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Naltrexone-Extended Release plus Bupropion-Extended Release for Treatment of Obesity

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In September 2014, a proprietary formulation of naltrexone-extended release plus bupropion-extended release (NB) (brand name, Contrave) was approved by the US Food and Drug Administration (FDA),¹ becoming the fourth medication approved for long-term weight management in patients with obesity.² Liraglutide (brand name, Saxenda), a glucagon-like peptide 1 receptor agonist, was also approved for obesity treatment in December 2014. Both naltrexone and bupropion are FDA-approved for other indications as monotherapies: bupropion, a dopamine/norepinephrine reuptake inhibitor, is approved to treat depression and to aid smoking cessation. Naltrexone, an opioid receptor antagonist, is approved to treat alcohol and opioid dependence.

Bupropion was investigated, but never FDA-approved, as monotherapy for obesity; studies found ~2.8kg placebo-subtracted weight loss at 6–12 months.³ Among its effects, bupropion is thought to stimulate secretion of anorexigenic α -melanocyte stimulating hormone (α MSH) from pro-opiomelanocortin-producing hypothalamic cells, but may also simultaneously induce secretion of the endogenous opioid products of pro-opiomelanocortin that might inhibit α MSH secretion, limiting bupropion's effectiveness. Naltrexone monotherapy has little efficacy for weight management. However, because naltrexone might specifically counteract the autoinhibitory actions of bupropion-stimulated endogenous opioids, NB combination therapy was investigated for obesity treatment.

NB is FDA-approved for adults with BMI $\geq 30\text{kg/m}^2$ or with BMI $\geq 27\text{kg/m}^2$ plus obesity-related comorbidities. Treatment is initiated with one 8mg naltrexone/90mg bupropion

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SZY reports no conflicts of interest. JAY reports that in 2015 he will be a site Principal Investigator for a multi-center trial to be conducted under a CRADA between NICHD and Zafgen Inc. to study beloranib for amelioration of obesity in the Prader-Willi syndrome.

tablet/day and increased over 3 weeks to the maintenance dose of two 8mg/90mg tablets twice daily, for a total daily dose of 32 mg/360mg (NB32). NB is not a Drug Enforcement Administration scheduled drug. According to the Drug ABC List Prices (Accessed by Richard Decederfelt, B.S.Pharm., M.S.I.S. on Dec 15 2014), the wholesale cost of NB is approximately \$200/month.

STUDIES OF EFFICACY AND SAFETY

Approval of NB by the FDA was based on the results of multiple clinical trials that included approximately 4500 overweight and obese participants. To date, 4 unique phase 3 studies of NB32, all called CONTRAVE Obesity Research (COR), have evaluated the efficacy of NB, and have reported 1year weight outcome data, using modified intent-to-treat analysis, and also reported attrition (Table 1a). Three studies enrolled adults with BMI 30–45kg/m² or 27–45kg/m² with dyslipidemia and/or controlled hypertension (COR-I,⁴ COR-II,⁵ COR-BMOD⁶); COR-Diabetes⁷ enrolled adults with BMI 27–45kg/m² and type 2 diabetes (T2D) managed by oral agents or diet. Most study participants were Caucasian women and only 2% were ≥65y. All studies compared NB32 to placebo and included a titration period to reach the full dose. Results for doses other than the FDA-approved NB32 are not discussed. Co-primary endpoints for all studies were percentage change in body weight and proportion of patients losing ≥5% initial weight at 1year. Consistent with FDA policy, analyses were based on modified-intent-to-treat, including all patients randomized to drug who returned for

1 post-baseline weight measurement while taking the drug, and used last-observation-carried-forward for missing data. The studies excluded patients with significant cardiovascular disease (CVD), stroke, seizure disorder, serious psychiatric disorder, or type 1 diabetes. All but COR-Diabetes excluded patients with T2D. COR-I, COR-II, and COR-Diabetes instructed study participants to follow a 500 kcal/day deficit diet and provided advice on lifestyle modification every 12 weeks. COR-BMOD provided intensive behavioral treatment delivered in 28 group sessions including prescribed diet and exercise goals.

Attrition in all studies was high, ranging from 42% to 50%, so that approximately only 53% of individuals who were enrolled in these trials completed 1year while taking study drug (Table 1a). Across studies, 24% of those taking NB withdrew due to adverse events (vs 12% taking placebo).¹ Nausea was the most common adverse event leading to withdrawal.

