial BMI of 30–45 kg m^2 (obese) or 27–45 kg m^2.	• The presence of a BED lifetime history; • Anorexia nervosa or bulimia was exclusionary.
Halseth et al., 2018 [22]	This trial examined the weight-related quality of life, control over eating behavior, and sexual function.	Sexual function in participants	• Compared with UC, participants treated with NB + CLI experienced greater improvements in weight-related quality of life, control over eating behavior, and sexual function.	• (Overweight) with dyslipidemia; • Controlled hypertension.	• Type 1 or 2 diabetes mellitus; • Myocardial infarction within 6 months before screening; • Angina.

3. Results

Our search strategy yielded a total of 848 research articles from the three databases. After title and abstract screening, 25 were eligible for further screening by full-text. The final number after this process was six articles [17–22] that entered the meta-analysis (Figure 1).

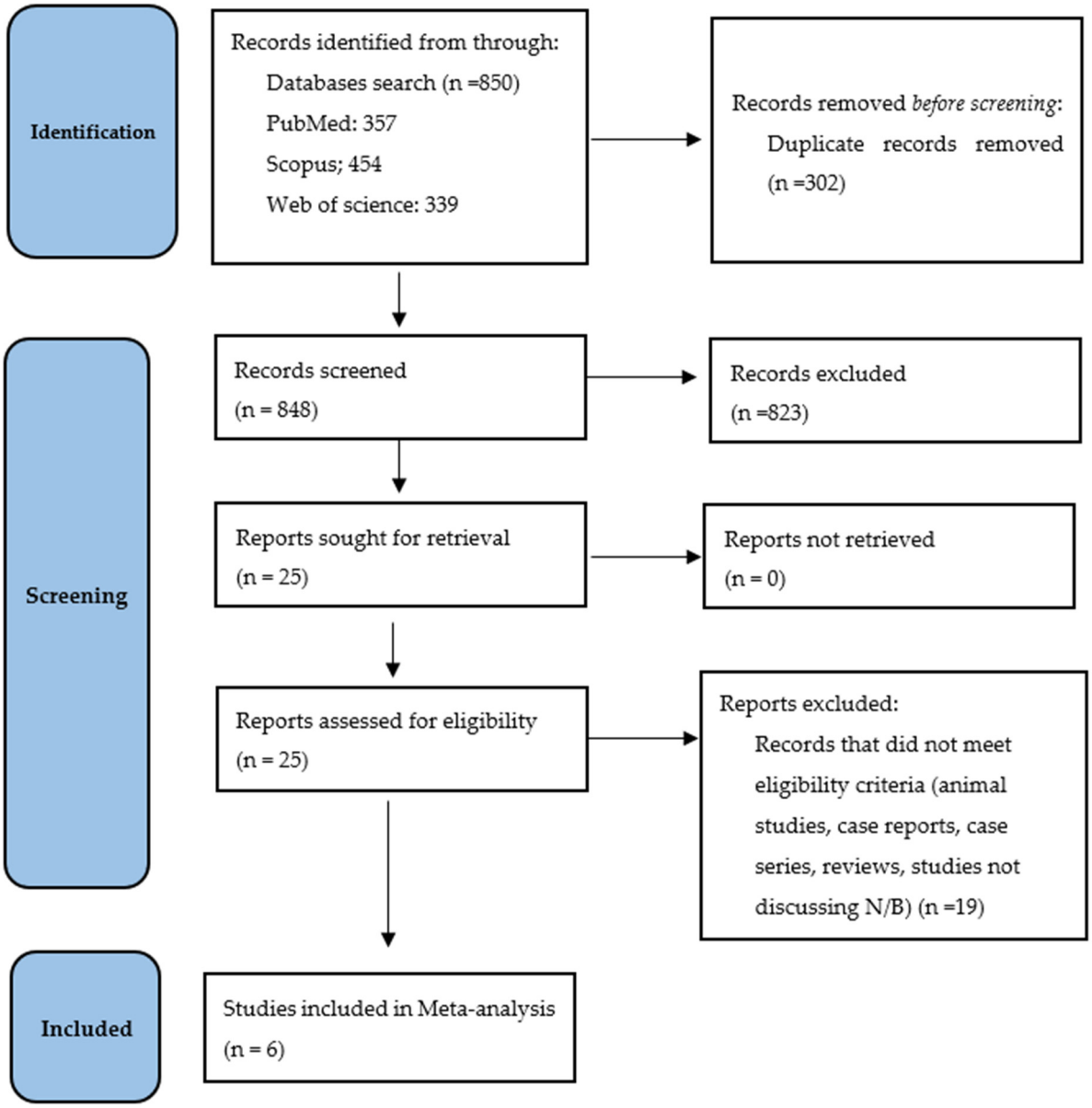

Figure 1. PRISMA flow diagram of the included studies and screening process.

The risk of bias assessment of the included studies showed that two studies [18,19] had a high risk of bias, two studies [21,22] had a low risk of bias, and two studies [17,20] had some concerns (Figure 2).

