Naltrexone/Bupropion: An Investigational Combination for Weight Loss and Maintenance

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Summary
Naltrexone/bupropion is an investigational combination for weight loss and maintenance in patients who are obese or have a BMI ≥ 27 kg/m² with comorbid diabetes, hypertension or hyperlipidemia. Pooled results from four phase 3 trials reveal placebo-subtracted mean weight loss of 4.7% (range 3.2–5.2%) with naltrexone/bupropion after 1 year (p < 0.001 vs. placebo in each trial). The placebo-subtracted proportion of patients achieving ≥5% weight loss with naltrexone/bupropion ranged from 26 to 33% (p < 0.001 vs. placebo in each trial). In the majority of phase 3 trials, naltrexone/bupropion significantly improved proportion of patients achieving ≥10% weight loss, waist circumference, triglycerides, high-density lipoprotein, fasting insulin, insulin resistance, and obesity-specific quality of life compared to placebo. In patients with diabetes, naltrexone/bupropion therapy decreased hemoglobin A1c (HbA1c) approximately 0.5% more than placebo (p < 0.001). Common side effects associated with naltrexone/bupropion include nausea, constipation, vomiting, dizziness, and dry mouth. Greater improvement in systolic blood pressure and pulse were seen with placebo compared to naltrexone/bupropion (p < 0.001). Further studies are necessary to determine the effect of naltrexone/bupropion on cardiovascular outcomes. The safety and efficacy of naltrexone/bupropion in weight management is reviewed in this article.

Introduction
An estimated 34% of American adults were obese, and an additional 34% were overweight in 2007–2008 [1]. Obesity is associated with diabetes, hypertension, hyperlipidemia, stroke, heart disease, respiratory problems, osteoarthritis, and several types of cancer [2]. Across all insurance sectors medical spending for an obese patient is approximately 42% higher annually compared to that for an individual with normal body weight [3].

Sustained loss of 5–10% of baseline body weight improves several cardiovascular risk factors, including hypertension, dyslipidemia, insulin resistance, and diabetes [4]. Caloric restriction, exercise, and behavioral modification are the cornerstones of weight management. When lifestyle interventions are unsuccessful, adjunct pharmacotherapy may be considered. The only medication currently approved for long-term weight loss and maintenance is orlistat. Noradrenergic appetite suppressants, such as phentermine, are marketed for short-term use only, a strategy that is not recommended for weight loss [2].

A medication that provides ample weight loss, improves cardiovascular risk, and is associated with an acceptable safety and side effect profile could benefit a widespread patient population. To be considered effective, weight loss medications must meet one of the following 1-year benchmarks outlined by the US Food and Drug Administration (FDA) [5]:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5%, and the difference is statistically significant.
- The proportion of subjects who lose greater than or equal to 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.
A challenge to achieving these benchmarks lies in the body’s mechanisms to maintain energy homeostasis. Caloric restriction and weight loss lead to neurohormonal adjustments which increase food intake and favor weight regain [6]. Thus, synergistic medication combinations for weight loss hold particular promise.

Naltrexone/bupropion (Contrave®; Orexigen Therapeutics, Inc., La Jolla, CA, USA) is an investigational combination therapy being studied for weight loss and maintenance in patients who are obese (BMI ≥ 30 kg/m²) or have a BMI of ≥27 kg/m² with comorbidities of diabetes, hypertension, or hyperlipidemia. Naltrexone is indicated in alcohol and opioid dependence with a usual dose of 50 mg daily [7]. Bupropion is approved for the treatment of major depressive disorder, seasonal affective disorder, and smoking cessation assistance and is typically given in 300 mg daily doses [8]. Both agents have been marketed in the USA since 1985 as monotherapy.

The FDA Advisory Committee voted 13:7 to approve naltrexone/bupropion on December 7, 2010 [9]. However, the FDA did not grant approval and requested a randomized controlled trial be conducted to assess cardiovascular events before the New Drug Application (NDA) is resubmitted [10]. On June 3, 2011, The manufacturer plans to initiate the study which could lead to approval in 2014 [11]. The purpose of this article is to review the pharmacology, efficacy, and safety of naltrexone/bupropion, an investigational combination for weight management.

