Naltrexone, Bupropion Led to More Weight Loss

BY ROBERT FINN

FROM THE LANCET

Two different doses of naltrexone in combination with bupropion resulted in significantly more weight loss than did a placebo in a 56-week trial involving 1,742 overweight and obese participants.

According to the study, published online in the journal the Lancet on July 30, patients taking 32 mg of naltrexone together with 360 mg sustained-release bupropion daily lost on average 6.1% of their body weight (6.1 kg or 13.4 pounds), significantly more than patients taking placebo, who lost 1.3% of their body weight (1.4 kg or 3.1 pounds).

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Patients taking a lower dose of naltrexone—16 mg daily—along with 360 mg bupropion lost 5.0% of their body weight (4.9 kg or 10.8 pounds). This too was significantly greater than placebo, according to Dr. Frank L. Greenway of Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, and colleagues (Lancet 2010 [doi:10.1016/S0140-6736(10)60888-4]).

Investigators conducted the study at 34 sites in the United States. The study population included men and women aged 18-65 years with a body mass index of 30-45 kg/m^2 and uncomplicated obesity or a BMI of 27-45 kg/m^2 with dyslipidemia or hypertension. Eighty-five percent of the participants were women, and 75% were white. Their weight averaged 99.5 kg (219.4 pounds). In addition to the study drugs or placebo, participants were instructed to follow a mild diet (500 kcal/day deficit) and were told to increase their physical activity.

Among patients who completed the trial, 62% on the higher dose medication and 55% on the lower dose medication lost at least 5% of their body weight, compared with just 23% of the patients taking placebo. Thirty-four percent of the completers on the higher-dose medication and 30% of those on the lower-dose medication lost at least 10% of their body weight, compared with 11% of those on placebo.

Patients on the combination treatment also experienced significant improvements in waist circumference, insulin resistance, HDL cholesterol, triglycerides, and high sensitivity C-reactive protein, compared with patients on placebo. However, while mean blood pressure decreased slightly from baseline in the placebo group, it was unchanged in either of the naltrexone-bupropion groups.

Only 50% of the participants completed all 56 weeks of the trial, with similar discontinuation rates in all three groups. While a total of 26 patients experienced serious adverse events, none of those was related to study treatments, according to the investigators.

Several adverse effects were significantly more frequent in the treatment groups than in the placebo group. These included nausea, headache, constipation, dizziness, vomiting, and dry mouth. No psychiatric adverse event, including insomnia, anxiety, and depression, was more common in the treatment groups than in the placebo group.

Compared with the placebo group, patients in the treatment groups reported experiencing significantly less hunger, and significantly less difficulty in controlling their eating. The naltrexone-bupropion combination is thought to affect two key systems in weight control. Bupropion affects the hypothalamic melanocortin system, which is thought to control feelings of hunger, while naltrexone affects the mesolimbic reward system. ■

VITALS

Major Finding: Patients receiving 32 mg naltrexone and 360 mg bupropion daily for 56 weeks lost 6.1% of their body weight on average compared with 1.3% for patients receiving placebo.

Data Source: Randomized, double-blind, placebo-controlled trial involving 1,742 men and women aged 18-65 years.

Disclosures: The study was funded by Orexigen Therapeutics, which manufactures the naltrexone-bupropion combination under the trade name Contrave. Dr. Greenway has received consulting fees and travel support from Orexigen; is a member of advisory boards for Orexigen, Baronova, Biologene, Catalyst Pharmaceutical Partners, GlaxoSmithKline, Jenny Craig, Leptos Biomedical, Novo Nordisk, Obecure, Schering-Plough Research Institute, NuMe, and Origin Biomed; is a consultant for Basic Research, Dow Chemical, General Nutrition, Lithera, Otsuka Pharmaceutical Development and Commercialization, and Third Rock Ventures; and has received research grants or has grants pending from Amylin, Lilly, Orexigen, Merck, Sanofi-Aventis, Arena Pfizer, Bristol-Myers Squibb, Nastech, Schering Plough, GlaxoSmithKline, and Hollis-Eden. He also holds three patents related to obesity treatment. Several of the other coauthors acknowledged membership on Orexigen's advisory board, receiving consulting fees as well as research grant support from Orexigen. Three other coauthors acknowledged being current or former employees of Orexigen and owning stock in the company.