Using the modified ITT approach, the placebo-subtracted mean weight loss at 1year with NB32 across all studies was 4.6% (95% CI 4.4 to 4.8%) or 4.9kg (CI 4.6–5.1kg) and ranged from 3.2% (3.4kg) in patients with T2DM⁷ to 5.2% (5.9kg) in patients without⁵ T2D. Mean total weight loss across studies for NB32 was 6.8% (CI 6.6–7.1%) or 7.3kg (CI 7.0–7.6kg) at 1year, ranging from 5.0% (5.4kg) in patients with diabetes receiving minimal behavioral intervention to 9.3% (9.7kg) in study participants receiving intensive behavioral treatment (Table 1b). In all studies, significantly more participants taking NB32 achieved a weight loss

≥5% at 1year than placebo, ranging from 44.5% (vs. 18.9%) in patients with T2D receiving minimal behavioral treatment⁷ to 66.4% (vs 42.5%) in patients without T2D undergoing intensive behavioral treatment.⁶ NB32 led to slight increases or smaller decreases in blood pressure and pulse than placebo, despite greater weight loss,⁸ and those taking NB were more likely to experience a hypertension-related adverse event.⁸ Change in LDL-cholesterol

was not different from placebo. Other CVD risks factors were improved with NB32 vs placebo, including increases in HDL-cholesterol, decreases in triglycerides, and small improvements in glucose and insulin. In patients with type 2 diabetes, glycated hemoglobin was improved (−0.6% for NB32 vs. −0.1% for placebo), and there was less use of “rescue” medications for poor glycemic control.⁷

ADVERSE EFFECTS AND CONTRAINDICATIONS

Common adverse effects include nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea.¹ Because NB can lead to elevations in blood pressure and pulse compared with placebo despite greater weight-loss, it should not be used in patients with uncontrolled hypertension; blood pressure and pulse should be assessed prior to starting NB and monitored regularly throughout treatment. The clinical significance of the pulse and blood pressure elevations with NB is unclear, and patients with recent CVD were excluded from the published clinical trials. Medications containing bupropion should not be administered to patients with a history of seizure disorders or with anorexia or bulimia nervosa due to reduced seizure threshold. NB should also not be used in patients who are using opioids or abruptly discontinuing use of alcohol, benzodiazepines, barbiturates, or anti-seizure medications. NB is contraindicated in pregnancy. Due to its bupropion component, the NB32 package insert includes a “black box” warning for potential increased risk of suicidality, and also notes that serious neuropsychiatric events have been reported in patients taking bupropion for smoking cessation.¹

Comment

After 1 year of treatment, NB32 led to a mean weight loss of 6.8% initial weight (7.3kg) and placebo-subtracted weight loss of 4.6% (4.9kg), and a greater likelihood of clinically-meaningful weight loss (≥ 5%), compared with placebo. These findings suggest somewhat better weight loss than with orlistat or lorcaserin, but less weight loss than with mid- or top-dose phentermine/topiramate-ER.² Patients who did not lose ≥ 5% by 12 weeks at the maintenance dose were unlikely to achieve clinically-meaningful weight loss at 1 year.⁸ In patients who received concomitant intensive lifestyle intervention, 66% lost ≥ 5% and 42% lost ≥ 10% of their initial weight after 1 year of treatment. This improved outcome compared to those receiving NB32 without intensive behavioral treatment reinforces recommendations to use pharmacotherapy together with lifestyle intervention.⁹ Based on previous FDA policy, the primary analyses for these studies was modified-ITT using last-observation-carried-forward, which can overestimate treatment effect, particularly when there is high attrition. The FDA recently announced that it was reconsidering their preferred analyses so that rather than using last-observation-carried-forward, sophisticated statistical models should be fit to estimate the intent-to-treat effect using data from all randomized subjects.