**Pharmacology**

Naltrexone is a pure opioid antagonist [7, 12]. Bupropion is a weak inhibitor of the neuronal reuptake of norepinephrine and dopamine [8]. These catecholamines stimulate pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus [12]. POMC is a precursor for α-melanocyte stimulating hormone (α-MSH) and β-endorphin. α-MSH acts on melanocortin-4 receptors to decrease food intake, whereas β-endorphin sends feedback inhibition to POMC neurons, decreasing this effect. Bupropion has limited weight loss efficacy as monotherapy likely due to this autoinhibitory feedback. As an opioid antagonist, naltrexone suppresses the negative feedback from β-endorphin. In vitro, bupropion and naltrexone monotherapy reversibly increased the frequency of action potentials to approximately 3–4 Hz in mouse POMC neurons [12]. However, combined application of bupropion and naltrexone increased POMC firing to approximately 11 Hz. Naltrexone/bupropion may also modulate food cravings through an effect on the dopamine reward pathway, as evidenced by improved responses to the question ‘generally, how difficult has it been to control your eating?’ on the Control of Eating questionnaire administered in all phase 3 trials [13].

**Pharmacokinetics**

The pharmacokinetics of naltrexone SR and bupropion SR are displayed in table 1. Naltrexone is reformulated as a sustained release (SR) dosage form in this combination product, which has bioequivalent exposure to naltrexone immediate release (IR) [13, 14].

Naltrexone/bupropion should be used with caution in patients who are elderly or have moderate or severe renal impairment. It should be avoided in patients with severe hepatic disease [7].