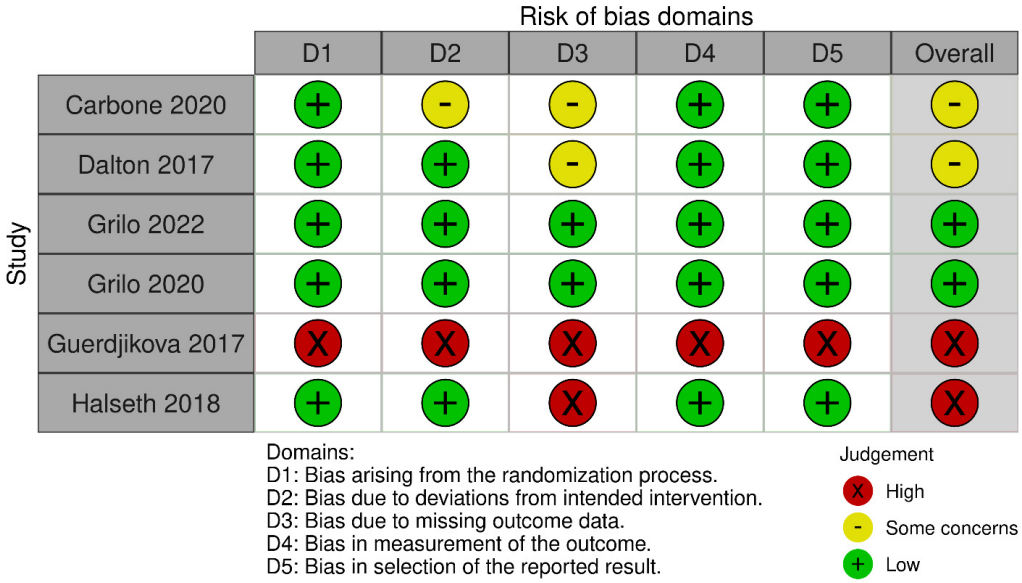

Figure 2. Risk of bias assessment of the included studies using ROB2 tool [17–22].

3.1. Summary and Baseline Characteristics

Five of the included studies were RCTs while one of them was an open-label uncontrolled study. The included RCTs compared patients taking NB to patients taking a placebo. A summary of the included studies and baseline characteristics are illustrated in Tables 1 and 2.

3.2. Statistical Analysis

3.2.1. Pre− and Post−Treatment Outcomes

This study showed that the use of an NB combination is associated with a statistically significant reduction in the weight of the patients compared to their weight before treatment with MD: −8.52 (95% CI: −10.01−−6.94, $p < 0.00001$) and with non-significant heterogeneity (Figure 3).

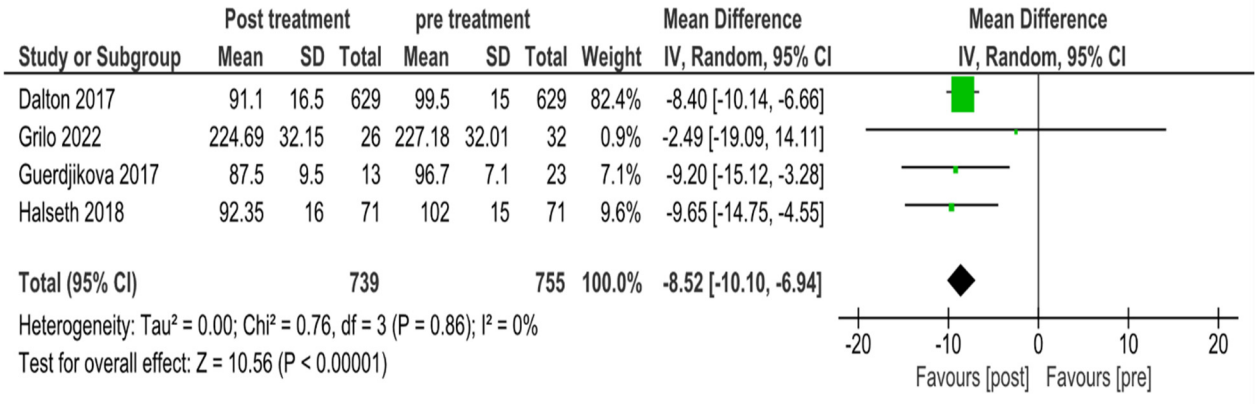

Figure 3. Analysis of mean difference of pre− and post-treatment weight of the included patients. Green shape: the confidence interval which represents the chance that the true effect in the population will lie within the range, black shape: represents the overall pooled effect from the included studies [17,18,21,22].

In addition, there was a statistically significant reduction in BMI after treatment compared to before treatment with MD: −4.95 (95%CI: −9.72−−0.17, $p = 0.04$), but with a significant heterogeneity (Figure 4).

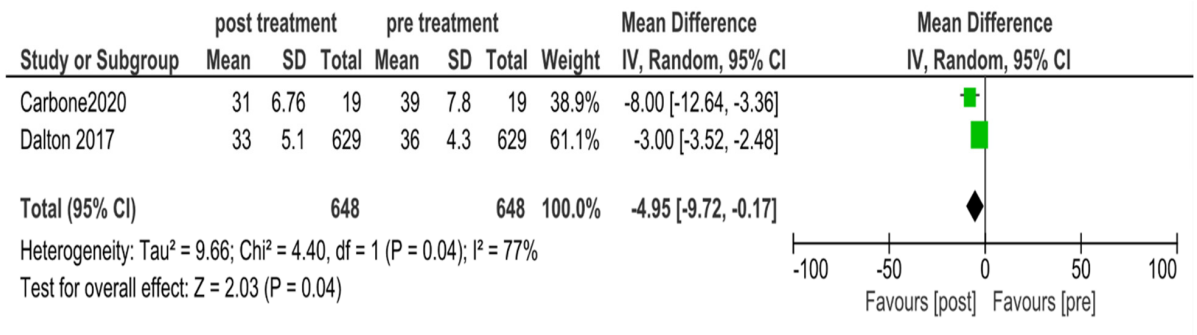

Figure 4. Analysis of mean difference of pre− and post−treatment BMI of the included patients. Green shape: the confidence interval which represents the chance that the true effect in the population will lie within the range, black shape: represents the overall pooled effect from the included studies [17,18].

Moreover, there was a significant reduction in BES after treatment with MD: −7.66 (95%CI: −14.36–0.96, $p = 0.02$) with significant heterogeneity (Figure 5).

