Role of Bupropion Plus Naltrexone for the Management of Obesity

Journal of Pharmacy Technology
2016, Vol. 32(3) 125–132
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DOI: 10.1177/8755122515624220
pharmatech.sagepub.com

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Abstract

Objective. The pharmacology, pharmacokinetics, efficacy, and safety of bupropion plus naltrexone for weight loss were reviewed. **Data Sources.** A MEDLINE search (1970 to November 2015) was conducted for English-language articles using specific MESH terms. **Study Selection and Data Extraction.** Published Phase 3 clinical trials with primary endpoints related to weight loss were included and critiqued in this review. **Study Selection and Data Extraction.** Five trials were retrieved and reviewed regarding the efficacy and safety of bupropion plus naltrexone among obese and overweight patients. **Data Synthesis.** Bupropion is a dopamine/norepinephrine reuptake inhibitor, and naltrexone is an opioid receptor antagonist. The combination of these agents has led to increased weight loss, compared to placebo, among overweight and obese patients with a body mass index (BMI) at or above 30 or BMI at or above 27 with a comorbid condition. The combination of bupropion and naltrexone can produce an average placebo-subtracted weight loss of 4.25% over 56 weeks. Gastrointestinal (ie, nausea, vomiting, constipation) and central nervous system adverse events (ie, headache, dizziness) were commonly reported, and there was a high dropout rate among participants. **Conclusions.** Bupropion plus naltrexone has demonstrated effective weight loss, in conjunction with lifestyle modifications, among overweight and obese patients with and without comorbidities. Bupropion plus naltrexone has not been studied among special patient populations, such as those with sleep apnea, osteoarthritis, or extreme BMIs. Additional clinical trials and postmarketing data will provide a better understanding of this medication for weight loss.

Keywords

overweight, obesity, obesity management, weight loss, pharmacotherapy, efficacy, safety, adverse events, bupropion, naltrexone

Introduction

Overweight is defined as a body mass index (BMI) between 25 and 29.9 kg/m², whereas obesity is defined as BMI at or above 30 kg/m².¹ In the United States, obesity has become an epidemic problem among adults, as the prevalence has increased steadily from 1990 to 2010.¹ According to the Centers for Disease Control and Prevention, it is estimated that 35.7% of adults are obese, and obesity is the second leading cause of preventable death.¹ Among ethnic groups, the prevalence of obesity is highest among African Americans (49.5%), compared to Hispanics (39.1%) and non-Hispanic whites (34.3%).¹ In 2008, roughly \$147 billion were spent toward obesity and other related medical costs.¹

Obesity is recognized as a disease state by the American Medical Association and is a risk factor for the development of diabetes, cardiovascular diseases (ie, stroke, hypertension), osteoarthritis, and certain types of cancers.^{2–5} It is important to educate and empower patients to modify their lifestyle habits. Lifestyle modifications include reduced caloric intake and increased physical activity. Behavioral modifications, such as tracking systems, can also affect a

patient's success with lifestyle changes. These nonpharmacological interventions are essential for weight loss and maintenance programs.^{3,6}

Obesity guidelines have been published to provide guidance on lifestyle modifications and use of pharmacologic treatment. Based on a systematic review, these guidelines recommend reduced caloric intake and increased physical activity as an initial step and continual intervention for obesity management.⁶ If lifestyle modifications are not successful after 6 months, then a pharmacologic intervention is recommended if a patient has a BMI at or above 27 kg/m² with a comorbid condition (ie, hypertension, diabetes) or BMI at or above 30 kg/m².⁶ Short-term goals may include

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reduction of weight by 5% or 10% from baseline.⁶ Long-term goals include reduction of morbidity and prevention of weight gain (ie, sustainability).

As an extended-release combination product, bupropion plus naltrexone (Orexigen/Takeda Pharmaceuticals) was approved by the Food and Drug Administration (FDA) in September 2014 as an adjunct with lifestyle modifications for chronic weight management (ie, 1 year or longer).^{7,8} It is branded as Contrave in the United States and Mysimba in Europe. It has a similar indication as other approved medications, such as lorcaserin and phentermine plus topiramate, and all are supported by the guidelines for pharmacologic interventions in obesity management.⁸⁻¹² The article reviews the clinical evidence of bupropion plus naltrexone for obesity management.

