Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Despite increasing public health concerns regarding obesity, few safe and effective drug treatments are available. Combination treatment with sustained-release naltrexone and bupropion was developed to produce complementary actions in CNS pathways regulating bodyweight. The Contrave Obesity Research I (COR-I) study assessed the effect of such treatment on bodyweight in overweight and obese participants.

Methods Men and women aged 18–65 years who had a body-mass index (BMI) of 30–45 kg/m^2 and uncomplicated obesity or BMI 27–45 kg/m^2 with dyslipidaemia or hypertension were eligible for enrolment in this randomised, double-blind, placebo-controlled, phase 3 trial undertaken at 34 sites in the USA. Participants were prescribed mild hypocaloric diet and exercise and were randomly assigned in a 1:1:1 ratio to receive sustained-release naltrexone 32 mg per day plus sustained-release bupropion 360 mg per day combined in fixed-dose tablets (also known as NB32), sustained-release naltrexone 16 mg per day plus sustained-release bupropion 360 mg per day combined in fixed-dose tablets (also known as NB16), or matching placebo twice a day, given orally for 56 weeks. The trial included a 3-week dose escalation. Randomisation was done by use of a centralised, computer-generated, web-based system and was stratified by study centre. Co-primary efficacy endpoints at 56 weeks were percentage change in bodyweight and proportion of participants who achieved a decrease in bodyweight of 5% or more. The primary analysis included all randomised participants with a baseline weight measurement and a post-baseline weight measurement while on study drug (last observation carried forward). This study is registered with ClinicalTrials.gov, number NCT00532779.

Findings 1742 participants were enrolled and randomised to double-blind treatment (naltrexone 32 mg plus bupropion, n=583; naltrexone 16 mg plus bupropion, n=578; placebo, n=581). 870 (50%) participants completed 56 weeks of treatment (n=296; n=284; n=290, respectively) and 1453 (83%) were included in the primary analysis (n=471; n=471; n=511). Mean change in bodyweight was –1·3% (SE 0·3) in the placebo group, –6·1% (0·3) in the naltrexone 32 mg plus bupropion group (p<0·0001 *vs* placebo) and –5·0% (0·3) in the naltrexone 16 mg plus bupropion group (p<0·0001 *vs* placebo). 84 (16%) participants assigned to placebo had a decrease in bodyweight of 5% or more compared with 226 (48%) assigned to naltrexone 32 mg plus bupropion (p<0·0001 *vs* placebo) and 186 (39%) assigned to naltrexone 16 mg plus bupropion (p<0·0001 *vs* placebo). The most frequent adverse event in participants assigned to combination treatment was nausea (naltrexone 32 mg plus bupropion, 171 participants [29·8%]; naltrexone 16 mg plus bupropion, 155 [27·2%]; placebo, 30 [5·3%]). Headache, constipation, dizziness, vomiting, and dry mouth were also more frequent in the naltrexone plus bupropion groups than in the placebo group. A transient increase of around 1·5 mm Hg in mean systolic and diastolic blood pressure was followed by a reduction of around 1 mm Hg below baseline in the naltrexone plus bupropion groups. Combination treatment was not associated with increased depression or suicidality events compared with placebo.

Interpretation A sustained-release combination of naltrexone plus bupropion could be a useful therapeutic option for treatment of obesity.

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Introduction

Obesity is associated with increased risk for type 2 diabetes, cardiovascular disease, cancer, and other disorders, yet few drugs for treatment of obesity are available.[1,2] Moderate weight loss of 5–10% improves glycaemic control, reduces risk of comorbid disorders such as hypertension and dyslipidaemia,[3,4] improves quality of life,[5] and might reduce mortality;[6] however, many individuals are not able to maintain moderately reduced bodyweight with diet and exercise alone.[7] Bariatric surgery can yield long-term weight loss of 15–25% but is generally deemed inappropriate for most overweight or obese individuals because of perioperative and postoperative risk.[7]

Research on CNS pathways that regulate food intake and bodyweight has identified two key systems: the hypothalamic melanocortin system, which integrates input related to energy balance and produces anorexigenic