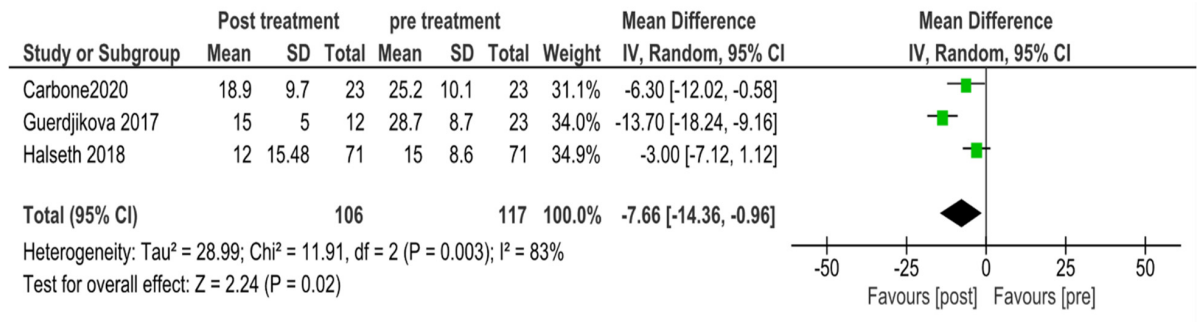

Figure 5. Mean difference of pre− and post−treatment BES. Green shape: the confidence interval which represents the chance that the true effect in the population will lie within the range, black shape: represents the overall pooled effect from the included studies [17,21,22].

The EDE-binge eating score and EDE-global score were statistically significantly reduced after treatment with NB combination compared to their value before treatment with MD: −7.65 (95%CI: −12.8−−0.51, $p = 0.004$) with non-significant heterogeneity, and MD: −0.41 (95%CI: −0.76−−0.05, $p = 0.02$) with non-significant heterogeneity, respectively (Figures 6 and 7).

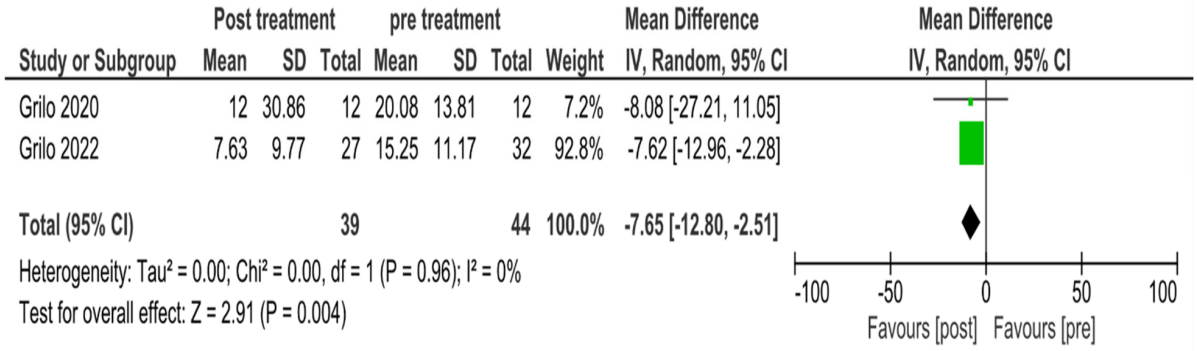

Figure 6. Mean difference of pre- and post-treatment EDE−binge eating score. Green shape: the confidence interval which represents the chance that the true effect in the population will lie within the range, black shape: represents the overall pooled effect from the included studies [19,20].

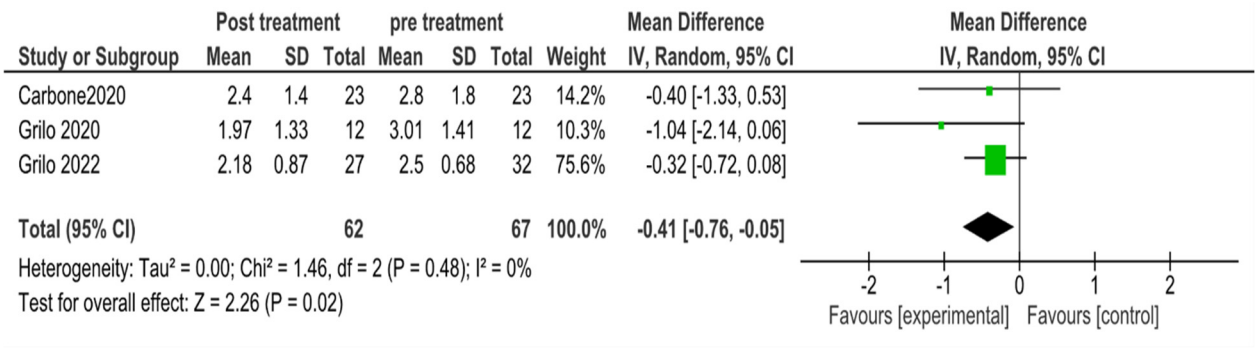

Figure 7. Mean difference of pre− and post−treatment EDE−global score. Green shape: the confidence interval which represents the chance that the true effect in the population will lie within the range, black shape: represents the overall pooled effect from the included studies [17,19,20].

3.2.2. Analysis of the Mean Change in the Drug and Placebo

The analysis between the mean change of weight, BMI, and BES among drug combination and placebo patients showed that the absolute mean change was statistically significantly higher in the drug combination group compared to the placebo group with MD: −4.31 (95%CI: −7.81−−0.81, p = 0.02), MD:−1.12 (95%CI: −2.14−−0.1, p = 0.03), and MD: −5.53 (95%CI: −9.82−−1.23, p = 0.01), respectively, with significant heterogeneity in weight only (Figures 8–10).