Data Sources and Selection

A MEDLINE search (1970 to November 2015) was conducted for English-language articles using the MESH terms obesity, obesity management, weight loss, bupropion, and naltrexone. Five published articles pertinent to the short- and long-term efficacy and safety of bupropion plus naltrexone among overweight or obese patients were critiqued and summarized in this article. Weight loss was the primary endpoint in these 5 trials. One article was excluded, as the primary endpoint was smoking quit rate and, therefore, did not focus on weight loss as its primary endpoint. Another article was excluded, as it was conducted among mice and was a Phase 2 trial among human subjects. Any study with evidence on bupropion or naltrexone monotherapy was not reviewed extensively in this article.

Pharmacology

Bupropion and naltrexone are FDA-approved for separate indications. Bupropion is a dopamine/norepinephrine reuptake inhibitor and approved for depression, seasonal affective disorder, and smoking cessation.^{13,14} Serotonin, norepinephrine, and dopamine are neurohormonal appetite regulators. Bupropion stimulates proopiomelanocortin (POMC) neurons in the hypothalamus to secrete α -melanocyte stimulating hormone.¹⁵⁻¹⁸ The α -melanocyte stimulating hormone has anorexic properties.¹⁵⁻¹⁸ As monotherapy, bupropion 300 to 400 mg per day has been investigated among overweight and obese individuals—with or without depression. Bupropion produced an average 3.4% placebo-subtracted weight loss over 6 to 12 months.¹⁵⁻¹⁷ In these trials, patients with a higher BMI at baseline and who were receiving 400 mg per day had a greater likelihood to achieve 5% weight loss from baseline.¹⁵⁻¹⁷ Based on this early evidence, it was theorized that bupropion could help with weight loss.

Naltrexone is an opioid antagonist and has indications for treatment of alcohol or opioid dependence.¹⁹ While

naltrexone does not have evidence as monotherapy for weight loss, it can augment bupropion's effect on the POMC neurons in the hypothalamus to cause appetite suppression.¹⁵⁻²³ Mu-receptors can cause autoinhibition of POMC neurons, limiting the effect of bupropion.¹⁵⁻²³ By blocking the mu-receptors with naltrexone, there is an increased activity of POMC neurons, promoting weight loss.¹⁵⁻²³ Based on the mechanism of action and evidence from preliminary data, bupropion plus naltrexone was investigated as a combination product for chronic weight management.¹⁷⁻²²

Pharmacokinetics

As an extended-release combination product, bupropion plus naltrexone cannot be taken with a high fat meal due to increased absorption and exposure. In the presence of a high fat meal, naltrexone's area under the curve (AUC) and maximum concentration (C_{max}) increased by 2.1- and 3.7-fold, whereas bupropion's AUC and C_{max} increased by 1.4- and 1.8-fold, respectively. AUC and C_{max} for naltrexone and bupropion remained elevated at steady state concentrations after a high-fat meal.⁸

Hydroxybupropion, threo-hydrobupropion, and erythro-hydrobupropion are the major metabolites of bupropion; these metabolites have a longer half-life and greater chance of accumulation than bupropion. After a single dose of extended-release bupropion for weight loss, the half-life of bupropion was 21 hours, in which steady-state can be achieved within 2 to 4 days. The average half-life is 24 hours, 31 hours, and 51 hours for extended-release bupropion in respect to hydroxybupropion, threo-hydrobupropion, and erythro-hydrobupropion, respectively. Hepatic metabolism through CYP2B6 is the main route for the formation of hydroxybupropion. Bupropion, along with its metabolites, can inhibit the CYP2D6 pathway. Bupropion and its metabolites are mainly eliminated via the kidneys (80%), while 10% is excreted through feces. There is no evidence linking the metabolites to the efficacy or safety of bupropion for weight loss; however, caution should be used in patients taking bupropion with hepatic or renal impairment due to calculated increases in metabolite concentrations.⁸

Naltrexone and its active metabolite (6- β -naltrexol) are primarily excreted via the kidneys (53% to 79%), whereas fecal elimination is the minor elimination pathway. After a single dose of naltrexone, the average half-life was 5 hours with no accumulation of naltrexone but approximately 3 times the accumulation ratio of 6- β -naltrexol (13 hours). Naltrexone should be used cautiously among patients with moderate or severe renal impairment due to the potential accumulation of 6- β -naltrexol.⁸