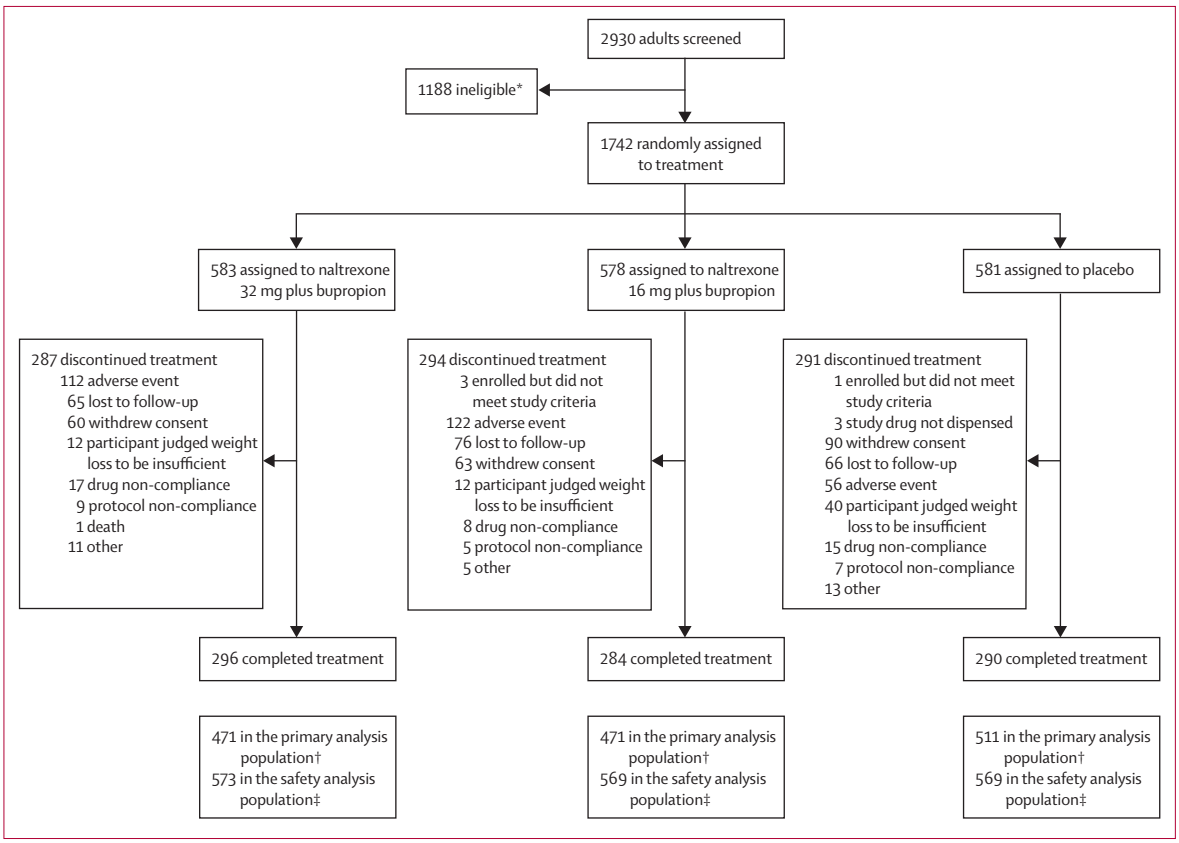


Figure 1: **Trial profile**
Study duration was 56 weeks, including a 3-week dose-escalation. *Reasons for ineligibility of excluded adults are not available. †The primary analysis population included all randomised participants with a baseline weight measurement and a post-baseline weight measurement while on study drug. Missing data was imputed by use of the last observation carried forward method. ‡The safety analysis included all randomised participants who took one or more tablets of study drug and had at least one investigator contact or assessment any time after starting treatment.

signalling, and the mesolimbic reward system, which modulates reward value and goal-oriented behaviour.[8] Development of successful drugs for treatment of obesity has been limited, possibly because of the complexity of these multiple systems and intrinsic bias towards energy conservation.[2,8] Combinations of drugs that target multiple systems are common in treatment of diabetes[9] and hypertension[10] and might be effective in obesity. Combined treatment with sustained-release naltrexone and bupropion (Contrave, Orexigen, La Jolla, CA, USA) was developed to stimulate hypothalamic pro-opiomelanocortin neurons with bupropion while simultaneously blocking opioid-mediated pro-opiomelanocortin autoinhibition with naltrexone.[11] Additionally, the pharmacology and therapeutic applications for naltrexone and bupropion in addictive disorders, as well as preclinical data indicating that synergism of these drugs in midbrain dopamine areas reduces food intake,[12] suggest that the mechanism of action of this combination might also be modulation of mesolimbic reward pathways.

Initial studies in overweight and obese adults suggest that treatment with a combination of naltrexone plus bupropion produces greater weight loss than the sum of the individual monotherapies.[11,13] Here, we present the largest of four recently completed phase 3 studies in the Contrave Obesity Research (COR) programme. COR-I was a 56-week trial that assessed the efficacy, safety, and tolerability of two doses of naltrexone plus bupropion over 1 year in overweight and obese participants.

Methods

Study design and participants

COR-I was a phase 3, randomised, double-blind, placebo-controlled, 56-week study. The protocol for the trial is available from the sponsor. Men and women aged 18–65 years were eligible for inclusion if they had BMI 30–45 kg/m² and uncomplicated obesity, or BMI 27–45 kg/m² and controlled hypertension or dyslipidaemia, or both. The study was undertaken in 34 centres in the USA from October, 2007, until May, 2009. Study centres were a combination of academic and primary care centres.

Women of childbearing potential were required to use effective contraception and excluded if they were pregnant or lactating. Participants were ineligible if they had obesity of known endocrine origin; type 1 or type 2 diabetes; cerebrovascular, cardiovascular, hepatic, or renal disease; previous surgical or device intervention

for obesity; or loss or gain of more than 4 kg within 3 months before randomisation. Additional exclusion criteria included history of seizures or serious psychiatric illness, treatment with bupropion or naltrexone in the previous 12 months, and history of drug or alcohol misuse in the previous 12 months. No additional weight loss drugs besides double-blind study treatment were allowed.

After commencement of the trial, the protocol was amended to include enrolment of participants taking β blockers, since these agents are common medications in people who are overweight or obese.

All participants provided written informed consent. The protocol was approved by each participating institution. The study complied with Good Clinical Practice standards and the Declaration of Helsinki.[14] An independent data safety monitoring committee undertook a prespecified interim safety review after 50% of the study population had completed 20 weeks of treatment.

Randomisation and masking

Participants were randomly assigned in a 1:1:1 ratio to receive a fixed oral dose of sustained-release 32 mg per day naltrexone plus sustained-release 360 mg per day bupropion (8 mg naltrexone/90 mg bupropion in each tablet, two tablets taken twice a day), sustained-release 16 mg per day naltrexone plus sustained-release 360 mg per day bupropion (4 mg naltrexone/90 mg bupropion in each tablet, two tablets taken twice a day), or matching placebo twice a day. The study included a 3-week dose escalation, beginning with a quarter of the full dose and increasing it weekly; the full dose was reached at week 4. Randomisation was done by use of a centralised, computer-generated, web-based system and was stratified by study centre. Participant enrolment and assignment to trial groups was done by an automated system. The computer-generated randomisation schedule was prepared by Almac Clinical Services and centrally administered by use of a web-based clinical supply management system (WebEZ). Study site personnel, participants, and the study team were masked to treatment assignment; blinding was maintained apart from in an emergency. Active drug and placebo tablets were identical in appearance.

Procedures and endpoints

Participant assessments were undertaken at screening and every 4 weeks. At baseline and at 12, 24, 36, and 48 weeks, participants in each group were instructed to follow a hypocaloric diet (500 kcal per day deficit based on the WHO algorithm for calculating resting metabolic rate) and were given advice on lifestyle modification (including instructions to increase physical activity). Data for compliance with diet and exercise instruction were not obtained.

The co-primary efficacy endpoints were percentage change in bodyweight and proportion of participants with a decrease in bodyweight of 5% or more from baseline at week 56. Additional endpoints were proportion of participants with decrease in bodyweight of 10% or more and 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. After commencement of the trial, the order of the closed testing procedure was revised (before unblinding of the study) on the basis of results of the first completed study in the COR programme.[15]

Bodyweight and vital signs were measured at each visit. Fasting glycaemic variables, high-sensitivity C-reactive protein, and lipids were measured at baseline, week 28, and week 56. Blood samples were analysed in a central laboratory (Quintiles Laboratories, Marietta, GA, USA). Questionnaires were administered at baseline and weeks 8, 16, 28, and 56. These included the Impact of Weight on Quality of Life-Lite (IWQOL-Lite),[5] Food Craving Inventory (FCI),[16] and Control of Eating Questionnaire (COEQ).[17] The FCI measures cravings for specific food items, which are aggregated into four subscales. The COEQ is composed of 20 visual analogue scales (shown to be reliable in appetite research[18,19]) designed to assess various aspects of appetite, food craving, eating behaviour, and mood. Participants who terminated the study early were encouraged to return for bodyweight and waist circumference measurements at week 28 or week 56.