Weight Loss in OA Delivered Benefits for Knee Cartilage

BY BRUCE JANCIN

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

ROME — Weight loss in obese patients with knee osteoarthritis has been shown for the first time in a prospective study to have beneficial structure-modifying effects upon knee cartilage.

This is a finding with enormous public health implications. Weight loss now becomes the only therapy ever shown to have salutary structural effects on knee articular cartilage. No drug has yet been shown to have such a benefit, Dr. Ana Ananda noted in presenting the study findings.

"We found that with a mean weight loss of 9%, which is fairly achievable… we can make meaningful, clinically important differences in terms of cartilage structure," she said in an interview.

"What this study suggests to us is, we should be going back to basics and at least starting with the basics—weight loss—in our patients with knee osteoarthritis, and maybe making more effort in terms of achieving that. It would hopefully prevent or delay the need for knee replacement down the line," added Dr. Ananda, a rheumatologist at the University of Sydney.

She presented the results of MR imaging studies conducted before and again 12 months after a weight-loss intervention in a group of patients with knee osteoarthritis and a body mass index greater than 35 kg/m^2.

Patients who achieved at least a 9% reduction in body weight at the 1-year mark demonstrated a significantly lower rate of loss in cartilage thickness in the medial compartment, compared with those who had lesser weight loss or weight gain at follow-up.

Moreover, patients with significant weight loss also showed improvement in cartilage quality, as reflected in increased proteoglycan content seen on delayed gadolinium-enhanced MRI. Evidence from other studies suggests loss in proteoglycan is perhaps the earliest osteoarthritis-induced change in cartilage; hence, it might be potentially reversible with an early weight loss intervention, she continued.

In all, 78 patients had baseline and follow-up measurements of knee cartilage thickness as a proxy for cartilage volume. Of these, 28 underwent bariatric surgery involving laparoscopic adjustable gastric banding with a mean 1-year weight loss of 17.5%, in contrast to the mean 2.5% weight loss in patients who participated in a dietary weight-loss program.

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The MRIs showed a graded inverse relationship between the percent weight loss and the rate of loss in cartilage thickness in the medial compartment, through which most of the load on the knee joint is transmitted. This relationship remained significant in a multivariate analysis adjusted for age, sex, baseline BMI, and knee range of motion.

The delayed gadolinium-enhanced MRI studies were done in 54 patients. The 24 with surgical weight loss demonstrated a mean 56-msec increase in delayed gadolinium-enhanced MRI index in the medial compartment during 1 year of follow-up, reflecting a substantial increase in cartilage proteoglycan content.

In contrast, the 30 patients with lesser, nonsurgical weight loss had a mean 23-msec decrease in the index. In a multivariate analysis, the correlation between percentage of body weight loss and increase in the delayed gadolinium-enhanced MRI index remained significant. For every 10% loss in body weight, a patient's cartilage proteoglycan index improved by about 40 msec.

A second study presented at the congress concluded that substantial weight loss has a chondroprotective effect, according to a study that assessed changes in pain scores, joint biomarkers, and markers of systemic inflammation as outcomes.

Dr. Pascal Richette of Lariboisière Hospital, Paris, reported on 44 obese patients with knee osteoarthritis who underwent bariatric surgery, with a resultant 20% decrease in BMI.

At 6 months post surgery, the group's mean osteoarthritis pain scores had dropped from a baseline of 50 out of a possible 100 points to 24.5 points. This was accompanied by significant functional improvement as measured on the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index subscales.

Serum levels of N-propeptide of type IIA procollagen (PIIANP), a biomarker of cartilage type II collagen synthesis, increased by 32%. Serum levels of cartilage oligomeric matrix protein (COMP), a biomarker for cartilage degradation, were down by 36%. Serum levels of interleukin-6 decreased by 26% from baseline, high-sensitivity C-reactive protein was down by 46%, and fibrinogen decreased by 5%, all indicative of reduced systemic inflammation. In addition, serum lipids and insulin resistance were significantly reduced.

Dr. Richette and Dr. Ananda reported having no conflicts of interest. ■