VIEWPOINT

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 (ER) plus bupropion-ER (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. This Viewpoint discusses naltrexone-bupropion ER and its potential use for the adjunctive treatment of patients with obesity.

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 an approximately 2.8-kg placebo-subtracted weight loss at 6 to 12 months.[3] Among its effects, bupropion is thought to stimulate secretion of anorexigenic α-melanocyte-stimulating hormone (αMSH) from pro-opiomelanocortin-producing hypothalamic cells, but it may also simultaneously induce secretion of the endogenous opioid products of pro-opiomelanocortin that might inhibit αMSH secretion, limiting the effectiveness of bupropion. Naltrexone monotherapy has little efficacy for weight management. However, because naltrexone might specifically counteract the autoinhibitory actions of bupropion-stimulated endogenous opioids, naltrexone-bupropion combination therapy was investigated for obesity treatment.

Naltrexone-bupropion is FDA-approved for use in adults with a body mass index (BMI) of at least 30 or with a BMI of at least 27 plus obesity-related comorbidities. Treatment is initiated with one 8-mg naltrexone/90-mg bupropion tablet per day and increased over 3 weeks to the maintenance dosage of two 8-mg/90-mg tablets twice daily, for a total daily dose of 32 mg/360 mg. Naltrexone-bupropion is not a US Drug Enforcement Administration scheduled drug. According to the Drug ABC List Prices, the wholesale cost of naltrexone-bupropion is approximately $200/mo.

Studies of Efficacy and Safety

Approval of naltrexone-bupropion by the FDA was based on the results of multiple clinical trials of approximately 4500 overweight and obese study participants. To date, 4 unique phase 3 studies of naltrexone-bupropion, all called CONTRAVE Obesity Research (COR), have evaluated the efficacy of the drug and have reported 1-year weight outcome data, using modified intent-to-treat (ITT) analysis as well as attrition (eTable in the Supplement). Three studies enrolled adults with a BMI of 30 through 45 or BMI of 27 through 45 with dyslipidemia, controlled hypertension, or both (COR-1,[4] COR-II,[5] COR-BMOD[6]). COR-Diabetes[7] enrolled adults with a BMI of 27 through 45 and type 2 diabetes managed with oral agents or diet. Most participants were white women and only 2% were 65 years or older. All studies compared naltrexone-bupropion with placebo and included a titration period to reach the full dose. Results for doses other than the FDA-approved formulation are not discussed.

Co-primary end points for all studies were percentage change in body weight and proportion of patients losing at least 5% of initial weight at 1 year. Consistent with FDA policy, analyses were based on modified ITT (all patients randomized who returned for ≥1 postbaseline 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 type 2 diabetes. COR-I, COR-II, and COR-Diabetes instructed participants to follow a 500-kcal/d 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 1 year while taking the study drug. Across studies, 24% of those taking naltrexone-bupropion 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 1 year with naltrexone-bupropion across all studies was 4.6% (95% CI, 4.4%-4.8%) or 4.9 kg (95% CI, 4.6-5.1 kg) and ranged from 3.2% (3.4 kg) in patients with type 2 diabetes[7] to 5.2% (5.9 kg) in patients without it.[5] Mean total weight loss across studies for naltrexone-bupropion was 6.8% (95% CI, 6.6%-7.1%) or 7.3 kg (95% CI, 7.0-7.6 kg) at 1 year, ranging from 5.0% (5.4 kg) in patients with diabetes receiving minimal behavioral intervention to 9.3% (9.7 kg) in those receiving intensive behavioral treatment (eTable in the Supplement). In all studies, significantly more participants taking naltrexone-bupropion achieved weight loss of at least 5% at 1 year than placebo, ranging from 44.5% (vs 18.9%) in patients with type 2 diabetes receiving minimal behavioral treatment[7] to 66.4% (vs 42.5%) in patients without diabetes undergoing intensive behavioral treatment.[6]