Safety assessments consisted of evaluation of treatment-emergent adverse events, concomitant medications, vital signs, and clinical laboratory measures (recorded at each visit); as well as electrocardiograms and physical examinations. Depressive symptoms (including sadness,

	Placebo (n=581)	Naltrexone 16 mg plus bupropion (n=578)	Naltrexone 32 mg plus bupropion (n=583)
Age (years)	43·7 (11·1)	44·4 (11·3)	44·4 (11·1)
Women	496 (85%)	490 (85%)	496 (85%)
Ethnic origin			
White	440 (76%)	427 (74%)	440 (75%)
Black	110 (19%)	122 (21%)	106 (18%)
Other	31 (5%)	29 (5%)	37 (6%)
Weight (kg)	99·5 (14·3)	99·5 (14·8)	99·7 (15·9)
Body-mass index (kg/m²)	36·2 (4·0)	36·2 (4·3)	36·1 (4·4)
Current smoker	65 (11%)	56 (10%)	65 (11%)
Hypertension*	113 (19%)	117 (20%)	130 (22%)
Dyslipidaemia†	288 (50%)	287 (50%)	284 (49%)

Data are mean (SD) or number of participants (%). Percentages may not add up to 100% because of rounding. *Diagnosed at baseline with hypertension or prescribed antihypertensive drugs. †Diagnosed at baseline with dyslipidaemia, hypercholesterolaemia, hypertriglyceridaemia, hyperlipidaemia, low HDL cholesterol, or with at least one of the following values before first dose of study drug: triglycerides 2·26 mmol/L or more, LDL cholesterol 4·14 mmol/L or more, total cholesterol 6·22 mmol/L or more, HDL cholesterol less than 1·04 mmol/L.

Table 1: **Demographics and baseline characteristics of study participants**

irritability, anxiety or tension, and suicidality), assessed by means of the Inventory of Depressive Symptomatology Self Report (IDS-SR),[20] and blood pressure were measured for efficacy and safety. Serious adverse events were defined by Good Clinical Practice guidelines.

Drug compliance was measured at every visit by pill count; a compliance rate of at least 70% was deemed acceptable. Non-compliant participants (<70% compliance rate) were counselled about the importance of compliance and re-educated on how to take study medication. Participants who were non-compliant for 2 consecutive months or who did not take study drug for more than 15 consecutive days were considered for discontinuation from study.

	Placebo	Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion
Number of participants			
Primary analysis population*	511	471	471
Sensitivity analysis (repeated-measures linear mixed-effects model)†	536	524	538
Sensitivity analysis (baseline observation carried forward)‡	581	578	583
Sensitivity analysis (completers)§	290	284	296
Change in bodyweight (%)			
Primary analysis population*	−1·3% (0·3)	−5·0% (0·3)	−6·1% (0·3)¶
Sensitivity analysis (repeated-measures linear mixed-effects model)†	−1·2% (0·3)	−5·4% (0·3)	−6·5% (0·3)
Sensitivity analysis (baseline observation carried forward)‡	−0·9% (0·3)	−3·3% (0·3)	−4·0% (0·3)
Sensitivity analysis (completers)§	−1·8% (0·5)	−6·7% (0·5)	−8·1% (0·5)
Change in bodyweight (kg)			
Primary analysis population*	−1·4 (0·3)	−4·9 (0·3)	−6·1 (0·3)
Sensitivity analysis (repeated-measures linear mixed-effects model)†	−1·0 (0·4)	−4·7 (0·4)	−5·9 (0·4)
Sensitivity analysis (baseline observation carried forward)‡	−0·9 (0·3)	−3·2 (0·3)	−3·9 (0·3)
Sensitivity analysis (completers)§	−1·9 (0·5)	−6·5 (0·5)	−8·0 (0·5)
Participants with weight loss of 5% or more			
Primary analysis population*	84 (16%)	186 (39%)	226 (48%)‖
Sensitivity analysis (baseline observation carried forward)‡	67 (12%)	156 (27%)	180 (31%)
Sensitivity analysis (completers)§	67 (23%)	155 (55%)	183 (62%)
Participants with weight loss of 10% or more			
Primary analysis population*	38 (7%)	95 (20%)	116 (25%)
Sensitivity analysis (baseline observation carried forward)‡	30 (5%)	85 (15%)	101 (17%)
Sensitivity analysis (completers)§	31 (11%)	85 (30%)	102 (34%)
Participants with weight loss of 15% or more			
Primary analysis population*	10 (2%)	41 (9%)	56 (12%)
Sensitivity analysis (baseline observation carried forward)‡	9 (2%)	40 (7%)	51 (9%)
Sensitivity analysis (completers)§	9 (3%)	40 (14%)	51 (17%)

Data are least squares mean (SE) or number of participants (%). p<0·0001 for all comparisons between naltrexone 32 mg plus bupropion and placebo and between naltrexone 16 mg plus bupropion and placebo except where noted. *Primary analysis population included all randomised participants with a baseline weight measurement and a post-baseline weight measurement while on study drug. Missing data was imputed by use of the last observation carried forward method. †A repeated-measures linear mixed-effects model based upon type III sums of squares in all randomised participants with a baseline bodyweight measurement and at least one post-baseline bodyweight measurement. ‡Includes all randomised participants with a baseline bodyweight measurement in which the baseline observation was carried forward for participants who prematurely discontinued study drug. §All randomised participants who completed 56 weeks of treatment. ¶p=0·0079 and ‖p=0·0099 for naltrexone 32 mg plus bupropion compared with naltrexone 16 mg plus bupropion (exploratory analysis performed for primary analysis population only).

Table 2: **Change in bodyweight at 56 weeks**

Statistical analysis

To achieve the targeted number of exposures at 1 year, approximately 1650 participants (550 in each group) were to be randomly assigned to treatment. This sample size was estimated to provide 99% power to detect a significant difference in mean weight loss of 5% or more (>6% *vs* 1% with SD 7%), and a 14% difference (64% *vs* 50%) in the proportion of participants with weight loss of 5% or more between each treatment group and placebo. These differences were calculated on the basis of previous experience.[13] Power estimates were determined by use of a two-sample *t* test for mean weight loss and a two-sample continuity-corrected χ^2 test for the proportion of participants with weight loss of 5% or more with a two-sided significance level of 5%.