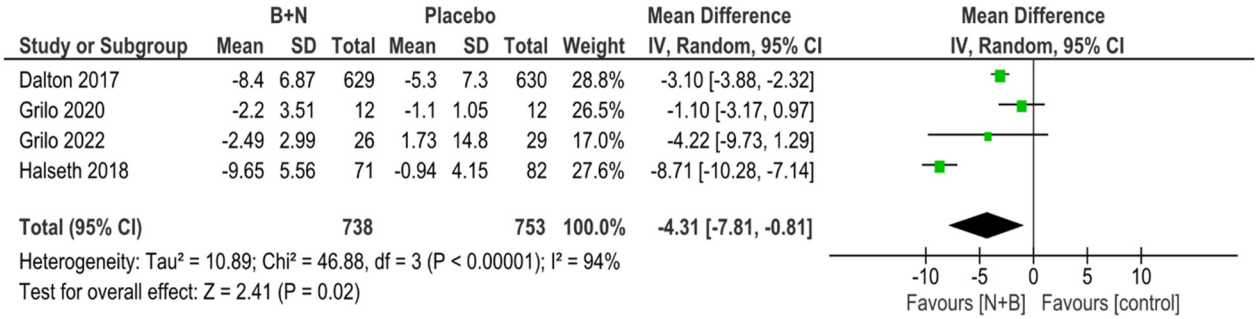

Figure 8. Analysis of mean difference between mean weight change in drug vs. placebo. Green shape: the confidence interval which represents the chance that the true effect in the population will lie within the range, black shape: represents the overall pooled effect from the included studies [18–20,22].

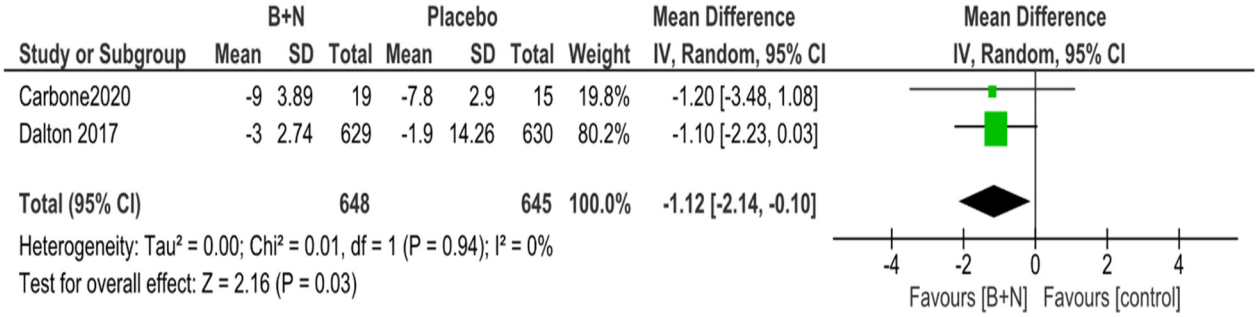

Figure 9. Analysis of mean difference between mean BMI change in drug vs. placebo. Green shape: the confidence interval which represents the chance that the true effect in the population will lie within the range, black shape: represents the overall pooled effect from the included studies [17,18].

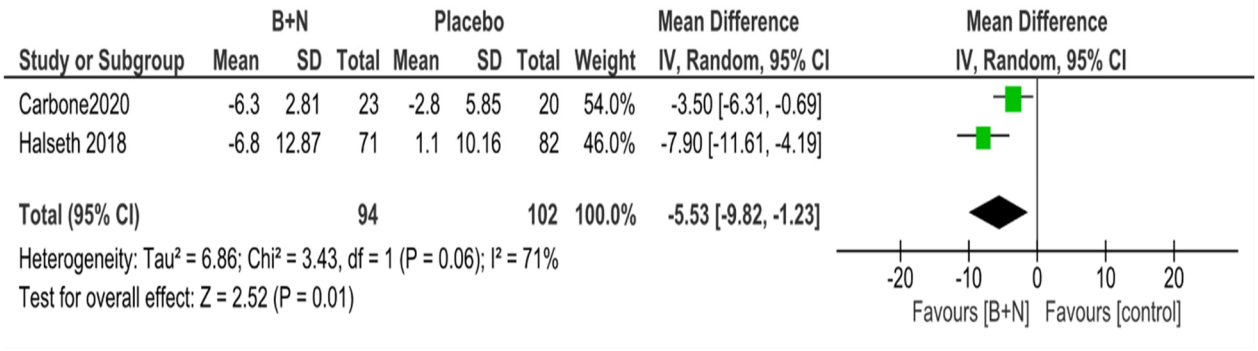

Figure 10. Analysis of mean difference between mean BES change in drug vs. placebo. Green shape: the confidence interval which represents the chance that the true effect in the population will lie within the range, black shape: represents the overall pooled effect from the included studies [17,22].

3.2.3. Discussion

NB may be an effective treatment for disordered eating behavior and weight loss in obese people, according to our findings. The impact of NB was examined across four primary domains, namely weight, BMI, BES, and EDE-Q.

