Combination treatment for obesity leads to substantial reductions in body weight

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Combination treatment for obesity using the drugs naltrexone and bupropion, plus diet and exercise, helps reduce bodyweight by a mean of 5% or more over a year, depending on the dosage used. The findings of the COR-I study are reported in an Article Online First and in an upcoming *Lancet*, written by Professor Frank L Greenway, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA, USA, and colleagues.

Naltrexone and bupropion combination treatment was developed to produce complementary actions in the body's central nervous system (CNS) which regulate bodyweight. In this randomised controlled trial, men and women aged 18-65 years with a body-mass index (BMI) of 30—45 kg/m^2 and uncomplicated obesity, or BMI 27—45 kg/m^2 with abnormal blood fats or high blood pressure, were enrolled from 34 sites in the USA.

Participants were prescribed a diet of moderately-reduced calories and exercise, plus one of three treatment regiments: sustained release (SR) naltrexone 32mg per day plus SR bupropion 360 mg per day combined in fixed dose tablets (NB32 group); SR naltexone 16mg per day plus SR bupropion 360 mg per day combined in fixed dose tablets (NB16 group); or matching placebo. All three groups received treatment twice daily for 56 weeks.

A total of 1742 patients were randomised, but only 50% of them completed all 56 weeks of treatment (NB32-296 patients; NB16-284;

placebo 290). Of the original 1742 enrolled, 1453 (83%) made the final analysis (NB32:471, NB16: 471, placebo: 511). The mean weight of the patients was around 100kg before the study. The mean weight loss at 56 weeks was 1.4kg in the placebo group, compared with 4.9kg in the NB16 group and 6.1kg in the NB32 group.

The proportions of patients achieving a weight loss of 5.0% or more also varied between groups. Almost half (48%) achieved this in the NB32 group, compared with 39% in the NB16 group and 16% in the placebo group. More patients in the NB32 group (25%) and NB16 group (20%) lost more than 10% of their bodyweight compared with the placebo group (7%)Nausea occurred in more than a quarter of patients in both NB groups, but in only 5% of placebo-treated patients. Headache, constipation, dizziness, vomiting, and dry mouth were also more frequent in both NB groups than in the placebo group. Most of these adverse events were, however, mild to moderate in severity and transient.

The authors note that although the study did include men, 85% of each group was comprised of women, who themselves were mainly middle-aged and white. They also note that the exact effect of the exercise part of the regimen remains unknown as data for this was not recorded; and they add this combination therapy needs to be trialed head-to-head against other therapies for comparisons of efficacy.

The authors add that a weight loss of 5 to 10% improves blood sugar control, and reduces the risk of abnormal blood fats and high blood pressure, and could reduce mortality. They say: "This combination improves control of eating and response to food cravings. Since many overweight adults report food cravings to be an important barrier to their ability to adhere to a diet, these actions could add to the usefulness of naltrexone plus bupropion in the treatment of obesity."

They conclude: "Although lifestyle modification is first-line therapy for obesity, adherence to this intervention is poor. The combination of naltrexone plus bupropion could be a useful addition to the current range of medications that facilitate adherence to lifestyle modification and produce clinically meaningful weight loss for treatment of obesity and obesity-related disorders."

In an accompanying Comment, Professor Arne Astrup, Department of Human Nutrition, University of Copenhagen, Denmark, points out that after 56 weeks, blood pressure was not reduced as much as would normally be seen with a 5-kg weight loss, and the reduction was less than that in the placebo group. He says: "Additionally, the combination treatment did not reduce LDL (bad) cholesterol more than did placebo. The investigators concluded that the combination improved several cardiometabolic risk factors; but how relevant are improvements in plasma triglycerides, HDL (good) cholesterol, and high-sensitivity C-reactive protein when the reductions in blood pressure and LDL cholesterol that normally occur with weight loss are absent?...more data are needed to get a better overall assessment of cardiovascular risk of this otherwise promising combination therapy for obesity."

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