**Clinical Studies**

The clinical efficacy of naltrexone/bupropion was compared to each monotherapy and placebo in a multicenter, randomized, double-blind, phase 2 clinical trial [15]. A total of 419 subjects with uncomplicated obesity were randomized to receive either bupropion SR 400 mg/day plus naltrexone IR 16 mg/day, 32 mg/day, or 48 mg/day; bupropion SR 400 mg/day; naltrexone IR 48 mg/day; or placebo. After 24 weeks the naltrexone monotherapy and placebo groups were discontinued with 1.2% and 0.8% body weight loss, respectively. After 48 weeks bupropion monotherapy and bupropion plus naltrexone 16 mg/day, 32 mg/day and 48 mg/day produced mean weight losses of 2.7%, 5.0%, 5.5%, and 6.6%, respectively (p < 0.05 for all combinations vs. monotherapy). Higher attri-
### Table 2. Study design, population characteristics and results for phase 3 trials of naltrexone/bupropion*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Treatment</th>
<th>Mean age (years) / female sex (%) / Caucasian (%) / BMI (kg/m²)</th>
<th>Primary results</th>
<th>Secondary results (NB32 vs. PBO)</th>
</tr>
</thead>
</table>
| Greenway [16]                   | 56 weeks        | 1:1:1     | 44/85/75/36                                                     | change in weight (%) | ≥10% weight loss (%): 25 vs. 7<br>≥15% weight loss (%): 12 vs. 2
|                                 | MC, R,          | NB16      |                                                   | NB16: –5.0<sup>a</sup> | change in waist (cm): –6.2 vs. –2.5
|                                 | DB, PC          | NB32      |                                                   | NB32: –6.1<sup>a</sup> | triglycerides (%): –12.7 vs. –3.1<sup>a</sup>
|                                 | N = 1,742       | PBO       |                                                   | PBO: –1.3       | HDL (mg/dl): 3.5 vs. 0.0<sup>a</sup>
|                                 |                 |           |                                                   | ≥5% weight loss (%) | LDL (mg/dl): –4.3 vs. –3.1<sup>b</sup>
|                                 |                 |           |                                                   | NB16: 39<sup>a</sup> | HsCRP (%): –29.0 vs. –16.7<sup>a</sup>
|                                 |                 |           |                                                   | NB32: 48<sup>a</sup> | FBG (mg/dl): –3.2 vs. –1.3<sup>a</sup>
|                                 |                 |           |                                                   | PBO: 16          | fasting insulin (%): –17.1 vs. –4.6
|                                 |                 |           |                                                   |                  | HOMA<sub>IN</sub> (%): –20.2 vs. –5.9
|                                 |                 |           |                                                   |                  | IWQOL-Lite score: 12.7 vs. 8.6<sup>a</sup>
| Hollander abstract [19]         | 56 weeks,       | 2:1:1     | 54/54/80/37                                                     | change in weight (%) | ≥10% weight loss (%): 19 vs. 6
|                                 |                 | DB, PC    |                                                   | PBO: –1.8        | HbA1c < 6.5% (%): 21 vs. 10<sup>a</sup>
|                                 |                 | N = 505   |                                                   | ≥5% weight loss (%) | change in HbA1c (%): –0.63 vs. –0.14
|                                 |                 |           |                                                   | NB32: 45         | waist (cm): –5.0 vs. –2.9<sup>a</sup>
|                                 |                 |           |                                                   | PBO: 19          | triglycerides (%): –11.2 vs. –0.8<sup>a</sup>
|                                 |                 |           |                                                   |                  | HDL (mg/dl): 3.0 vs. –0.3
|                                 |                 |           |                                                   |                  | LDL (mg/dl): –1.4 vs. 0.0<sup>a</sup>
|                                 |                 |           |                                                   |                  | HsCRP (%): –20.9 vs. –13.3<sup>a</sup>
|                                 |                 |           |                                                   |                  | FBG (mg/dl): –11.9 vs. –4.0<sup>a</sup>
|                                 |                 |           |                                                   |                  | fasting insulin (%): –13.5 vs. –10.4<sup>a</sup>
|                                 |                 |           |                                                   |                  | HOMA<sub>IN</sub> (%): –20.6 vs. –14.7<sup>a</sup>
|                                 |                 |           |                                                   |                  | IWQOL-Lite score: 9.3 vs. 7.9<sup>a</sup>
| Rubino abstract [18]            | 56 weeks,       | 2:1:1     | 44/84/85/36                                                     | change in weight (%) | ≥10% weight loss (%): 28 vs. 6
| FDA Advisory [13]               |                 | MC, R,    |                                                   | NB32: –6.4       | HbA1c < 7.0% (%): 44 vs. 26
|                                 |                 | DB, PC    |                                                   | PBO: –1.2        | HbA1c < 6.5% (%): 21 vs. 10<sup>a</sup>
|                                 |                 | N = 1,496 |                                                   | ≥5% weight loss (%) | change in HbA1c (%): –0.63 vs. –0.14
|                                 |                 |           |                                                   | NB32: 51         | waist (cm): –5.0 vs. –2.9<sup>a</sup>
|                                 |                 |           |                                                   | PBO: 17          | triglycerides (%): –11.2 vs. –0.8<sup>a</sup>
|                                 |                 |           |                                                   |                  | HDL (mg/dl): 3.0 vs. –0.3
|                                 |                 |           |                                                   |                  | LDL (mg/dl): –1.4 vs. 0.0<sup>a</sup>
|                                 |                 |           |                                                   |                  | HsCRP (%): –20.9 vs. –13.3<sup>a</sup>
|                                 |                 |           |                                                   |                  | FBG (mg/dl): –11.9 vs. –4.0<sup>a</sup>
|                                 |                 |           |                                                   |                  | fasting insulin (%): –13.5 vs. –10.4<sup>a</sup>
|                                 |                 |           |                                                   |                  | HOMA<sub>IN</sub> (%): –20.6 vs. –14.7<sup>a</sup>
|                                 |                 |           |                                                   |                  | IWQOL-Lite score: 9.3 vs. 7.9<sup>a</sup>
| Wadden [17]                     | 56 weeks,       | 1:3:1     | 46/90/70/37                                                     | change in weight (%) | ≥10% weight loss (%): 42 vs. 20
|                                 |                 | MC, R,    |                                                   | NB32+BMOD: –9.3  | ≥15% weight loss (%): 29 vs. 11
|                                 |                 | DB, PC    |                                                   | PBO+BMOD: –5.1   | change in waist (cm): –10.0 vs. –6.8
|                                 |                 | +BMOD     |                                                   | NB32+BMOD: 66    | triglycerides (%): –16.6 vs. –8.5<sup>a</sup>
|                                 |                 | PBO       |                                                   | PBO+BMOD: 43     | HDL (mg/dl): 4.1 vs. 0.9
|                                 |                 |           |                                                   |                  | LDL (mg/dl): 5.4 vs. 8.1<sup>b</sup>
|                                 |                 |           |                                                   |                  | HsCRP (%): –25.9 vs. –16.8<sup>a</sup>
|                                 |                 |           |                                                   |                  | FBG (mg/dl): –2.4 vs. –1.1<sup>b</sup>
|                                 |                 |           |                                                   |                  | fasting insulin (%): –28.0 vs. –15.5<sup>a</sup>
|                                 |                 |           |                                                   |                  | HOMA<sub>IN</sub> (%): –29.9 vs. –16.6<sup>a</sup>
|                                 |                 |           |                                                   |                  | IWQOL-Lite score: 13.4 vs. 10.3

