

# Naltrexone SR/Bupropion SR (Contrave)

## A New Approach to Weight Loss in Obese Adults

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### INTRODUCTION

Obesity is an epidemic with a high impact in the U.S.,<sup>1</sup> with more than 72 million adults affected.<sup>1</sup> The prevalence of this disease is rapidly increasing; in 2009, almost 2.4 million more adults were considered obese than in 2007.<sup>1</sup> Obesity in adults is defined as having a body mass index (BMI) of 30 kg/m<sup>2</sup> or higher.<sup>2</sup> In 2008, 34% of American adults were considered obese.<sup>3</sup>

Obesity increases the risk of serious health conditions such as coronary heart disease, type-2 diabetes, metabolic syndrome, stroke, and some cancers. An estimated 300,000 deaths per year may be attributed to obesity. Individuals who are considered obese have a 50% to 100% increased risk of premature death from all causes when compared with individuals at a healthy weight.<sup>3</sup> All-cause mortality is generally lowest with a BMI of 20.0 to 24.9 kg/m<sup>2</sup>.<sup>4</sup>

Weight gain leading to obesity occurs when a person's food intake is greater than energy expended. Genes, metabolism, cultural background, and socioeconomic status can contribute to weight gain; behavior and environment also play a large role. The latter two factors provide the greatest opportunity for prevention and treatment.<sup>2</sup>

Although diet and lifestyle changes

should always be encouraged, many people have difficulty making these changes and are not able to maintain weight loss with these tools alone. Pharmacological treatments can be beneficial in regulating food intake and body weight in those individuals. A combination product of naltrexone sustained release (SR) and bupropion SR (Contrave, Orexigen Therapeutics) is being studied for the long-term treatment of obesity. This product works by stimulating and inhibiting various pathways of the central nervous system (CNS), resulting in weight reduction and maintenance of weight loss.

### CHEMICAL AND PHYSICAL PROPERTIES

Naltrexone, a pure opioid antagonist, is a synthetic relative of oxymorphone and naloxone. A white crystalline compound, it is soluble in water.<sup>5</sup>

Bupropion, an antidepressant of the amino-ketone class, is a dopamine reuptake inhibitor. Its structure closely resembles that of diethylpropion, an anorexiant and sympathomimetic agent. Bupropion is a white crystalline compound that is highly soluble in water. It is related to the phenylethylamines, which are known for their stimulant effects.<sup>5</sup>

### MECHANISM OF ACTION

The mechanism by which the combination of naltrexone SR/bupropion SR induces weight loss is not entirely understood. Research on CNS pathways that regulate food intake and body weight has identified the hypothalamic melanocortin system and the mesolimbic reward system. These systems are the target of this combination.<sup>6</sup>

Pro-opiomelanocortin (POMC)-producing neurons in the hypothalamus release  $\alpha$ -melanocyte-stimulating hormone (MSH) and  $\beta$ -endorphin.  $\alpha$ -MSH mediates the anorectic effect of POMC, whereas  $\beta$ -endorphin is responsible for autoinhibitory feedback, which inactivates the anorectic effect.<sup>7-9</sup> Bupropion can be used to stimulate the POMC neu-

rons, whereas naltrexone can be used to block the autoinhibitory feedback that is associated with a decline in weight reduction.<sup>7,8</sup> It is suggested that the combination's mechanism of action might also regulate the mesolimbic reward pathways, which may lead to further weight reduction by modulating reward values and goal-oriented behaviors.<sup>6,8</sup>

### PHARMACOKINETICS

#### Absorption and Distribution<sup>5</sup>

Naltrexone undergoes rapid and almost complete absorption after oral administration. Approximately 96% of the dose is absorbed from the gastrointestinal (GI) tract. Peak plasma levels ( $C_{max}$ ) of naltrexone, as well as those of the active metabolite 6- $\beta$ -naltrexol, occur within one hour after oral administration. Protein binding of naltrexone is only 21%.

Bupropion is rapidly absorbed after oral administration. The time to  $C_{max}$  is approximately five hours. Administration with food does not affect  $C_{max}$  or bupropion's area-under-the-curve (AUC) concentration. Bupropion is 84% protein-bound.