In terms of weight, we analyzed the data from four studies [17,18,21,22]. We meta-analyzed the mean difference in weight between pre- and post-treatment with NB and the mean difference in the weight change between NB and the placebo. Doses in the included studies ranged from a 32–50 mg naltrexone sustained release (SR)/300–360 mg bupropion. NB was shown to cause more statistically significant weight loss in participants from these studies than in controls (mean difference, −4.31; 95% CI, −7.81, −0.81). Moreover, patients from these studies had statistically significantly lower weight post- than pre-treatment with NB (MD = −8.52; 95% CI = −10.10, −6.94). In terms of BMI change, only two studies reported their patients' BMI data [15,21]. In those studies, NB was shown to be effective in lowering BMI in selected patients more than the placebo (mean difference, −1.12; 95% CI, −2.14, −0.10). Moreover, there was a statistically significant decrease in the BMI of patients after treatment compared to before treatment, with a mean difference of −4.95 (95%CI: −9.72–−0.17, $p = 0.04$). Carbone et al. [17] report that 85% of included patients lost at least 5% of their body weight at the 16th week of treatment. In addition, they reported that included patients have lost, on average, 8% of their weight. Traditionally used anti-obesity medications approved by the FDA, such as lorcaserin, orlistat, phentermine/topiramate extended-release, and liraglutide, however effective, have been reported to cause undesired side effects, contraindications, or pharmacological interactions [19,20]. Bupropion is a dopamine and norepinephrine reuptake inhibitor that has been widely used as an antidepressant since its FDA approval in 1989 and in smoking cessation since 1997. The FDA approved Naltrexone for the treatment of opioid dependence in 1984 and alcohol use disorder in 1994. In 2014, the FDA approved NB for the treatment of obesity [13]. Whereas monotherapy with Bupropion has been proven effective in inducing modest weight loss, Naltrexone is associated with negligible weight loss effects, hence it is used in combination with Bupropion [13,23]. Their weight-reducing effect can be explained by their effect on the hypothalamic system, which regulates homeostasis, controlling food intake and energy expenditure [24]. Nevertheless, naltrexone, when used in combination with bupropion, has a synergistic effect, promoting energy expenditure and, thus, causing effective weight reduction whether or not they suffer from pathological eating disorders [24–29].

Studies conducted in vivo [30] have demonstrated that the combination injection of naltrexone and bupropion is more effective than administering each medication separately while decreasing food consumption. Furthermore, the favorable effect of NB on food addiction may be further explained by the significant connection between the neural substrates of the two systems [17,31]. Research has shown that the intensity of food

addiction is directly correlated with more severe eating psychopathology (e.g., frequency of binges) and psychological impairment [32,33]. Food addiction, BED, and obesity are extensively related [34]. Similar to adults with drug use disorders [35,36], adults with food addiction have enhanced dopamine-related brain activations [37], as well as the increased activation of dopamine D1 and μ-opioid receptors in response to food stimuli [38]. Similar explanations could apply to the improvement of other unhealthy eating patterns, such as emotional eating, grazing, and carbohydrate cravings.

Regarding BES, we meta-analyzed the mean difference in the score between both the pre- and post-NB treatment group and between the NB and placebo treatment groups. Two studies reported the mean difference in BES pre- and post-NB-treatment [15,17]. The meta-analysis for these studies' results yielded a statistically significant reduction in the BES score (mean difference, −5.53; 95% CI, −9.82, −1.23). Three studies [15–17] reported the BES scores before and after treatment with NB. A meta-analysis of these studies showed that NB significantly reduced the BES scores (MD = −7.66, 95%CI = −14.36, −0.96). Studies have shown that BES is a poor diagnostic tool for BED, as it has poor concurrence between it and other scales or diagnostic criteria [28,30,31]. Instead, it has good properties as a measure of behavioral manifestations and feelings associated with BED, showing high scores among patients with greater levels of binge eating behavior [39]. Ranging from zero to 46, BES scores can be summarized categorically into three levels: no significant binge eating (BES < or = 17), moderate levels of binge eating (BES = 18–25), and severe binge eating (BES > or = 27) [22]. BES scores have previously been used to evaluate pharmacological treatment for obesity in patients with (rimonabant and sibutramine) and without (pramlitide) BED [32–34]. These studies reported a decrease in BES scores ranging from 25 to 51%. In terms of EDE scores, we meta-analyzed the mean difference in the EDE scores between pre- and post-treatment with NB in addition to the mean difference in the EDE scores between NB and the placebo. Our meta-analysis showed that three studies reported the global EDE scores in both the NB treatment group and placebo [15,18,22], and the results of their meta-analysis showed a statistically significant reduction in the score (mean difference, −0.41; 95% CI, −0.76, −0.05) which was more than with the placebo. Specifically, in the binge eating domain of EDE, we performed a meta-analysis of two studies and the results were more favorable and statistically significant post- rather than pre-treatment with NB (mean difference, −7.65; 95% CI, −12.80, −2.51) [18,22]. EDE measures decreased food intake. Hence, a decreased EDE score signifies decreased binge behavior associated with BED [17].

Previously prescribed medications for controlling pathological eating disorders, such as sibutramine, rimonabant, or pramlintide, have been either withdrawn from the market or their research halted due to safety concerns [36–38]. Lisdexamfetamine is the only FDA-approved drug for treating pathological eating disorders. While it significantly reduced the number of binge episodes, it was not completely free of undesirable side effects. Moreover, it is not indicated for weight loss as its effects on obesity were not thoroughly studied. In addition, similar sympathomimetic medication classes for weight loss, such as Sibutramine [40], have been associated with cardiovascular side effects [23]. This study establishes the efficacy of NB in both reducing binge eating episodes (reduction in BES) and promoting weight loss (reduction in EDE). Its effect on reducing binge episodes can be explained by its effect on the mesolimbic dopamine system which is related to the reward system and the regulation of feeding behavior [41]. This can be also explained by its action on μ-opioid receptors which are related to "liking" and "wanting" [42].

Many patients report adverse effects, even though the majority of drugs that are not indicated for the treatment of BED—such as antidepressants like fluoxetine, sertraline, citalopram, escitalopram, and vortioxetine—are generally well tolerated [43]. However, there was no discernible weight reduction among the antidepressant medication-treated participants, most likely because the studies on a chronic illness like BED were only 8 weeks long [7].