Unless otherwise specified, efficacy analyses were done on a prospectively defined population that included all randomised participants with a baseline weight measurement and a post-baseline weight measurement while on study drug; the analysis at 56 weeks was done with the last observation carried forward on study drug. General linear models (ANCOVA) including terms for treatment and study centre and baseline values as covariate were used to analyse continuous endpoints. Categorical endpoints were analysed with a logistic regression model that included treatment and study centre as main effects and baseline bodyweight as covariate. To maintain the family-wise type I error rate at 5%, secondary endpoints were analysed in a predetermined sequence for each experimental group versus placebo, beginning with the proportion of participants with a decrease in bodyweight of 10% or more, and continuing with the change from baseline in each of the following: waist circumference, HDL cholesterol, triglycerides, IWQOL-Lite total score, high-sensitivity C-reactive protein, insulin, glucose, HOMA-IR (insulin resistance, derived from the homoeostasis model assessment), COEQ item 19, LDL cholesterol, systolic and diastolic blood pressure, and IDS-SR total score.

Formal testing was undertaken in a step-down manner until any endpoint failed to reach p<0·05, after which nominal p values are reported and findings are deemed exploratory. To reduce skewness to a minimum, values for triglycerides, high-sensitivity C-reactive protein, insulin, and HOMA-IR were $\log_{10}$ transformed before running ANCOVA models. The percentage change from baseline was calculated by back-transforming the least squares geometric mean minus one. For all other secondary endpoints, results are presented as least

squares mean of the absolute change and least squares mean of the percentage change where appropriate.

Sensitivity analyses for change in bodyweight include all randomised participants with a baseline bodyweight measurement in which the baseline observation was carried forward for participants who prematurely discontinued study drug, a repeated-measures linear mixed-effects model based upon type III sums of squares in all randomised participants with a baseline bodyweight measurement and at least one post-baseline bodyweight measurement, and all randomised participants who completed 56 weeks of treatment. The safety analysis included all randomised participants who took one or more tablets of study drug and had at least one investigator contact or assessment any time after starting treatment. All statistical analyses were done with Windows SAS version 9.1. Continuous results are provided as least squares mean (SE) unless otherwise indicated.

This trial is registered with ClinicalTrials.gov, number NCT00532779.

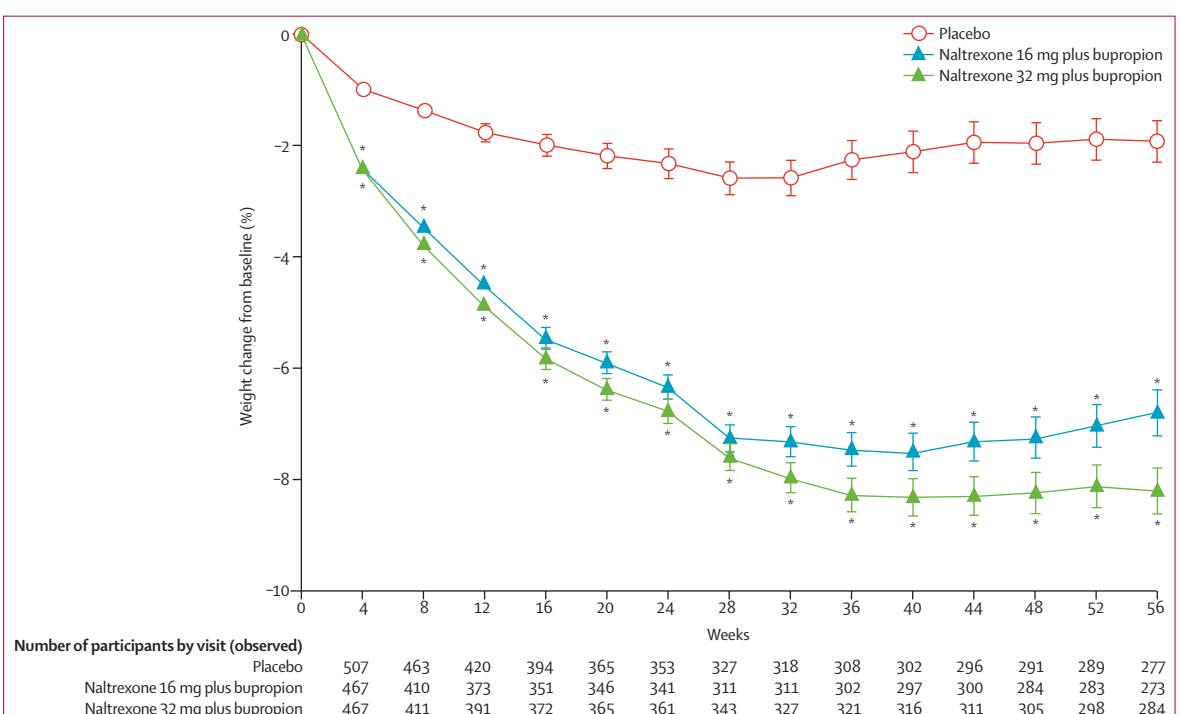
Role of the funding source

The sponsor of the study provided study drug and collaborated with the investigators in protocol design, data interpretation, and preparation of the report. The full set of raw data is available from Orexigen Therapeutics. All authors had access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 1482 women and 260 men were randomly assigned to double-blind treatment. Table 1 shows demographics and baseline characteristics of study participants. 870 (50%) participants completed 56 weeks of treatment. Rates of discontinuation were similar across treatment groups. More participants in the naltrexone plus bupropion groups discontinued because of adverse events than did participants in the placebo group ($p<0·0001$; figure 1); discontinuation generally occurred early in the study (by weeks 4 and 8). More participants in the placebo group discontinued because of insufficient weight loss ($p<0·0001$) and withdrawal of consent ($p=0·0126$) than did participants in the combination treatment groups. Rate of discontinuation was higher during the first 16 weeks of the study in both the placebo (180 of 291) and combination treatment groups (naltrexone 32 mg plus bupropion, 204 of 287; naltrexone 16 mg plus bupropion, 218 of 294).

Weight loss in participants assigned to naltrexone plus bupropion began early (week 4) and was sustained for the duration of the 56-week trial (table 2, figure 2). Maximum weight loss in the combination treatment groups was generally achieved between 28 weeks and 36 weeks. In the primary analysis population, weight loss was significantly greater in the naltrexone 32 mg plus bupropion (mean change in bodyweight –6·1%) and naltrexone 16 mg plus bupropion (–5·0%) groups than in the placebo group (–1·3%). Weight loss in participants who completed 56 weeks of treatment was also greater in the combination



Number of participants by visit (observed)														
Placebo	507	463	420	394	365	353	327	318	308	302	296	291	289	277
Naltrexone 16 mg plus bupropion	467	410	373	351	346	341	311	311	302	297	300	284	283	273
Naltrexone 32 mg plus bupropion	467	411	391	372	365	361	343	327	321	316	311	305	298	284

Figure 2: **Change in bodyweight**
Observed least squares mean (SE) percentage change from baseline in bodyweight and number of participants at each visit during 56 weeks. *p<0·0001 compared with placebo.