#### Metabolism and Elimination<sup>5</sup>

Naltrexone undergoes extensive first-pass metabolism, and oral bioavailability ranges from 5% to 40%. This medication is metabolized via a non-cytochrome-mediated dehydrogenase conversion to 6- $\beta$ -naltrexol, an active metabolite, and two other minor metabolites, 2-hydroxy-3-methoxy-6- $\beta$ -naltrexol and 2-hydroxy-3-methylnaltrexone. Although the parent drug and its metabolites are excreted mainly by the kidney, the fecal route is considered a minor elimination pathway. The mean elimination half-life of naltrexone is four hours, and the mean elimination half-life of 6- $\beta$ -naltrexol is 13 hours.

Bupropion undergoes extensive hepatic metabolism via cytochrome P450 (CYP) 2B6 to hydroxybupropion as well as non-CYP-mediated metabolism to erythrohydrobupropion and threo-hydrobupropion. All three metabolites are

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active, but their activity is only 20% to 50% as potent as that of the bupropion. The drug is excreted primarily by the kidney as metabolites.

## ADVERSE DRUG EFFECTS

According to two published clinical trials,<sup>6,7</sup> the most commonly reported adverse drug events (AEs) for naltrexone SR/bupropion SR were gastrointestinal in nature. Nausea was reported in 27% to 34% of participants, with an increased incidence associated with a higher dosage of the naltrexone component. Headache was reported more often in treatment groups (14% to 24% of participants) than in placebo groups.

In both clinical trials, the incidence of constipation (15%–24%), dizziness (7%–14%), and dry mouth (8%) was higher with the study drug than with placebo. In one of the trials, there were reports of transient increases in systolic blood pressure (BP) by about 1.5 mm Hg. However, there was a mean decrease in systolic BP, compared with baseline, at the end of both studies.

## DRUG INTERACTIONS<sup>5</sup>

There are no known significant drug-drug interactions involving naltrexone. There is a potential for drug interactions with bupropion because of its extensive metabolism, especially with agents that are metabolized by the CYP 2B6 isoenzyme. Bupropion is not metabolized by CYP 2D6, but there is a potential for a drug interaction when it is given with medications that are metabolized by this isoenzyme.

## CLINICAL EFFICACY

### Greenway et al.<sup>6</sup> and Wadden et al.<sup>7</sup>

Two 56-week, multicenter, randomized, double-blind, placebo-controlled trials of naltrexone SR/bupropion SR were conducted. The phase 3 Greenway trial was designed to investigate weight loss in overweight and obese adults. The Wadden trial was designed to examine the efficacy and safety of naltrexone SR/bupropion SR as an adjunct to intensive behavior modification in the treatment of obesity. To be eligible to be enrolled in either study, patients had to meet the following criteria:

- They had to be between 18 and 65 years of age.

- They had to have a BMI of 30 to 45 kg/m<sup>2</sup> and uncomplicated obesity, or a BMI of 27 to 45 kg/m<sup>2</sup> and controlled hypertension or dyslipidemia, or both.
- Women of childbearing age had to be using effective contraception.

Patients were excluded from these studies if:

- their obesity was of known endocrine origin (i.e., either type-1 or type-2 diabetes).
- they had cerebrovascular, cardiovascular, hepatic, or renal disease.
- they had undergone previous surgery or a device intervention for obesity.
- they had lost or gained more than 4 kg within three months before randomization in the study.
- they had a history of seizures, serious psychiatric illness, or drug or alcohol misuse in the previous 12 months.
- bupropion or naltrexone had been prescribed in the preceding 12 months.
- they were pregnant or lactating.

In the Greenway trial, of the 1,742 patients who were enrolled and received treatment, 870 completed the 56 weeks of treatment. In a 1:1:1 ratio, participants received naltrexone SR 32 mg/bupropion SR 360 mg (n = 583), naltrexone SR 16 mg/bupropion SR 360 mg (n = 578), or matching placebo (n = 581). A mild hypocaloric diet and an exercise program were also prescribed for all participants.