Concomitant use of bupropion plus naltrexone and monoamine oxidase inhibitors is contraindicated due to the increased risk for hypertensive reactions caused by

bupropion's inhibition of dopamine and norepinephrine reuptake. Bupropion plus naltrexone is not recommended in patients taking opioid pain medications due to naltrexone's blockade of opioid pain receptors. This combination product should be avoided with CYP2B6 inducers, such as certain protease inhibitors and anticonvulsants, which may reduce the efficacy of bupropion by lowering AUC and C_{max} . Coadministration of bupropion plus naltrexone with medications that are metabolized by the CYP2D6 enzyme should be handled with caution due to the effect of bupropion on the isoenzyme and increased risk of adverse events of the concomitant drug. Therefore, a dose reduction may be warranted in bupropion plus naltrexone if prescribed concomitantly with certain antidepressants, antipsychotics, β -blockers, or antiarrhythmics. Lastly, caution should be used when bupropion plus naltrexone is coadministered with other drugs that lower seizure threshold.⁸

Among certain patient populations, dose adjustments may be required. A patient with end-stage renal disease should not take this combination product; however, a patient with moderate to severe renal impairment can be prescribed a limited daily dose of no more than 180/16 mg per day. The maximum dose is 90/8 mg per day for a patient with hepatic disease. Patients should be educated to swallow the tablet whole; the tablet cannot be crushed or chewed, as it is an extended-release product.⁸

Clinical Trials

In the first trial of bupropion plus naltrexone, which had a primary endpoint of weight loss, 419 adult participants with uncomplicated obesity (defined as BMI 30 to 40 kg/m²) were randomized and blinded to placebo, bupropion sustained-release monotherapy (400 mg per day), naltrexone immediate-release monotherapy (48 mg per day), or bupropion (400 mg per day) plus naltrexone (either as 16, 32, or 48 mg per day).¹⁹ Results were analyzed and reported as an intent-to-treat population. Participants receiving the combination regimens had the greatest reduction in weight from baseline after 24 week, compared to placebo, naltrexone 48 mg, and bupropion ($P < .05$). The change in weight from baseline was 1.2% with naltrexone monotherapy, 2.7% with bupropion monotherapy, 5.4% with combination regimen of naltrexone 16 and 32 mg, and 4.3% with combination regimen of naltrexone 48 mg. Fifty-two percent and 51% of participants in the combination regimens of naltrexone 16 and 32 mg achieved weight loss of 5% or more, compared to placebo (15%), naltrexone monotherapy (10%), and bupropion monotherapy (26%; $P < .05$ for these comparisons). There were more adverse events among participants, particularly nausea, for those receiving any combination regimen of bupropion plus naltrexone.¹⁹ Completion rate was 63% among participants, with the lowest rate in the bupropion 400 mg plus naltrexone 48 mg group. The

combination of bupropion 400 mg plus naltrexone 16 and 32 mg demonstrated improvements in weight loss among patients who were obese.¹⁹

Daily dosage strengths of 360 mg of bupropion plus 32 mg of naltrexone were investigated in more than 2000 individuals in the Contrave Obesity Research (COR) program. The program consisted of 4 randomized trials—COR-BMOD, COR-I, COR-II, COR-Diabetes—to assess the effectiveness, safety, and tolerability of bupropion plus naltrexone in overweight and obese individuals. These COR trials were independent of each other but had similarities in study design, patient populations, and endpoints.²⁰⁻²³ Table 1 summarizes the COR trials in terms of study design and inclusion criteria.²⁰⁻²³ The COR-BMOD, COR-I, and COR-II have the same inclusion and exclusion criteria. Patients were excluded from these trials if they had a diagnosis of diabetes mellitus, significant renal or hepatic impairment, condition-induced obesity, significant comorbidities, unstable weight over the previous 3 months, surgical interventions for obesity, contraindications, or drug-drug interactions with bupropion or naltrexone. In the COR-Diabetes trial, exclusion criteria was similar to the other COR trials, but it did not include participants with type 1 diabetes. Bupropion plus naltrexone was available as a combination tablet in 90 mg and 8 mg, respectively, for each trial. The product was titrated weekly for 4 weeks. The initial dose was 1 tablet orally (90/8 mg) in the morning with a maximum dose of 2 tablets (180/16 mg) in the morning and evening (total daily dose of 360/32 mg). In the clinical trials, a predictable response to the combination product was determined if more than 5% of baseline weight occurred at 12 weeks. Primary endpoints were percent change in weight from baseline and proportion of patients achieving 5% or more weight reduction from baseline. Table 2 summarizes the primary endpoints and safety findings from the COR clinical trials.²⁰⁻²³ Within these trials, modified intent-to-treat analysis was conducted for data among all individuals who were randomized at baseline and had one postbaseline weight. Additional details from the clinical trials and related primary outcomes are discussed in further detail below.²⁰⁻²³