BMOD = Behavioral modification; DB = double-blind; FBG = fasting blood glucose; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HOMA<sub>IN</sub> = homeostasis model assessment for insulin resistance; HsCRP = high-sensitivity C-reactive protein; IWQOL = Impact of Weight on Quality of Life; LDL = low-density lipoprotein; MC = multicenter; NB16 = naltrexone 16 mg plus bupropion; NB32 = naltrexone 32 mg plus bupropion; PBO = placebo; PC = placebo-controlled; R = randomized; wk = week; yr = year.

*p < 0.001 for all comparisons between naltrexone/bupropion and placebo except where noted.

<sup>a</sup>p < 0.0001.

<sup>b</sup>Not significant.

<sup>c</sup>p < 0.05.
tion rates were observed in the bupropion plus naltrexone 48 mg/day group (73%) compared to the bupropion plus naltrexone 16 mg/day and 32 mg/day groups (52% and 46%, respectively). Early discontinuation during the first 24 weeks accounted for most cases, with adverse events and lost to follow-up cited as the most common reasons.

The Contrave Obesity Research (COR) Program consists of four phase 3 trials: COR-I, COR-II, COR-Behavioral Modification (COR-BMOD), and COR-Diabetes Mellitus (COR-DM). The study designs, population characteristics, and results are displayed in table 2. All studies were designed and sponsored by Orexigen Therapeutics, Inc. The COR-I, COR-II, and COR-BMOD studies included patients who were 18–65 years of age with a BMI of 30–45 kg/m² without comorbidities or a BMI of 27–45 kg/m² with controlled hypertension and/or dyslipidemia [13, 16–18]. Patients were excluded if they had diabetes. The COR-DM study included patients with a BMI of 27–45 kg/m² who were 18–70 years of age, were diagnosed with type 2 diabetes (hemoglobin A1c (HbA1c) 7–10%), and were not prescribed insulin [13, 19]. All trials excluded patients with type 1 diabetes; cerebrovascular, cardiovascular, hepatic, renal, or psychiatric disease; previous surgical or device intervention for obesity; seizure disorder; or recent history of drug or alcohol dependence [13]. Co-primary endpoints in the COR Program were percentage change in body weight and proportion of participants with a decrease in body weight of at least 5% from baseline at week 56.

COR-I, COR-II, and COR-DM trial participants received lifestyle counseling at baseline and every 12 weeks [13, 16]. Lifestyle recommendations included decreasing energy consumption by 500 kcal/day and increasing physical activity. Participants in the COR-BMOD trial attended 90-min multidisciplinary group visits weekly for 16 weeks and monthly thereafter [17]. Subjects were prescribed 1,200–2,000 kcal/day diets based on initial body weight and encouraged to engage in physical activity for 180 min/week for the first 6 months, increasing to 360 min/week thereafter.