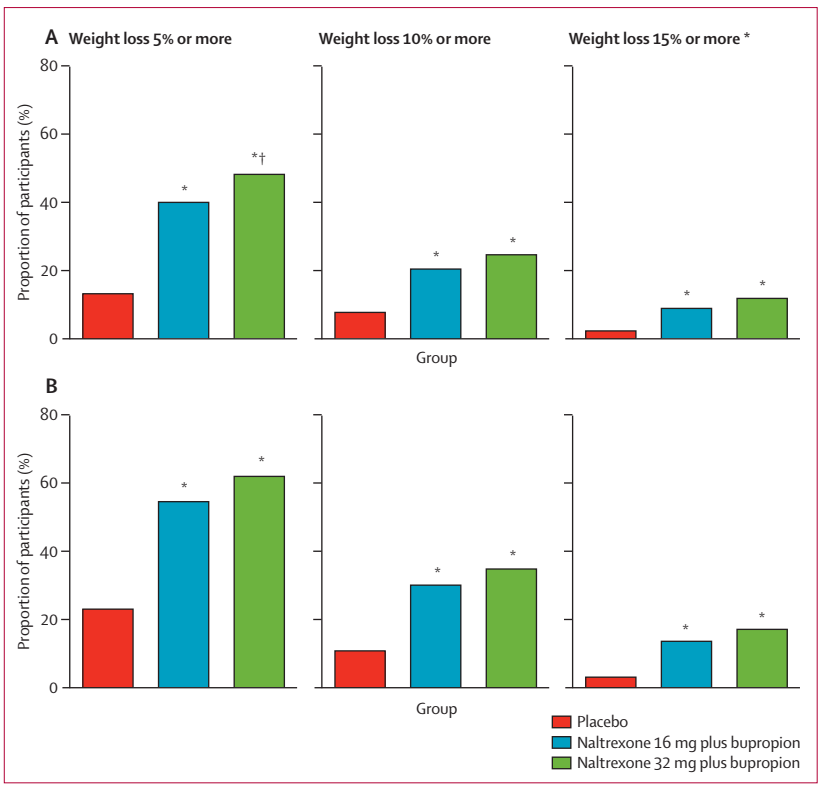


Figure 3: **Proportion of participants who lost at least 5%, 10%, and 15% of baseline weight at week 56**
(A) Primary analysis population. (B) Participants who completed 56 weeks of treatment. *p<0·0001 compared with placebo. †p=0·0099 for naltrexone 32 mg plus bupropion compared with naltrexone 16 mg plus bupropion (exploratory analysis performed for primary analysis population only).

treatment groups (naltrexone 32 mg plus bupropion, –8·1%; naltrexone 16 mg plus bupropion, –6·7%) than in the placebo group (–1·8%); consistent results were recorded in the other sensitivity analyses (table 2).

More participants in the naltrexone plus bupropion groups achieved a decrease in bodyweight of 5% or more, 10% or more, and 15% or more than did participants in the placebo group (table 2, figure 3). Greater weight loss and a higher proportion of participants achieving weight loss of 5% or more were seen in the naltrexone 32 mg plus bupropion group than in the naltrexone 16 mg plus bupropion group. There were no significant interactions on percentage change in bodyweight or proportion of participants achieving weight loss of 5% or more between treatment groups and any of the following: sex, ethnic origin, baseline BMI, smoking status, hypertension, or dyslipidaemia (data not shown). Although there was a treatment by age interaction (p=0·0241, median age 45 years), combination treatment continued to result in significantly greater weight loss than did placebo in both age groups. Mean change in bodyweight for participants younger than the median age was –0·8% (SE 0·4) in the placebo group, –6·2% (0·4) in the naltrexone 32 mg plus bupropion group (p<0·0001 *vs* placebo), and –3·8% (0·4) in the naltrexone 16 mg plus bupropion group (p<0·0001 *vs* placebo). Mean change in bodyweight for participants older than the median age was –1·7% (0·4) in the placebo group, –6·0% (0·4) in the naltrexone 32 mg plus bupropion group (p<0·0001 *vs* placebo), and –5·9% (0·4) in the naltrexone 16 mg plus bupropion group (p<0·0001 *vs* placebo).

See Online for webappendix

Participants assigned to combination treatment showed significant improvements from baseline to 56 weeks in waist circumference, insulin resistance, and concentrations of HDL cholesterol, triglycerides, and high-sensitivity C-reactive protein compared with participants assigned to placebo (table 3). Fasting insulin and glucose concentrations also improved more in the naltrexone 32 mg plus bupropion group than in the placebo group. Participants assigned to naltrexone plus bupropion showed greater improvements in IWQOL-Lite total score and the following subscales than did participants assigned to placebo (data not shown): physical function (naltrexone 32 mg plus bupropion *vs* placebo, p<0·0001; naltrexone 16 mg plus bupropion *vs* placebo, p<0·0001), self-esteem (p<0·0001; p=0·0015), sexual life (p=0·0052; p=0·0063), public distress (p=0·0220; p=0·0040), and work (for naltrexone 32 mg plus bupropion only, p=0·0101 *vs* placebo). Greater improvement in IWQOL-Lite total and subscale scores in the combination treatment groups compared with the placebo group occurred as early as week 8. Mean blood pressure decreased from baseline to 56 weeks in the placebo group, but was generally unchanged in the naltrexone plus bupropion groups. There were no clinically significant changes in IDS-SR total score.

Results from the COEQ showed an association between assignment to naltrexone plus bupropion and improved control of eating and reduced food cravings (figure 4). By week 8, greater improvements were seen in participants assigned to naltrexone plus bupropion than in those assigned to placebo in COEQ items indicating reduced hunger or desire for sweet, non-sweet, or starchy foods; increased feeling of fullness; reduced incidence and strength of food cravings; reduced eating in response to food cravings; and increased ability to resist food cravings and control eating (all p<0·05). These improvements generally persisted for the duration of the trial, particularly in the naltrexone 32 mg plus bupropion group (webappendix). FCI total or subscale scores did not differ between combination treatment and placebo groups (data not shown).

Adverse events in the naltrexone plus bupropion groups were most frequently gastrointestinal in nature (table 4). The most common of these, nausea (naltrexone 32 mg plus bupropion *vs* placebo, p<0·0001; naltrexone 16 mg plus bupropion *vs* placebo, p<0·0001), was generally mild to moderate in intensity, transient, and did not result in discontinuation for most participants who reported it (table 5). Nausea was typically first reported during dose escalation in the experimental groups; the rate of onset seemed to plateau shortly after

reaching full dose and then was similar to the rate reported in the placebo group.