The Wadden study included 793 participants who were randomly assigned, in a 1:3 ratio, to receive either placebo or naltrexone SR 32 mg/day plus bupropion SR 360 mg/day. Participants in both groups were prescribed an intensive program of behavior modification. Baseline demographics were similar in all groups.

Primary efficacy endpoints were the percentage of change in body weight and the proportion of patients who achieved a decrease of 5% or more in weight from baseline at week 56. Numerical results of the primary outcome measures are listed in Table 1.

At the end of the study, participants receiving naltrexone SR 32 mg lost more

weight than the groups receiving naltrexone SR 16 mg and placebo. More participants in the naltrexone SR/bupropion SR groups achieved a decrease in body weight of 5% or more than the placebo subjects; however, a higher proportion of participants receiving naltrexone SR 32 mg lost more weight and achieved a weight loss of 5% or more compared with those receiving naltrexone SR 16 mg.

Additional endpoints were the proportion of participants with a decrease in body weight of 10% or more, a decrease of 15% or more, change in cardiometabolic risk factors, patient-reported measures of appetite, control of eating and food craving, depressive symptoms, and weight-related quality of life. Improvements were seen in all additional endpoints for both naltrexone SR/bupropion SR groups, including significant decreases in waist circumference, insulin resistance, and lipid levels. Participants reported reduced hunger and greater ability to control eating. However, only participants in the Greenway trial reported more control over food cravings.

The most commonly reported AE in the naltrexone SR/bupropion SR groups was mild-to-moderate, transient nausea (Table 2). The rate of nausea was highest during dose escalation, and the rate of onset seemed to plateau after the full dose was reached. Other AEs reported were constipation, dizziness, and dry mouth.

In the Greenway trial, the naltrexone/bupropion groups experienced a transient increase in systolic BP. This increase of approximately 1.5 mm Hg was not observed in the Wadden trial; however, an overall decrease in systolic BP from baseline was noted at the end of both studies.

Rates of discontinuation of treatment were similar between all naltrexone SR/bupropion SR groups. More treated participants stopped therapy because of AEs, compared with the placebo participants, who withdrew because of insufficient weight loss.

Greenway et al. concluded that naltrexone SR/bupropion SR would be a beneficial addition to the management of obesity by improving the ability to control eating behavior and response to food cravings. This combination has the potential to facilitate adherence to lifestyle modifications and produce clinically

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**TABLE 1 Primary and Secondary Outcomes for Participants Completing 56 Weeks Of Contrave Therapy in Two Trials**

	Greenway et al.*			Wadden et al.†	
	Placebo (n = 290)	NBSR 16 mg (n = 284)	NBSR 32 mg (n = 296)	Placebo (n = 106)	NBSR 32 mg (n = 301)
Change in body weight (%)	-1.8%	-6.7%	-8.1%	-7.3%	-11.5%
Change in body weight (kg)	-1.9	-6.5	-8.0		
Participants with a weight loss of 5% or more	67 (23%)	155 (55%)	183 (62%)	60.4%	80.4%
Participants with a weight loss of 10% or more	31 (11%)	85 (30%)	102 (34%)	30.2%	55.2%
Participants with a weight loss of 15% or more	9 (3%)	40 (14%)	51 (17%)	17.9%	39.5%

NBSR = naltrexone SR/bupropion SR combination.  
 The dose of naltrexone SR is noted in the table (16 and 32 mg). The dose of bupropion SR is fixed at 360 mg/day.  
 \* For all comparisons,  $P < 0.0001$  compared with placebo.  
 † For all comparisons,  $P < 0.001$ .

significant weight loss in obese people.

The Wadden investigators concluded that naltrexone SR/bupropion SR plus an intensive program of behavioral modification produced significantly greater mean weight loss compared with behavior modification alone. The findings provide additional support for the efficacy of naltrexone SR/bupropion SR combined therapy for weight management.

The efficacy of Contrave is also discussed in the article by Motycka et al. on page 288 in this month's issue of *P&T*.