The first trial (COR-BMOD) randomized 793 study participants to placebo plus behavior modification (BMOD) or naltrexone SR 16 mg plus bupropion SR 180 mg twice-daily plus BMOD.²⁰ The average patient was a middle-aged (45-46 years), Caucasian female (89% to 91.6%) with a BMI of 36 kg/m² and a weight of 100 kg. All participants received an intensive program of BMOD via registered dietitians, behavioral psychologists, or exercise specialists. Lifestyle modifications were promoted in individual and group sessions. On an individual basis, participants were taught to consume a balanced diet, reduce caloric intake based on body weight, reduce portion sizes, keep a food diary, and exercise 180 minutes per week. During group

Table 1. COR Trials With Bupropion Plus.

Authors	Study Design	Inclusion Criteria
Greenway et al	Randomized (1:1:1), multicenter, double-blinded, placebo-controlled trial	Individuals 18 to 65 years of age with BMI 30 to 45 kg/m ² or 27 to 45 kg/m ² with hypertension or dyslipidemia
Apovian et al	Randomized (2:1), multicenter, double-blinded, placebo-controlled trial	Individuals 18 to 65 years of age with BMI 30 to 45 kg/m ² or 27 to 45 kg/m ² with hypertension or dyslipidemia
Wadden et al	Randomized (1:1:1), multicenter, double-blinded, placebo-controlled trial	Individuals 18 to 65 years of age with BMI 30 to 45 kg/m ² or 27 to 45 kg/m ² with hypertension or dyslipidemia
Hollander et al	Randomized (2:1), multicenter, double-blinded, placebo-controlled trial	Individuals 18 to 70 years of age with type 2 diabetes (+/- oral antihyperglycemic medications, hemoglobin A1c between 7% and 10%, fasting glucose level less than 270 mg/dL) with BMI 27 to 45 kg/m ² , systolic blood pressure less than 145 mm Hg and diabetes blood pressure less than 95 mm Hg

Abbreviation: BMI, body mass index.

sessions, participants were taught about various topics on weight loss, in which activities and other assignments were completed on specifically designed handouts. After 56 weeks, bupropion plus naltrexone plus BMOD showed an average placebo-subtracted weight loss of 4.2% ($P < .001$). There was a statistically significant difference in the proportion of participants who achieved a 5% weight loss with naltrexone SR 16 mg plus bupropion SR 180 mg twice-daily plus BMOD ($P < .001$ vs placebo). This trial showed the effectiveness of a multimodal approach to obesity management, as an active medication was added to a rigorous lifestyle modification program.²⁰

COR-I trial randomized 1742 study participants to either placebo, naltrexone SR 16 mg plus bupropion SR 360 mg per day, or naltrexone SR 32 mg plus bupropion SR 360 mg per day.²¹ The patient population was similar to the

COR-BMOD trial in terms of average age (43-44 years), gender (85% female), ethnicity (74% to 76% Caucasian), and baseline weight (99.5 kg). Participant assessments were conducted at 4-week intervals. All participants were instructed to follow hypocaloric diets (500 kcal per day deficit based on the World Health Organization algorithm for calculating resting metabolic rate) and were given advice on lifestyle modifications (ie, physical activity). After 56 weeks, bupropion plus naltrexone showed a dose-dependent weight loss of 3.7% and 4.8%, respectively, as placebo-subtracted weight loss ($P < .0001$ vs placebo). There was a statistically significant difference in the proportion of participants who achieved a 5% weight loss with naltrexone SR 16 mg plus bupropion SR 360 mg per day ($P = .0099$), as well as naltrexone SR 32 mg plus bupropion SR 360 mg per day ($P = .0079$), compared to placebo. Compared to the COR-BMOD trial, COR-I demonstrated the benefit of bupropion plus naltrexone in accomplishing weight loss results over a 1-year period, with less aggressive lifestyle modifications.²¹