After a transient increase of approximately 1·5 mm Hg during the first 8 weeks, mean systolic blood pressure in the combination treatment groups returned to baseline after week 12 and decreased by approximately 1 mm Hg below baseline for the remainder of the study. The placebo group showed an approximate 1·5 mm Hg

	Placebo	Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion	p value for comparison with placebo	
				Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion
Waist circumference (cm)					
Baseline	110·0 (12·2)	109·8 (11·2)	108·8 (11·3)	..	..
Change	−2·5 (−3·3 to −1·6)	−5·0 (−5·9 to −4·2)	−6·2 (−7·1 to −5·4)	<0·0001*	<0·0001*
Triglycerides (mmol/L)†					
Baseline	1·28 (0·02)	1·33 (0·02)	1·31 (0·02)	..	..
Percentage change	−3·1% (−6·6 to 0·6)	−8·0% (−11·4 to −4·4)	−12·7% (−15·8 to 9·5)	0·0461*	<0·0001*
HDL cholesterol (mmol/L)					
Baseline	1·35 (0·35)	1·35 (0·35)	1·34 (0·35)	..	..
Change	0·00 (−0·02 to 0·02)	0·09 (0·06 to 0·11)	0·09 (0·07 to 0·11)	<0·0001*	<0·0001*
Percentage change	0·8% (−1·0 to 2·5)	7·6% (5·9 to 9·4)	8·0% (6·3 to 9·7)	..	..
LDL cholesterol (mmol/L)					
Baseline	3·10 (0·90)	3·23 (0·84)	3·08 (0·84)	..	..
Change	−0·08 (−0·15 to −0·02)	−0·10 (−0·16 to −0·03)	−0·11 (−0·17 to −0·05)	0·8112	0·4838
Percentage change	−0·5% (−2·6 to 1·6)	−1·5% (−3·6 to 0·6)	−2·0% (−4·0 to 0·1)	..	..
hsCRP (mg/L)†					
Baseline	3·57 (2·81)	3·89 (2·64)	3·83 (2·80)	..	..
Percentage change	−16·7% (−23·7 to −9·0)	−28·0% (−34·1 to −21·4)	−29·0% (−34·8 to −22·7)	0·0159*	0·0076*
Fasting insulin (pmol/L†)					
Baseline	78·7 (12·9)	79·0 (13·5)	77·2 (13·3)	..	..
Percentage change	−4·6% (−10·5 to 1·6)	−11·8% (−17·3 to −6·0)	−17·1% (−22·0 to −12·0)	0·0628	0·0007*
Fasting blood glucose (mmol/L)					
Baseline	5·21 (0·62)	5·28 (0·64)	5·23 (0·67)	..	..
Change	−0·07 (−0·13 to −0·01)	−0·13 (−0·19 to −0·07)	−0·18 (−0·24 to −0·12)	0·1584	0·0104*
Percentage change	−0·7% (−1·9 to 0·5)	−1·9% (−3·1 to −0·7)	−2·6% (−3·7 to −1·4)	..	..
HOMA-IR†					
Baseline	2·6 (2·0)	2·6 (2·0)	2·6 (2·0)	..	..
Percentage change	−5·9% (−12·1 to 0·7)	−14·3% (−20·1 to −8·1)	−20·2% (−25·3 to −14·8)	0·0442	0·0003*
IWQOL-Lite total score‡					
Baseline	71·8 (17·2)	70·7 (17·0)	70·3 (16·5)	..	..
Change	8·6 (−7·5 to 9·6)	11·7 (10·6 to 12·7)	12·7 (11·6 to 13·8)	<0·0001*	<0·0001*
Systolic blood pressure (mm Hg)					
Baseline	119·0 (9·8)	119·5 (9·9)	118·9 (9·9)	..	..
Change	−1·9 (−2·7 to −1·2)	0·3 (−0·5 to 1·1)	−0·1 (−0·9 to 0·7)	<0·0001	0·0008
Diastolic blood pressure (mm Hg)					
Baseline	77·3 (6·6)	76·6 (7·2)	77·1 (7·2)	..	..
Change	−0·9 (−1·4 to −0·3)	0·1 (−0·5 to 0·7)	0·0 (−0·5 to 0·6)	0·0150	0·0217
IDS-SR total score§					
Baseline	6·2 (5·0)	6·5 (5·5)	6·7 (5·5)	..	..
Change	−0·7 (−1·1 to −0·3)	0·0 (−0·4 to 0·4)	−0·3 (−0·7 to 0·1)	0·0080	0·1017

Data are for the primary analysis population. Baseline values are mean (SD); change and percentage change values are least squares mean (95% CI). hsCRP=high-sensitivity C-reactive protein. HOMA-IR=homoeostasis model assessment for insulin resistance. IWQOL-Lite=Impact of Weight on Quality of Life-Lite questionnaire. IDS-SR=Inventory of Depressive Symptomatology Self Report. *Endpoints that were significant according to the prespecified sequential closed testing procedure undertaken to correct for multiple comparisons. †Values that were $\log_{10}$ transformed before statistical analyses (to reduce skewness). Baseline values are geometric mean (SD); percentage change values are least squares geometric mean minus one (95% CI). ‡IWQOL-Lite total score is based on a scale from 0 to 100, where a score of 0–70 indicates severe impairment, 71–79 indicates moderate impairment, 80–87 indicates mild impairment, and 88–100 indicates no impairment. §IDS-SR total score is based on 30 items, where the score can range from 0 to 84; a total score of 13 or lower indicates no depression.

Table 3: **Secondary endpoints at 56 weeks**

reduction from baseline during the first 12 weeks, after which reductions ranged from 1·5 mm Hg to 3 mm Hg below baseline. A similar trend was seen for diastolic blood pressure. Change in pulse rate varied by study visit, generally fluctuating around baseline values in participants in the placebo group and around 1·5–2·5 beats per min higher than baseline values in participants in the combination treatment groups. In all treatment groups, greater weight loss was associated with greater reductions in mean blood pressure. IDS-SR total score and key items measuring sadness, irritability, anxiety or tension, and suicidality did not differ between naltrexone plus bupropion and placebo groups (data not shown). Combination treatment was not associated with increased frequency of treatment-emergent symptoms of depression, suicidality, other mood-related adverse events, or sexual dysfunction adverse events.