In terms of aiding in weight loss, lowering the frequency of binge episodes on a weekly and daily basis, and enhancing the psychopathology of borderline eating disorders, topiramate outperforms the placebos [44]. The current information on the tolerance of NB appears to be consistent with earlier reports [45,46] in terms of its safety profile. While nausea was a common adverse effect during the treatment's titration period, most of these cases were mild and did not warrant discontinuing the medication; instead, they were handled with dose adjustments or a lower titration. Although data in the literature suggested that bupropion's sympathomimetic effects could cause elevations or hypertensive crises, raising concerns for cardiovascular safety, NB showed a relatively safe profile with no rare or serious side effects: no patient experienced hypertensive crises, and no patient transitioned into hypo- or maniacal phases, even when the drug was administered to patients with bipolar disorders or in combination with other antidepressants [46,47]. As previously mentioned, bupropion medication can raise the risk of seizures; as such, it should not be used in patients who are underweight or who suffer from anorexia or bulimia nervosa.

Poor compliance and early dropout were predicted by the existence of an apprehensive trait [46]. This could be attributed to the more challenging nature of the path—both pharmacologically and in terms of the corresponding lifestyle modification—which was required in order to start the protocol research and to lose weight. These findings also point to the necessity of more precisely identifying individuals who can be treated and who are driven enough to stick with a treatment plan.

Despite the significant findings and contributions of the present systematic review, there were several unavoidable limitations that should be acknowledged. Firstly, the number of included studies is relatively limited, which may affect the generalizability of our results. Moreover, the included studies varied in terms of sample size and treatment duration, which introduced heterogeneity that could influence the overall conclusions. Additionally, most included studies had a relatively short follow-up period and, hence, limited our understanding of the long-term effects of NB treatment. Lastly, our meta-analysis focused on weight reduction and changes in specific scales, without extensively exploring the other relevant outcomes, such as psychological well-being or quality of life.

Based on our findings, several research and practice recommendations can be made. Firstly, future studies should focus on conducting more RCTs with larger sample sizes to further evaluate the safety and efficacy of NB in treating BED. Additionally, future studies should investigate the long-term effects and maintenance of weight loss with NB. Physicians should consider using NB as a viable treatment option for patients suffering from pathological eating behaviors and obesity. Lastly, using the BES and EDE can be valuable in assessing the treatment response and adherence to medication in addition to monitoring improvements in behavioral manifestations associated with BED.

The present systematic review provides insights into using NB in treating BED. To our knowledge, it is the first time that the published literature on this topic has been synthesized and meta-analyzed to provide recommendations for future research and guidelines. Our findings suggest that NB can effectively treat pathological binge eating behavior and promote weight loss among obese patients. NB demonstrated significant weight reduction and favorable BMI changes in the analyzed studies. Moreover, NB had favorable effects on the BES and EDE scales, showing significant improvements.

4. Conclusions

NB demonstrated high efficacy in the treatment of BED as obviously shown in the weight and BMI improvements, in addition to the BED and EDE-Q scales. This provides a promising treatment option for BED with an effect on the weight gain and the psychological parameters of BED.