COR-II trial randomized participants ($n = 1496$) to placebo or naltrexone SR 16 mg plus bupropion SR 180 mg twice-daily.²² The average patient was a middle-aged (44 years), Caucasian female (85%) with a BMI of 36 kg/m², and a weight of 100 kg. COR-II had the same intervals for follow-up, and all participants were counseled on the same instructions for lifestyle modifications from the COR-I trial. After 28 weeks, bupropion plus naltrexone showed a greater weight loss, resulting in a placebo-subtracted difference of 5.2% ($P < .001$). There was a statistically significant difference in the proportion of participants who achieved a 5% weight loss with naltrexone SR 16 mg plus bupropion SR 180 mg twice-daily at week 28 ($P < .001$) versus placebo. There were 224 participants with a suboptimal response (ie, nonresponder) to bupropion 360 mg plus naltrexone 32 mg per day. Rerandomization occurred to bupropion 360 mg plus naltrexone 32 or 48 mg, and there was no statistically significant difference among the nonresponders in weight loss (-1.3% vs -1.0% , respectively; $P = .77$). This trial demonstrated similar results to the COR-I in the efficacy of bupropion plus naltrexone for obesity management. The evidence with nonresponders determined that if a patient's response within the first 8 to 12 weeks was not successful, then sustainability with weight loss decreased.²² From the COR-II trial, patients should discontinue the combination product if less than 5% of total body weight from baseline has been lost by week 12 of therapy.⁸

COR-Diabetes trial is the only study conducted among participants with diabetes ($n = 505$).²³ In this trial, there were similarities in the patient population, except the COR-Diabetes trial had older patients (63 years) compared to the COR-BMOD, COR-I, and COR-II trials. During a 3-week escalation period, study participants were given a quarter of the full dose with dose titrations weekly; the full dose was

Table 2. Summary of the Efficacy and Safety Endpoints From the COR Trials²⁰⁻²³.

Study	Patient Population (n)	Interventions	Treatment Period (weeks)	Weight Loss (%)	Proportion of Patients (%) With 5% Weight Loss	Proportion of Patients (%) With 10% Weight Loss	Nausea (%)	Constipation (%)
COR-BMOD ²⁰	793	Placebo + BMOD	56	5.1	60.4	30.2	10.5	14.0
		Bupropion SR 360 mg + Naltrexone SR 32 mg + BMOD		9.3	80.4	55.2	34.1	24.1
COR-I ²¹	1742	Placebo	56	1.3	16.0	7.0	5.3	5.6
		Bupropion SR 360 mg + Naltrexone SR 16 mg		5.0	39.0	20.0	27.2	15.8
		Bupropion SR 360 mg + Naltrexone SR 32 mg		6.1	48.0	25.0	29.8	15.7
COR-II ²²	1496	Placebo	28	1.9	22.3	9.4	6.9	7.1
		Bupropion SR 360 mg + Naltrexone SR 32 mg		6.5	68.8	35.7	29.2	19.1
COR-Diabetes ²³	505	Placebo	56	2.2	24.0	8.0	7.1	7.1
		Bupropion SR 360 mg + Naltrexone SR 32 mg		5.9	53.1	26.3	42.3	17.7

reached by week 4. For randomization, the interventions included placebo or naltrexone SR 32 mg plus bupropion SR 360 mg per day. All participants were instructed to follow hypocaloric diets and were given advice on lifestyle modifications, which included increased physical activity. After 56 weeks, patients receiving bupropion plus naltrexone showed an average placebo-subtracted weight loss of 3.2% ($P < .001$). Approximately 53.1% of participants achieved a 5% weight loss with naltrexone SR 32 mg plus bupropion SR 360 mg per day at week 56, compared to 24% with placebo ($P < .001$). The combination product could be an effective option among patients with type 2 diabetes, who are overweight and obese.