The proportion of participants reporting a serious adverse event did not differ between naltrexone 32 mg plus bupropion (nine [1·6%] of 573) or naltrexone 16 mg plus bupropion (nine [1·6%] of 569) and placebo (eight [1·4%] of 569) groups. None of these serious adverse events were regarded as related to study treatment by the investigators. There were no seizures or serious adverse events of hypertension. There were three cardiovascular serious adverse events: one pericardial effusion (placebo group), one cardiac failure (naltrexone 32 mg plus bupropion group), and one death due to acute myocardial infarction (a participant with multiple cardiovascular risk factors assigned to naltrexone 32 mg plus bupropion); investigators did not regard these

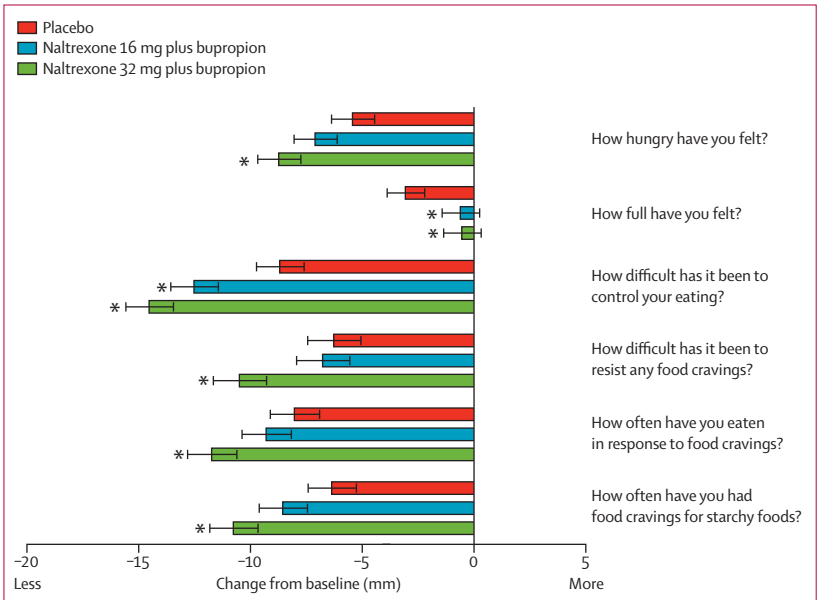


Figure 4: **Change in selected items from the Control of Eating Questionnaire at week 56**
Least squares mean (SE) change from baseline in hunger, eating, and food craving-related items that showed improvements (p<0·05) for naltrexone 32 mg plus bupropion compared with placebo at weeks 8 and 56; primary analysis population. Responses reflect experiences during the 7 days before answering the questionnaire. *p<0·05 compared with placebo.

	Placebo (n=569)	Naltrexone 16 mg plus bupropion (n=569)	Naltrexone 32 mg plus bupropion (n=573)
Adverse events			
Participants reporting any adverse event	390 (68·5%)	455 (80·0%)†	476 (83·1%)†
Nausea	30 (5·3%)	155 (27·2%)†	171 (29·8%)†
Headache	53 (9·3%)	91 (16·0%)†	79 (13·8%)†
Constipation	32 (5·6%)	90 (15·8%)†	90 (15·7%)†
Upper respiratory tract infection	64 (11·2%)	49 (8·6%)	57 (9·9%)
Dizziness	15 (2·6%)	44 (7·7%)†	54 (9·4%)†
Insomnia	29 (5·1%)	36 (6·3%)	43 (7·5%)
Vomiting	14 (2·5%)	36 (6·3%)†	56 (9·8%)†
Sinusitis	34 (6·0%)	34 (6·0%)	30 (5·2%)
Dry mouth	11 (1·9%)	42 (7·4%)†	43 (7·5%)†
Nasopharyngitis	31 (5·4%)	32 (5·6%)	29 (5·1%)
Diarrhoea	28 (4·9%)	31 (5·4%)	26 (4·5%)
Hot flush	7 (1·2%)	13 (2·3%)	30 (5·2%)†
Participants reporting any psychiatric adverse event	62 (10·9%)	76 (13·4%)	85 (14·8%)
Insomnia	29 (5·1%)	36 (6·3%)	43 (7·5%)
Anxiety	12 (2·1%)	12 (2·1%)	9 (1·6%)
Depression	6 (1·1%)	9 (1·6%)	3 (0·5%)
Safety endpoints‡			
Systolic blood pressure (LOCF; mm Hg)			
Baseline	119·0 (9·8)	119·3 (9·9)	119·0 (9·8)
Change	−2·1 (0·4)	0·2 (0·4)†	−0·4 (0·4)†
Systolic blood pressure (observed; mm Hg)			
Baseline	119·7 (9·7)	119·5 (9·9)	118·9 (9·5)
Change	−2·8 (0·5)	−0·4 (0·5)†	−1·6 (0·5)
Diastolic blood pressure (LOCF; mm Hg)			
Baseline	77·3 (6·7)	76·6 (7·2)	77·1 (7·2)
Change	−1·0 (0·3)	−0·0 (0·3)†	−0·1 (0·3)†
Diastolic blood pressure (observed; mm Hg)			
Baseline	77·5 (6·7)	76·2 (7·4)	77·1 (7·2)
Change	−1·4 (0·4)	−0·5 (0·4)	−0·8 (0·4)
Pulse rate (LOCF; beats per min)			
Baseline	71·8 (8·0)	71·4 (8·7)	72·0 (8·7)
Change	−0·1 (0·3)	1·5 (0·3)†	1·0 (0·3)†
Pulse rate (observed; beats per min)			
Baseline	71·6 (7·9)	71·1 (8·6)	72·4 (8·6)
Change	−1·0 (0·4)	1·1 (0·4)†	0·4 (0·4)†

Adverse event data are number of participants (%); safety analysis population. Baseline values are mean (SD), change values are least squares mean (SE) for change from baseline to week 56. No participants in any of the groups had an adverse event related to suicidality. There were no events of suicidal attempt, completed suicide, self-injurious ideation, or overdose. *Any adverse event with a frequency of 5% or more in either naltrexone plus bupropion group; any psychiatric event occurring in 1% of participants or more in any treatment group. One participant can report several events. †p<0·05 compared with placebo. ‡Values are based on the safety analysis population at week 56, with the last observation carried forward (LOCF) for participants who prematurely discontinued or with observed values at week 56 (placebo, n=281; naltrexone 16 mg plus bupropion, n=276; naltrexone 32 mg plus bupropion, n=292).

Table 4: **Adverse events and safety endpoints***

events as related to study drug. There were no clinically significant effects of naltrexone plus bupropion on electrocardiogram findings or safety laboratory measures (data not shown).