Naltrexone-bupropion treatment led to slight increases or smaller decreases in blood pressure and pulse than placebo, despite greater weight loss,[8] and those taking the drug were more likely to experience a hypertension-related adverse event.[8] Change in LDL cholesterol was not differ-

ent from placebo. Other CVD risks factors were improved with naltrexone-bupropion 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 naltrexone-bupropion 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 of naltrexone-bupropion include nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea.[1] Because naltrexone-bupropion can lead to elevations in blood pressure and pulse compared with placebo despite greater weight loss, this drug should not be used in patients with uncontrolled hypertension; blood pressure and pulse should be assessed prior to treatment and monitored regularly. The clinical significance of the pulse and blood pressure elevations with naltrexone-bupropion 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. Naltrexone-bupropion should also not be taken by patients who are using opioids or abruptly discontinuing use of alcohol, benzodiazepines, barbiturates, or antiseizure medications. Naltrexone-bupropion is contraindicated in pregnancy. Due to its bupropion component, the 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]

Clinical Considerations

After 1 year of treatment, naltrexone-bupropion led to a mean weight loss of 6.8% of initial weight (7.3 kg) and placebo-subtracted weight loss of 4.6% (4.9 kg) and a greater likelihood of clinically meaningful weight loss (≥5%) vs placebo. These findings suggest somewhat better weight loss with naltrexone-bupropion than with orlistat or lorcaserin, but less weight loss than with mid-dose or high-dose phentermine/topiramate-ER.[2] Patients who did not lose at least 5% by 12 weeks while taking the maintenance dose were unlikely to achieve clinically meaningful weight loss at 1 year.[8] Among patients who received concomitant intensive lifestyle intervention, 66% lost at least 5% and 42% lost at least 10% of their initial weight after 1 year of treatment. This improved outcome, compared with those receiving naltrexone-bupropion without intensive behavioral treatment, reinforces recommendations to use pharmacotherapy plus lifestyle intervention.[9] Based on previous FDA policy, the primary analyses for weight loss outcomes in these studies was based on 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 the preferred analyses so that rather than using last-observation-carried-forward, sophisticated statistical models should be fit to estimate the ITT effect using data from all randomized study participants.

Naltrexone-bupropion 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 naltrexone-bupropion . The effect of treatment with naltrexone-bupropion on CVD outcomes, particularly in patients at high risk, is unknown. A CVD outcomes study that randomized approximately 8900 patients is under way (ClinicalTrials.gov NCT01601704); an interim analysis has excluded a hazard ratio of 2.0 for excess risk of major adverse CV events associated with naltrexone-bupropion compared with placebo.[10]

For patients who respond to naltrexone-bupropion with clinically meaningful weight loss and improvements in obesity-related conditions, continued indefinite treatment may be warranted. If weight loss of at least 5% is not attained after 12 weeks at the full dose, the patient should be reevaluated and the medication discontinued. The approval of naltrexone-bupropion adds another medication to the options from which clinicians can choose 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.

ARTICLE INFORMATION

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr J. Yanovski reports being a Commissioned Officer in the US Public Health Service, Department of Health and Human Services. He also reports that he will be a site principal investigator for a multicenter trial to be conducted under a CRADA (cooperative research and development agreement) between NICHD and Zafgen to study beloranib for amelioration of obesity in the Prader-Willi syndrome. No other disclosures were reported.

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REFERENCES

1. Contrave (naltrexone HCl and bupropion HCl) Extended-Release Tablets [package insert revised 9/2014]. La Jolla, CA: Orexigen Therapeutics; 2014.

2. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA*. 2014;311(1):74-86.

3. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med*. 2005;142(7):532-546.

4. Greenway FL, Fujioka K, Plodkowski RA, et al; COR-I Study Group. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I). *Lancet*. 2010;376(9741):595-605.

5. Apovian CM, Aronne L, Rubino D, et al; COR-II Study Group. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)*. 2013;21(5):935-943.

6. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)*. 2011;19(1):110-120.

7. Hollander P, Gupta AK, Plodkowski R, et al; COR-Diabetes Study Group. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care*. 2013;36(12):4022-4029.

8. FDA Briefing Document. Orexigen Therapeutics Inc, data on file. New Drug Application 200063: Contrave (Naltrexone 4mg, 8mg/Bupropion HCL 90mg extended release tablet). http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm235671.pdf. Accessed February 12, 2015.

9. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults. *J Am Coll Cardiol*. 2014;63(25 pt B):2985-3023.

10. Orexigen announces successful interim analysis of Contrave Light study. http://ir.orexigen.com/phoenix.zhtml?c=207034&p=irol-newsArticle&ID=1879629. 2013. Accessed December 13, 2014.