**DISCUSSION**

Naltrexone SR/bupropion SR (Contrave), developed by Orexigen, had been in clinical trials for the long-term treatment of obesity in adults. In March 2010, Orexigen had submitted a New Drug Application (NDA) to the FDA for regu-

latory approval. In February 2011, however, the FDA declined its approval because of concerns about the long-term cardiovascular safety profile in overweight and obese subjects. The FDA advised Orexigen that before Contrave could be approved, the company had to conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to show that the risk of major cardiovascular AEs in overweight and obese patients receiving the drug does not adversely affect the risk-benefit profile. Orexigen plans to work closely with the FDA to determine the next steps in the approval process.<sup>10,11</sup>

Contrave is the latest in a string of proposed weight-loss drugs that have been rejected by the FDA. In October 2010, the FDA rejected the NDA for lorcaserin (APD-356, Lorcqess, Arena) stating that

safety concerns outweighed the drug's "marginal" effectiveness in weight loss because of a possible link between the drug and tumors in rats.<sup>12</sup> In the same month, the FDA also rejected the NDA for a topiramate/phentermine combination (Qnexa, Vivus) and forced the withdrawal of sibutramine (Meridia, Abbott) from the market after 13 years because of an increased risk of heart attacks and strokes.<sup>12,13</sup> The FDA requested an evaluation of Qnexa's potential for causing birth defects and heart problems.<sup>13</sup>

The FDA has not approved any new prescription oral weight-loss drug since orlistat (Xenical, Roche/Genentech) in 1999. Orlistat remains the only drug approved for long-term use in weight management. Alli (GlaxoSmithKline) is an FDA-approved nonprescription form of orlistat. A study from Canada cautions

**TABLE 2 Commonly Reported Adverse Events in Two Trials of Contrave**

	Greenway et al.*			Wadden et al.		
	Placebo (n = 569)	NBSR 16 mg (n = 569)	NBSR 32 mg (n = 573)	Placebo (n = 200)	NBSR 32 mg (n = 584)	P Value
Nausea	30 (5.3%)	155 (27.2%)	171 (29.8%)	21 (10.5%)	199 (34.1%)	<0.001
Headache	53 (9.3%)	91 (16.9%)	79 (13.8%)	35 (17.5%)	139 (23.8%)	0.076
Constipation	32 (5.6%)	90 (15.8%)	90 (15.7%)	28 (14.0%)	141 (24.1%)	0.003
Dizziness	15 (2.6%)	44 (7.7%)	54 (9.4%)	9 (4.5%)	85 (14.6%)	<0.001
Vomiting	14 (2.5%)	36 (6.3%)	56 (9.8%)	13 (6.5%)	64 (11.0%)	0.074
Dry mouth	11 (1.9%)	42 (7.4%)	43 (7.5%)	6 (3.0%)	47 (8.0%)	0.014

NBSR = naltrexone SR/bupropion SR combination.  
 The dose of naltrexone SR is noted in the table (16 and 32 mg). The dose of bupropion SR is fixed at 360 mg/day.  
 \* For all comparisons,  $P < 0.05$  compared with placebo.  
 P values for Wadden et al. are noted in the table.

of a possible link between orlistat and renal disease.<sup>14</sup> However, this information is not established yet, as this was only an observational study. It may be prudent to monitor renal function periodically in patients taking orlistat.

In 1997, the fenfluramine–phentermine (Fen-Phen) diet-drug combination was pulled from the market because of reports of damaged heart valves. This resulted in costly legal settlements. Since then, drug companies have shied away from developing weight-loss drugs.<sup>10</sup> The recent string of rejections from the FDA may lead to further hesitation from the few drug companies that are still trying to make headway in the weight-loss market. With the obesity epidemic on the rise, this delay is truly unfortunate.

## CONCLUSION

The effects of naltrexone SR/bupropion SR (Contrave) may be beneficial in the long-term treatment of adult obesity, but further investigation of the drug's safety profile is required before the FDA can grant approval. Studies have shown benefits of greater reductions in weight when compared with dietary changes or behavior therapy alone. Along with behavior and dietary modifications, this medication decreased body weight by 5% to 15% and sustained weight loss; however, dietary and lifestyle changes should always remain the first-line treatment of obesity. If and when Contrave becomes available in the marketplace, clinicians should assess whether a patient is committed to weight loss goals and lifestyle changes before prescribing this product.

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