Discussion

This study substantiates phase 2 findings showing that treatment with naltrexone plus bupropion combined with mild diet and exercise in overweight or obese patients is associated with greater weight loss and greater improvement in several cardiometabolic risk factors than is placebo. Combination treatment was generally well tolerated. Mean weight loss in participants assigned to naltrexone 32 mg plus bupropion for up to 56 weeks was 6·1 kg compared with 1·4 kg in participants assigned to placebo. Participants in the naltrexone 32 mg plus bupropion group were three times more likely to lose at least 5% and 10% of their bodyweight than were participants in the placebo group. Weight loss in the placebo group was minimal and consistent with mild hypocaloric diet and exercise instruction.[21]

Secondary efficacy measures were generally consistent with the expected effect of greater weight loss in the combination treatment groups. Compared with placebo, weight-related quality of life was significantly improved in the naltrexone plus bupropion groups, mainly as a result of increased physical function and self-esteem. Treatment with naltrexone 32 mg plus bupropion was associated with significantly greater weight loss and generally greater improvements in cardiometabolic risk factors and weight-related quality of life than was the naltrexone 16 mg plus bupropion regimen.

Consistent with the known effects of bupropion,[22–24] combination treatment resulted in a small and transient increase from baseline in mean systolic and diastolic blood pressure. Mean blood pressure in the naltrexone plus bupropion groups was subsequently decreased from baseline for the remainder of the study; these reductions were smaller than those seen in the placebo group. Although treatment with naltrexone plus bupropion partly attenuated the favourable effect of weight loss on blood pressure, greater weight loss was associated with larger decreases in systolic and diastolic blood pressure in all treatment groups. Overall, the effects of treatment with naltrexone plus bupropion on cardiometabolic risk factors are consistent with the health benefits of clinically meaningful weight loss and might confer reduced long-term risk.[25,26] The ability of this combination to modify long-term clinical outcomes in obese patients requires further study.

Although more adverse events were reported in the naltrexone plus bupropion groups than in the placebo group, adverse events in participants assigned to combination treatment were mostly mild to moderate in severity and transient, typically occurred during the titration phase, and were consistent with the known safety and tolerability profiles of the individual drugs.[27,28] The proportion of participants who reported nausea, which has been associated with naltrexone,[28] was lower in this study than in phase 2 studies of immediate-release naltrexone,[13] suggesting improved tolerability with a sustained-release formulation. Insomnia and dry mouth, which are associated with bupropion,[27] were reported by participants in this study at or below previously reported rates.[27] Combination treatment was not associated with increased depression or suicidality compared with placebo.

Obesity is increasingly recognised as a serious public health issue.[1] In addition to primary emphasis on lifestyle modification, new therapeutic options with acceptable risk-benefit profiles are needed, particularly in view of the paucity and limitations of currently approved anti-obesity agents.[2,29] Treatment with naltrexone 32 mg plus bupropion for up to 56 weeks was associated with 4·7 kg placebo-subtracted weight loss, compared with the 4·2 kg and 2·9 kg net weight loss with sibutramine and orlistat reported in a recent meta-analysis.[29] Moreover, the clinical and safety profiles of naltrexone and bupropion have been well characterised in more than 20 years of clinical trials and practical experience in patients. Although the absence of head-to-head assessments with other pharmaceutical treatments for obesity limits direct efficacy and safety comparisons, the current findings suggest that the combination of naltrexone plus bupropion could be a valuable new therapeutic option for obesity. Naltrexone and bupropion were rationally chosen to take advantage of recent mechanistic understanding of CNS pathways that regulate homoeostatic and hedonic mechanisms associated with bodyweight and eating behaviour. The validation of these mechanisms through preclinical and clinical trials furthers our understanding of the CNS pathways involved in obesity and weight loss.

Growing evidence suggests that some forms of obesity are associated with dysregulation of CNS reward pathways.[30] The effects of bupropion and naltrexone in addictive disorders, as well as preclinical evidence suggesting synergism of these drugs in reward pathways, is consistent with findings suggesting that this combination improves control of eating and response to

	Placebo (n=569)	Naltrexone 16 mg plus bupropion (n=569)	Naltrexone 32 mg plus bupropion (n=573)
Any adverse event leading to discontinuation	56 (9·8%)	122 (21·4%)†	112 (19·5%)†
Gastrointestinal disorders	9 (1·6%)	42 (7·4%)†	48 (8·4%)†
Nausea	2 (0·4%)	26 (4·6%)	36 (6·3%)
Nervous system disorders	15 (2·6%)	30 (5·3%)†	19 (3·3%)
Dizziness	3 (0·5%)	13 (2·3%)†	7 (1·2%)
Headache	4 (0·7%)	9 (1·6%)	5 (0·9%)
Psychiatric disorders	11 (1·9%)	13 (2·3%)	12 (2·1%)
Depression	2 (0·4%)	6 (1·1%)	1 (0·2%)

Data are number of participants (%); safety analysis population. *Any adverse event leading to discontinuation of 1% of participants or more in any treatment group. †p<0·05 compared with placebo.

Table 5: **Adverse events leading to discontinuation***

food cravings. Since many overweight adults report food cravings to be an important barrier to their ability to adhere to a diet,[31] these actions could add to the usefulness of naltrexone plus bupropion in treatment of obesity.

This study has some limitations. First, the trial had a generally healthy population comprised mainly of middle-aged white women and a completion rate of approximately 50% in all groups. These are common limitations in phase 3 trials in obesity, and women are more likely to seek pharmacotherapy for weight loss than are men.[32] Furthermore, the effect of early withdrawal was assessed and all sensitivity analyses support the results of the primary analysis. Second, although this 56-week study expands upon shorter phase 2 studies, adults with diabetes or active cardiovascular disease were excluded, and safety findings might not be generalisable to patients with obesity who have higher cardiovascular risk. Extended studies will better determine any long-term benefits of combination treatment with naltrexone plus bupropion. Third, because data for adherence to diet and exercise instruction was not obtained, the contribution of these interventions to the study outcome cannot be fully understood. Finally, this study compared naltrexone plus bupropion with placebo; until head-to-head studies are undertaken, the ability to compare this combination with currently available pharmacotherapies for obesity is limited.

Treatment with sustained-release naltrexone plus bupropion offers a new approach to management of obesity that might improve the ability to control eating behaviour and response to food cravings. Although lifestyle modification is first-line therapy for obesity, adherence to this intervention is poor.[7,33] 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.

Contributors

FLG was the principal investigator for the study. FLG, MG, and ED were involved in study concept and design, with contribution from investigators. JE was the primary statistician. All authors participated in data analysis and interpretation. FLG wrote the report in collaboration with a medical writer. FLG and the medical writer revised the report with participation from all authors. All authors reviewed and approved the report before submission.

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Conflicts of interest

FLG 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. FLG holds three patents related to obesity treatment. KF is a member of the advisory board and has received consulting fees and research grant support from Orexigen. RAP has received a research grant and travel support from Orexigen. SM has received research grant support from Orexigen. MG has received consulting fees and travel support from Orexigen. JE is a former employee at Orexigen. DDK and ED are employees at and hold stock in Orexigen.

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