NB is an option for adjunctive treatment in patients with obesity who are unable to lose sufficient weight to improve health with lifestyle intervention alone.¹ No study has demonstrated reductions in CVD morbidity or mortality with NB. The effect of treatment with NB on CVD outcomes, particularly in patients at high risk, is unknown. A CVD outcomes study that randomized approximately 8,900 patients is underway

(ClinicalTrials.gov Identifier: NCT01601704); an interim analysis has excluded a hazard ratio of 2.0 for excess risk of major adverse cardiovascular events associated with NB compared to placebo.¹⁰

In patients who respond to NB with clinically-meaningful weight loss and improvements in obesity-related conditions, continued indefinite treatment may be warranted. If weight loss of 5% is not attained after 12 weeks at the full dose, the patient should be re-evaluated, and the medication discontinued. The approval of NB adds another medication to the tools clinicians can use to treat patients with obesity. Availability of medications with differing mechanisms of action, weight loss efficacy, effects on cardiometabolic risk factors, and adverse event profiles can allow better individualization of therapy to enhance benefit while minimizing risk.

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Table 1

(A): Studies of Naltrexone-ER plus Bupropion-ER, with One-Year Weight Change (B)

A. Studies of Naltrexone-ER plus Bupropion-ER									
Source (Location)	Participant Characteristics ^a	Number Randomized		Dosage/d		Lifestyle Intervention	Attrition, % ^b		
		Intervention	Placebo	Intervention	Placebo				
Greenway et al, ⁴ 2010 (United States) (COR-I)	85% Women, BMI 30–45 or BMI 27–45 with controlled hypertension and/or dyslipidemia	583	581	8 mg naltrexone ER/90 mg bupropion ER, 2 tablets, 2x/d	2 tablets 2x/d	Caloric reduction 500 kcal/d, infrequent standardized nutritional and exercise counseling.	50		
Wadden et al, ⁶ 2011 (United States) (COR-BMOD)	90% Women, BMI 30–45 or BMI 27–45 with controlled hypertension and/or dyslipidemia	591	202	8 mg naltrexone ER/90 mg bupropion ER, 2 tablets, 2x/d	2 tablets 2x/d	Intensive group behavior modification program over 28 sessions including prescribed caloric (e.g. 1200 kcal/day for weight > 249 lb) and physical activity goals.	42		
Apovian et al, ⁵ 2013 (United States) (COR-II)	85% Women, BMI 30–45 and/or BMI 27–45 with controlled hypertension and/or dyslipidemia	878	495	8 mg naltrexone ER/90 mg bupropion ER, 2 tablets, 2x/d	2 tablets 2x/d	Caloric reduction 500 kcal/d, Infrequent standardized lifestyle counseling	49		
Hollander et al, ⁷ 2013 (United States) (COR-Diabetes)	56% Women, BMI 27–45 with DM-2 treated with diet or oral diabetes medications, HbA1C 7%–10%	335	170	8 mg naltrexone ER/90 mg bupropion ER, 2 tablets, 2x/d	2 tablets 2x/d	Caloric reduction 500 kcal/d, Infrequent standardized lifestyle counseling	46		
B. One-Year Weight Change in Studies of Naltrexone-ER 32mg plus Bupropion-ER 360mg ^c									
1-y Change									
	Loss Relative to Baseline Weight, kg		Loss Relative to Baseline Weight, %		5% Loss of Baseline Weight, %		10% Loss of Baseline Weight, %		
	Intervention	Placebo	Intervention	Placebo	Intervention	Placebo	Intervention	Placebo	
Greenway et al, ⁴ 2010 (COR-I)	−6.0	−1.3	6.1	1.3	48.0	16.4	25.0	7.0	
Wadden et al, ⁶ 2011 (COR-BMOD)	−9.7	−5.5	9.3	5.1	66.4	42.5	41.5	20.2	
Apovian et al, ⁵ 2013 (COR-II)	−7.3	−1.4	6.4	1.2	50.5	17.1	28.3	5.7	
Hollander et al, ⁷ 2013 (COR-Diabetes)	−5.4	−2.0	5.0	1.8	44.5	18.9	18.5	5.7	

Abbreviations: ER=extended release; BMI, body mass index; DM-2, diabetes mellitus type 2.

^a All participants were adults. BMI was calculated as weight in kilograms divided by height in meters squared.

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Attrition for each study was calculated from the total number of participants who were randomized to receive treatment. Results for weight change are reported from modified intention-to-treat analyses of participants with at least one post-baseline body weight measurement while receiving study medication, with the last observation carried forward. Some results reported in the studies (e.g., for follow-up intervals other than 1 year or for non-FDA-approved dosages) are not included. Data for weight loss in kg for all 4 studies obtained via personal communication (Kelly Kim, RPh, Takeda Pharmaceuticals International, Inc., Dec. 8, 2014). Some data for attrition were obtained from FDA documents.⁸