Author Contributions: M.H.-E.M.: Idea validation, meta-analysis, revision. M.A.S.: Writing and editing. A.A.: Editing, data extraction. R.M.F.G.: Writing and editing. I.S.: Screening, data extraction, risk of bias assessment. M.H.: Screening, data extraction, risk of bias assessment. M.A.: Review and editing. All authors have read and agreed to 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: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Kessler, R.C.; Berglund, P.A.; Chiu, W.T.; Deitz, A.C.; Hudson, J.I.; Shahly, V.; Aguilar-Gaxiola, S.; Alonso, J.; Angermeyer, M.C.; Benjet, C.; et al. The Prevalence and Correlates of Binge Eating Disorder in the World Health Organization World Mental Health Surveys. *Biol. Psychiatry* **2013**, *73*, 904–914. [CrossRef] [PubMed]
2. Fornaro, M.; Solmi, M.; Perna, G.; De Berardis, D.; Veronese, N.; Orsolini, L.; Ganança, L.; Stubbs, B. Lisdexamfetamine in the treatment of moderate-to-severe binge eating disorder in adults: Systematic review and exploratory meta-analysis of publicly available placebo-controlled, randomized clinical trials. *Neuropsychiatr. Dis. Treat.* **2016**, *12*, 1827–1836. [CrossRef] [PubMed]
3. Association, A. Diagnostic and statistical manual of mental disorders (DSM-IV-TR), text revision. *Corsini Encycl. Psychol.* **2000**, 1–3. [CrossRef]
4. Balodis, I.M.; Grilo, C.M.; Potenza, M.N. Neurobiological features of binge eating disorder. *CNS Spectr.* **2015**, *20*, 557–565. [CrossRef] [PubMed]
5. Coffino, J.A.; Udo, T.; Grilo, C.M. Rates of Help-Seeking in US Adults With Lifetime DSM-5 Eating Disorders: Prevalence Across Diagnoses and Differences by Sex and Ethnicity/Race. *Mayo Clin. Proc.* **2019**, *94*, 1415–1426. [CrossRef]
6. Wilson, G.T.; Wilfley, D.E.; Agras, W.S.; Bryson, S.W. Psychological Treatments of Binge Eating Disorder. *Arch. Gen. Psychiatry* **2010**, *67*, 94. [CrossRef]
7. Stefano, S.C.; Bacaltchuk, J.; Blay, S.L.; Appolinário, J.C. Antidepressants in short-term treatment of binge eating disorder: Systematic review and meta-analysis. *Eat. Behav.* **2008**, *9*, 129–136. [CrossRef] [PubMed]
8. McElroy, S.L.; Arnold, L.M.; Shapira, N.A.; Keck, P.E.; Rosenthal, N.R.; Karim, M.R.; Kamin, M.; Hudson, J.I. Topiramate in the Treatment of Binge Eating Disorder Associated With Obesity: A Randomized, Placebo-Controlled Trial. *Am. J. Psychiatry* **2003**, *160*, 255–261. [CrossRef]
9. Claudino, A.M.; De Oliveira, I.R.; Appolinario, J.C.; Cordás, T.A.; Duchesne, M.; Sichieri, R.; Bacaltchuk, J. Double-Blind, Randomized, Placebo-Controlled Trial of Topiramate Plus Cognitive-Behavior Therapy in Binge-Eating Disorder. *J. Clin. Psychiatry* **2007**, *68*, 1324–1332. [CrossRef]
10. McElroy, S.L.; Shapira, N.A.; Arnold, L.M.; Keck, P.E.; Rosenthal, N.R.; Wu, S.-C.; Capece, J.A.; Fazzio, L.; Hudson, J.I. Topiramate in the Long-Term Treatment of Binge-Eating Disorder Associated with Obesity. *J. Clin. Psychiatry* **2004**, *65*, 1463–1469. [CrossRef]
11. McElroy, S.L.; Hudson, J.; Ferreira-Cornwell, M.C.; Radewonuk, J.; Whitaker, T.; Gasior, M. Lisdexamfetamine Dimesylate for Adults with Moderate to Severe Binge Eating Disorder: Results of Two Pivotal Phase 3 Randomized Controlled Trials. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* **2016**, *41*, 1251–1260. [CrossRef]
12. Grilo, C.M.; Reas, D.L.; Mitchell, J.E. Combining Pharmacological and Psychological Treatments for Binge Eating Disorder: Current Status, Limitations, and Future Directions. *Curr. Psychiatry Rep.* **2016**, *18*, 55. [CrossRef]
13. Saunders, K.H.; Umashanker, D.; Igel, L.I.; Kumar, R.B.; Aronne, L.J. Obesity Pharmacotherapy. *Med. Clin. N. Am.* **2018**, *102*, 135–148. [CrossRef]
14. McElroy, S.L.; Guerdjikova, A.I.; Kim, D.D.; Burns, C.; Harris-Collazo, R.; Landbloom, R.; Dunayevich, E. Naltrexone/Bupropion Combination Therapy in Overweight or Obese Patients With Major Depressive Disorder: Results of a Pilot Study. *Prim. Care Companion CNS Disord.* **2013**, *15*, 25594. [CrossRef]
15. Moawad, M.H.-E.; Sadeq, M.A.; Abbas, A.; Ghorab, R.M.F.; Serag, I.H.I.; Hashem, M.H.; Alkasaby, M. Efficacy of Naltrexone/Bupropion in Treatment of Binge Eating: A Systematic Review and Meta-Analysis. 2023. [CrossRef]
16. RoB 2: A Revised Cochrane Risk-of-Bias Tool for Randomized Trials | Cochrane Bias. Available online: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials (accessed on 27 September 2023).
17. Carbone, E.A.; Caroleo, M.; Rania, M.; Calabrò, G.; Staltari, F.A.; de Filippis, R.; Aloi, M.; Condoleo, F.; Arturi, F.; Segura-Garcia, C. An open-label trial on the efficacy and tolerability of naltrexone/bupropion SR for treating altered eating behaviours and weight loss in binge eating disorder. *Eat. Weight Disord.-Stud. Anorex. Bulim. Obes.* **2021**, *26*, 779–788. [CrossRef]
18. Dalton, M.; Finlayson, G.; Walsh, B.; Halseth, A.E.; Duarte, C.; Blundell, J.E. Early improvement in food cravings are associated with long-term weight loss success in a large clinical sample. *Int. J. Obes. 2005* **2017**, *41*, 1232–1236. [CrossRef]
19. Grilo, C.M.; Lydecker, J.A.; Fineberg, S.K.; Moreno, J.O.; Ivezaj, V.; Gueorguieva, R. Naltrexone-Bupropion and Behavior Therapy, Alone and Combined, for Binge-Eating Disorder: Randomized Double-Blind Placebo-Controlled Trial. *Am. J. Psychiatry* **2022**, *179*, 927–937. [CrossRef]