Results from the COR-II trial met the first FDA efficacy benchmark for mean percent weight loss. The COR-I, COR-II, and COR-DM trials met the second FDA efficacy benchmark for proportion of subjects with at least 5% weight loss. In the majority of phase 3 studies, treatment with naltrexone/bupropion resulted in significant improvement in percentage of patients achieving ≥10% weight loss, waist circumference, triglycerides, high-density lipoprotein (HDL), fasting insulin, insulin resistance, and obesity-specific quality of life as assessed through the Impact of Weight on Quality of Life-Lite questionnaire.

**Adverse Effects**

Nausea (33 vs. 7%), constipation (19 vs. 7%), headache (18 vs. 10%), vomiting (11 vs. 3%), dizziness (10 vs. 3%), insomnia (9 vs. 6%), dry mouth (8 vs. 2%), and diarrhea (7% vs. 5%) were common side effects that occurred more frequently with naltrexone/bupropion than placebo [13]. Tremor, hot flush, tinnitus, upper abdominal pain, and hyperhidrosis occurred in approximately 3–4% of patients treated with naltrexone/bupropion and 1% of patients treated with placebo. In pooled phase 3 trials, adverse effects led to discontinuation in 24% of the naltrexone/bupropion group and 12% of the placebo group. Nausea, headache, dizziness, and vomiting were the most frequent adverse effects leading to discontinuation. Serious adverse effects were infrequent and equally distributed among treatment groups (2.5 vs. 1.7%), except more patients receiving naltrexone/bupropion experienced cholecystitis/cholelithiasis (0.3 vs. 0.07%). Depression-related events occurred in 2.9% of the naltrexone/bupropion group and 3.4% of the placebo group. Three patients assigned to naltrexone/bupropion had a myocardial infarction (0.12%), but overall cardiac disorders did not differ between groups (0.2 vs. 0.3%). Two patients (0.06%) had a seizure while assigned to naltrexone/bupropion therapy.

Greater improvement in blood pressure and pulse were seen with placebo compared to naltrexone/bupropion [13]. After 56 weeks of treatment in pooled phase 3 trials, change in systolic blood pressure (SBP) from baseline was −0.86 mm Hg and −2.33 mm Hg with naltrexone/bupropion and placebo, respectively (p < 0.001). The 56-week change in diastolic blood pressure (DBP) was −1.01 mm Hg and −1.50 mm Hg, respectively (p = 0.08). The between-group differences for SBP and DBP were the greatest after 8 weeks of treatment. Hypertension was reported as an adverse event in 5.3% of patients assigned naltrexone/bupropion and 4.0% of those assigned placebo. At week 56, change in pulse from baseline was 0.3 beats per minute (bpm) versus −0.98 bpm with naltrexone/bupropion and 1% of patients treated with naltrexone/bupropion and placebo, respectively (p < 0.001). Tachycardia occurred at a rate of 0.6% with naltrexone/bupropion and 0.2% with placebo. The greatest between-group difference for pulse occurred at week 24. Patients who lost at least 5% body weight with naltrexone/bupropion had a similar change in blood pressure and pulse compared to those who did not achieve 5% weight loss with placebo.

**Drug Interactions**

Bupropion is metabolized by CYP2B6 and inhibits CYP2D6 [8, 13]. Medications that induce CYP2B6, including lopinavir/ritonavir, rifampin, carbamazepine, phenoxytoin and phenobarbital, may decrease the effect of bupropion. Medications that inhibit CYP2B6 are not expected to increase the effects of bupropion due to its multiple metabolic pathways [13]. Bupropion may increase the effect of CYP2D6 substrates, including selective serotonin reuptake inhibitor and tricyclic antidepressants, venlafaxine, antipsychotics, metoprolol, propafenone, and flecainide. Bupropion is contraindicated with concomi-
tant monoamine oxidase inhibitors and should not be used with medications that lower the seizure threshold [8]. Naltrexone should not be used in patients using opioid analgesics [7].