Limitations of Clinical Trials

In general, bupropion plus naltrexone has been evaluated in multiple high-quality trials regarding its safety and efficacy for weight loss. The average participant in each of these trials as listed above is important to note for clinical practice, such as Caucasian ethnicity, classification of obesity, female with hypertension, and hyperlipidemia.²⁰⁻²³ The effectiveness of bupropion plus naltrexone is uncertain in other patient populations, including Hispanic or African American patients. Specifically, the percentage of African American patients varied from 10.6% to 24.5%, whereas Hispanic or Asian patients were accounted for in the other category, but specific percentages were not provided.²⁰⁻²³ There are no trials to show efficacy in patients who have lost more than 4 kg in the last 3 months or previously used bupropion or naltrexone. The COR-I trial was the only trial that included participants who smoke. In this small subset, which was approximately 10% to 11% of participants, there were no

differences observed for percent change in bodyweight or proportion of participants achieving weight loss of 5% or more between treatment groups.²¹ There are no head-to-head trials with other oral agents (ie, orlistat, lorcaserin, or phentermine plus topiramate) or subcutaneous agent (ie, liraglutide) for chronic weight loss. Additional weight loss and continual weight management long term (after 1 year) is uncertain, because current evidence only evaluates participants for 56 weeks. There is also no evidence of sustainability of successful patient weight loss when bupropion plus naltrexone is discontinued. Lastly, the manufacturer of bupropion plus naltrexone had influence over every aspect of the clinical trials. Specifically, the FDA approved bupropion plus naltrexone but will reconsider the statistical analysis for future clinical trials for obesity management.

Adverse Events

In the 4 COR trials, gastrointestinal and central nervous system side effects were observed among participants receiving the combination of bupropion plus naltrexone.²⁰⁻²³ The most common gastrointestinal adverse events were nausea and constipation, which are summarized in Table 2. Nausea can be expected with bupropion or naltrexone monotherapy; therefore, it is not surprising that the combination of these 2 medications caused this side effect. Nausea was mostly mild-to-moderate in intensity and occurred primarily during the dose escalation phase. In most cases, nausea resolved with continuation of the medication. Some patients (4.6% to 9.6%) discontinued bupropion plus naltrexone due to nausea. Patients who were taking bupropion plus naltrexone also experienced statistically significant increased dry mouth and vomiting as compared to placebo-treated patients. The

most common central nervous system adverse events were dizziness and headache. Other discontinuation rates due to adverse events were less than 2.6% and varied among the 4 COR trials.²⁰⁻²³ The overall dropout rate ranged from 21.4% to 24.3% across the COR trials.²⁰⁻²³ The effect of bupropion plus naltrexone on blood pressure and heart rate varied across the COR trials, from significant blood pressure increases to insignificant reductions in blood pressure. Although there are mixed results, blood pressure and heart rate need to be evaluated in potential patients.

Therapeutic Considerations

For a medication to be approved for weight loss by the FDA, the medication should meet specific criteria.⁷ The criteria were created due to withdrawal of medications, such as sibutramine, or failure of developing medications to reach market. Under these criteria, the FDA would be able to compare a medication's benefit-to-risk profile. The first criterion is that any active medication should be statistically superior to placebo, with a placebo-subtracted difference of 5% or more in weight loss from baseline. The second criterion indicates that at least 35% of patients receiving the active medication should achieve a 5% or more weight loss from start to end of the trial. The third criterion is that the active medication has a doubled percentage of patients achieving weight loss, compared to placebo. An active medication only has to meet 1 of the 3 criteria to be reviewed for approval by the regulatory agency.⁷ Bupropion plus naltrexone did not meet the FDA criteria, as it produced an average placebo-subtracted weight loss of 4.9 kg (4.6%); however, the maximum doses of bupropion plus naltrexone did produce greater than 5% placebo-subtracted weight loss in the COR-I and COR-II trials.^{21,22} Among all the COR trials, the number needed to treat is 5 and 7 for a patient to lose 5% or 10% baseline weight loss, respectively.²⁰⁻²³ However, every patient may not tolerate the maximum dose. The maximum dose also had more than 35% of patients with 5% weight loss, which was double than the placebo arm in the COR-I, COR-II, and COR-Diabetes trials.²¹⁻²³ Bupropion plus naltrexone has been investigated in randomized and double-blinded trials. However, results can be overestimated, especially if there is a high dropout rate in a modified intent-to-treat analysis. The attrition rate varied from 42% to 50% in the COR program with an average rate of 53% at 1 year. Twenty-four percent of participants dropped out of the trial due to an adverse event.²⁰⁻²³ From the COR program, the number needed-to-harm would be 9 for a patient to discontinue the maximum dose of bupropion plus naltrexone due to an adverse event and 4 for a patient to encounter the most common adverse event.²⁰⁻²³