20. Grilo, C.M.; Lydecker, J.A.; Morgan, P.T.; Gueorguieva, R. Naltrexone + Bupropion Combination for the Treatment of Binge-eating Disorder with Obesity: A Randomized, Controlled Pilot Study. *Clin. Ther.* **2021**, *43*, 112–122.e1. [CrossRef]
21. Guerdjikova, A.I.; Walsh, B.; Shan, K.; Halseth, A.E.; Dunayevich, E.; McElroy, S.L. Concurrent Improvement in Both Binge Eating and Depressive Symptoms with Naltrexone/Bupropion Therapy in Overweight or Obese Subjects with Major Depressive Disorder in an Open-Label, Uncontrolled Study. *Adv. Ther.* **2017**, *34*, 2307–2315. [CrossRef]
22. Halseth, A.; Shan, K.; Gilder, K.; Malone, M.; Acevedo, L.; Fujioka, K. Quality of life, binge eating and sexual function in participants treated for obesity with sustained release naltrexone/bupropion: Effect of NB on patient-reported outcomes. *Obes. Sci. Pract.* **2018**, *4*, 141–152. [CrossRef]
23. Reas, D.L.; Grilo, C.M. Pharmacological treatment of binge eating disorder: Update review and synthesis. *Expert Opin. Pharmacother.* **2015**, *16*, 1463–1478. [CrossRef]
24. Witkamp, R.F. Current and future drug targets in weight management. *Pharm. Res.* **2011**, *28*, 1792–1818. [CrossRef] [PubMed]
25. Anderson, J.W.; Greenway, F.L.; Fujioka, K.; Gadde, K.M.; McKenney, J.; O'Neil, P.M. Bupropion SR enhances weight loss: A 48-week double-blind, placebo- controlled trial. *Obes. Res.* **2002**, *10*, 633–641. [CrossRef] [PubMed]
26. White, M.A.; Grilo, C.M. Bupropion for overweight women with binge-eating disorder: A randomized, double-blind, placebo-controlled trial. *J. Clin. Psychiatry* **2013**, *74*, 400–406. [CrossRef] [PubMed]
27. Leibel, R.L.; Rosenbaum, M.; Hirsch, J. Changes in energy expenditure resulting from altered body weight. *N. Engl. J. Med.* **1995**, *332*, 621–628. [CrossRef]
28. Morton, G.J.; Cummings, D.E.; Baskin, D.G.; Barsh, G.S.; Schwartz, M.W. Central nervous system control of food intake and body weight. *Nature* **2006**, *443*, 289–295. [CrossRef] [PubMed]
29. Patel, D.K.; Stanford, F.C. Safety and tolerability of new-generation anti-obesity medications: A narrative review. *Postgrad. Med.* **2018**, *130*, 173–182. [CrossRef] [PubMed]
30. Billes, S.K.; Sinnayah, P.; Cowley, M.A. Naltrexone/bupropion for obesity: An investigational combination pharmacotherapy for weight loss. *Pharmacol. Res.* **2014**, *84*, 1–11. [CrossRef]
31. Kessler, R.M.; Hutson, P.H.; Herman, B.K.; Potenza, M.N. The neurobiological basis of binge-eating disorder. *Neurosci. Biobehav. Rev.* **2016**, *63*, 223–238. [CrossRef]
32. Gearhardt, A.N.; White, M.A.; Potenza, M.N. Binge eating disorder and food addiction. *Curr. Drug Abuse Rev.* **2011**, *4*, 201–207. [CrossRef]
33. Gearhardt, A.N.; White, M.A.; Masheb, R.M.; Morgan, P.T.; Crosby, R.D.; Grilo, C.M. An examination of the food addiction construct in obese patients with binge eating disorder. *Int. J. Eat. Disord.* **2012**, *45*, 657–663. [CrossRef] [PubMed]
34. Jiménez-Murcia, S.; Agüera, Z.; Paslakis, G.; Munguia, L.; Granero, R.; Sánchez-González, J.; Sánchez, I.; Riesco, N.; Gearhardt, A.N.; Dieguez, C.; et al. Food Addiction in Eating Disorders and Obesity: Analysis of Clusters and Implications for Treatment. *Nutrients* **2019**, *11*, 2633. [CrossRef] [PubMed]
35. Davis, C.; Levitan, R.D.; Kaplan, A.S.; Kennedy, J.L.; Carter, J.C. Food cravings, appetite, and snack-food consumption in response to a psychomotor stimulant drug: The moderating effect of "food-addiction". *Front. Psychol.* **2014**, *5*, 91874. [CrossRef] [PubMed]
36. Gordon, E.L.; Ariel-Donges, A.H.; Bauman, V.; Merlo, L.J. What Is the Evidence for "Food Addiction"? A Systematic Review. *Nutrients* **2018**, *10*, 477. [CrossRef] [PubMed]
37. Gearhardt, A.N.; Yokum, S.; Orr, P.T.; Stice, E.; Corbin, W.R.; Brownell, K.D. Neural correlates of food addiction. *Arch. Gen. Psychiatry* **2011**, *68*, 808–816. [CrossRef] [PubMed]
38. Colantuoni, C.; Schwenker, J.; McCarthy, J.; Rada, P.; Ladenheim, B.; Cadet, J.L.; Schwartz, G.J.; Moran, T.H.; Hoebel, B.G. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. *Neuroreport* **2001**, *12*, 3549–3552. [CrossRef]
39. Gormally, J.; Black, S.; Daston, S.; Rardin, D. The assessment of binge eating severity among obese persons. *Addict. Behav.* **1982**, *7*, 47–55. [CrossRef] [PubMed]
40. Weight Loss Agents. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*; National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, USA, 2012. Available online: http://www.ncbi.nlm.nih.gov/books/NBK548929/ (accessed on 25 June 2023).
41. Gladis, M.M.; Wadden, T.A.; Foster, G.D.; Vogt, R.A.; Wingate, B.J. A comparison of two approaches to the assessment of binge eating in obesity. *Int. J. Eat. Disord.* **1998**, *23*, 17–26. [CrossRef]
42. Peciña, S.; Berridge, K.C. Hedonic hot spot in nucleus accumbens shell: Where do mu-opioids cause increased hedonic impact of sweetness? *J. Neurosci. Off. J. Soc. Neurosci.* **2005**, *25*, 11777–11786. [CrossRef]
43. Amodeo, G.; Cuomo, A.; Bolognesi, S.; Goracci, A.; Trusso, M.A.; Piccinni, A.; Neal, S.M.; Baldini, I.; Federico, E.; Taddeucci, C.; et al. Pharmacotherapeutic strategies for treating binge eating disorder. Evidence from clinical trials and implications for clinical practice. *Expert Opin. Pharmacother.* **2019**, *20*, 679–690. [CrossRef]
44. Leombruni, P.; Lavagnino, L.; Fassino, S. Treatment of obese patients with binge eating disorder using topiramate: A review. *Neuropsychiatr. Dis. Treat.* **2009**, *5*, 385–392. [CrossRef] [PubMed]
45. Bello, N.T. Update on drug safety evaluation of naltrexone/bupropion for the treatment of obesity. *Expert Opin. Drug Saf.* **2019**, *18*, 549–552. [CrossRef] [PubMed]

46. Halpern, B.; Mancini, M.C. Safety assessment of combination therapies in the treatment of obesity: Focus on naltrexone/bupropion extended release and phentermine-topiramate extended release. *Expert Opin. Drug Saf.* **2017**, *16*, 27–39. [CrossRef] [PubMed]
47. Appolinario, J.C.; Godoy-Matos, A.; Fontenelle, L.F.; Carraro, L.; Cabral, M.; Vieira, A.; Coutinho, W. An open-label trial of sibutramine in obese patients with binge-eating disorder. *J. Clin. Psychiatry* **2002**, *63*, 28–30. [CrossRef] [PubMed]