**Dosage and Administration**

Naltrexone/bupropion is formulated as 4/90 mg and 8/90 mg tablets [13]. One 4/90 mg tablet daily may be considered as a conservative initial dose. The recommended initial dose titration schedule for 8/90 mg tablets is as follows: one tablet in the morning for week 1, one tablet twice daily for week 2, two tablets in the morning and one in the evening for week 3, and two tablets twice daily starting on week 4. The maintenance dose is 16 mg of naltrexone SR and 180 mg of bupropion SR (taken as two 8/90 mg tablets) twice daily. It can be taken with or without food.

**Future Application**

Naltrexone/bupropion is an investigational combination for weight management. It is being developed as an adjunct to lifestyle modification for weight loss and maintenance in patients who are obese or have a BMI of ≥27 kg/m² with obesity-related disease (e.g., diabetes, dyslipidemia, or hypertension). The agent is also currently in phase 3 trials for smoking cessation. Pooled results from four phase 3 trials reveal placebo-subtracted mean weight loss of 4.7% with naltrexone/bupropion [13]. The placebo-subtracted proportion of patients achieving ≥5% weight loss with naltrexone/bupropion ranged from 26 to 33%.

Naltrexone/bupropion has not been studied in head-to-head comparison with other medications for weight management. The lipase inhibitor orlistat is currently the only medication FDA approved for long-term weight management. In October 2010, the FDA denied approval of the investigational serotonin 2C agonist lorcaserin (Lorcet®) and combination phentermine/topiramate (Qnexa®, Vivus Pharmaceuticals, San Diego, CA, USA) for weight management [20, 21]. Additional information about carcinogenicity in rats with lorcaserin and teratogenicity and cardiovascular risk with phentermine/topiramate was requested prior to resubmission of the NDAs. Placebo-controlled trials of individual agents suggest that naltrexone/bupropion has greater weight loss efficacy than orlistat or lorcaserin, but is less effective than phentermine/topiramate. Prescription dose orlistat results in approximately 2.9% placebo-subtracted body weight loss, and 21% more subjects attained ≥5% weight loss with orlistat compared to placebo [22]. Patients assigned to lorcaserin 10 mg twice daily lost approximately 2.5% more body weight compared to placebo, and 25% more patients achieved ≥5% weight loss in phase 3 trials [23, 24]. Medium-dose (7.5/46 mg) and high-dose (15/92 mg) phentermine/topira-

caine and lorcaserin, and thrice daily for orlistat.

Naltrexone/bupropion treatment resulted in significant improvement in several cardiometabolic risk factors, including waist circumference, triglycerides, and HDL [13]. Low-density lipoprotein and C-reactive protein were improved, but differences did not reach significance in all trials. Compared to placebo, naltrexone/bupropion significantly improved fasting insulin and insulin resistance in patients without diabetes and reduced HbA1c 0.5% in patients with diabetes. The effect of naltrexone/bupropion on cardiometabolic risk factors is consistent with the benefits of clinically meaningful weight loss; however, the improvement in blood pressure and pulse were attenuated.

The effect of weight loss agents on blood pressure and pulse is an important consideration. Recently, the noradrenergic/serotonergic appetite suppressant sibutramine was removed from the market due to an increased risk of cardiovascular events in high-risk patients [27]. Compared to placebo, sibutramine therapy increased SBP by 1.7 mm Hg, DBP by 2.4 mm Hg, and pulse by 4.5 bpm [22]. Naltrexone/bupropion therapy decreased SBP and DBP with differences of approximately 1.5 and 0.5 mm Hg, respectively, compared to placebo. Naltrexone/bupropion increased heart rate by approximately 1 bpm compared to placebo. Providers should consider discontinuation of naltrexone/bupropion in patients who do not achieve ≥5% weight loss after 4 months of therapy or who experience clinically relevant and sustained increases in blood pressure or pulse [13].

**Conclusion**

Based on a review of the available data, naltrexone/bupropion is an effective agent for weight management. Further studies are necessary to determine the effect of naltrexone/bupropion on cardiovascular outcomes.

**Disclosure Statement**

The authors have no conflicts of interest to disclose.
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