It is difficult to compare bupropion plus naltrexone to other oral agents for chronic weight management. When evaluating other evidence to oral medications, bupropion

plus naltrexone has slightly better weight reductions to lorcaserin, but is not as effective as phentermine plus topiramate. Even though it has not been directly compared to phentermine plus topiramate, bupropion plus naltrexone has a different safety profile. In addition, bupropion plus naltrexone is not a controlled substance due to its low abuse potential. Lorcaserin and phentermine plus topiramate have abuse potential and are labeled as controlled schedule IV. Due to blinding methods, it could be difficult to conduct a study between bupropion plus naltrexone and liraglutide.²⁴⁻³⁰ To overcome blinding, dummy injections or oral formulations could be used to compare bupropion plus naltrexone to any dissimilar formulation. Overall, bupropion plus naltrexone can be effective choice when added to lifestyle interventions, such as reduced caloric intake and increased physical activity.

Any patient who may be a candidate for bupropion plus naltrexone should be evaluated prior to initiation based on current disease states, past medical history, and current medications. Bupropion plus naltrexone should not be used among patients with uncontrolled hypertension. Blood pressure and pulse should be monitored prior and during treatment. Patients taking antihypertensive medications with bupropion plus naltrexone should be monitored frequently. From the COR trials, there were positive and negative effects on blood pressure, including an average 1 beat per minute increase in heart rate with bupropion plus naltrexone. There were also positive effects on lipid concentrations, but the clinical relevance of the cardiovascular findings is unclear. There is some preliminary evidence from the Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects with Cardiovascular Risk Factors (LIGHT study).^{31,32} Approximately 9000 patients have been enrolled in the LIGHT study, designed to span 4 years. The study was halted after analysis of 50% of the preliminary data from the first 25% of patients, which showed no benefit and a possible increase in cardiovascular deaths. Based on the data, bupropion plus naltrexone reduced the risk of major cardiovascular events by 41%, including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and cardiovascular mortality. While the results may seem positive, more cardiovascular events occurred with bupropion plus naltrexone in the second quarter of the study (hazard ratio 0.88). Overall, the placebo group had 102 events, compared to 90 with bupropion plus naltrexone. Therefore, the true effect of bupropion plus naltrexone among patients at high risk of cardiovascular events is unknown and not statistically significant.^{31,32} The FDA mandates evaluation of the impact of bupropion plus naltrexone on cardiovascular outcomes; therefore, additional studies can be anticipated.

Patients with anorexia or bulimia nervosa cannot take bupropion plus naltrexone. Bupropion can lower the seizure threshold and should be avoided among patients with

seizures or those are taking antiepileptic medications. Due to naltrexone, patients taking opioids, alcohol, and benzodiazepines should not be prescribed bupropion plus naltrexone as abrupt withdrawal of these substances could cause seizures. In addition, there could be an additive effect on the central nervous system when bupropion plus naltrexone is taken with alcohol. This medication is contraindicated among pregnant women. All patients should be educated about the risk of suicidality, which is a black-box warning due to bupropion.⁸

Summary

Every patient seeking to lose weight should be educated on reduced caloric intake and increased physical activity. Pharmacologic therapy may be indicated if lifestyle modifications have not been successful over 6 months. Clinical trials have shown the efficacy of bupropion plus naltrexone, compared to placebo, in obesity management. The effect of bupropion plus naltrexone has not been defined in special populations, such as patients with sleep apnea, osteoarthritis, and extreme BMIs (ie, above 40 kg/m²). In the published trials, the average weight loss is 6.8% from baseline and 4.3% placebo-subtracted from baseline. In addition, approximately 66% and 42% of patients randomized to treatment lost 5% and 10% of weight from baseline, respectively, with bupropion plus naltrexone. Adverse events are the most common reason patients stop the medication. There is a potential for overestimated results from the clinical trials due to the statistical analysis with a high attrition rate. Currently, a cardiovascular outcome study is ongoing, which will provide additional information about the role of bupropion plus naltrexone for weight loss.^{31,32} Any patient initiated on bupropion plus naltrexone should be followed up closely to monitor efficacy and safety.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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