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Effect of Lorcaserin Alone and in Combination with Phentermine on Food Cravings after 12 week-treatment: Randomized Sub-study

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Abstract

Objective—This study evaluated the effect of lorcaserin 10mg twice daily (LOR BID) or with phentermine, 15mg/day (LOR BID+PHEN QD) and 15mg twice daily (LOR BID+PHEN BID) in conjunction with energy restriction, on food cravings.

Methods—235 patients without diabetes, but with obesity or overweight and ≥1 comorbidity received (LOR BID), (LOR BID+PHEN QD), or (LOR BID+PHEN BID) for 12 weeks, in a randomized double-blind study. The Food Craving Inventory (FCI) and the Control of Eating Questionnaire (COEQ) were administered over 12 weeks.

Results—The FCI total score and the subscale scores reduced from baseline in all groups. The least squares means (95% confidence intervals) for the total scores were −0.65 (−0.75, −0.55),

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−0.75 (−0.84, −0.65), and −0.84 (−0.95, −0.74) in the LOR BID, LOR BID+PHEN QD, and LOR BID+PHEN BID groups, respectively. Cravings assessed by COEQ reduced from baseline in all groups. In general, the combination treatments were more effective than lorcaserin alone. At week 12, except for fruit juice and dairy products, general and specific cravings reduced in LOR BID +PHEN BID compared to LOR BID ($p<0.05$).

Conclusions—Lorcaserin in combination with phentermine improves control of food cravings during short-term energy restriction.

Keywords

Craving; lorcaserin; phentermine; Food Craving Inventory; Hunger; Control of Eating Questionnaire

Introduction

Food cravings refer to a motivational state whereby an individual experiences an intense desire to eat a specific food.[1] It is the intensity of the state that distinguishes food cravings from ordinary food choices, and it is the specificity of the food, drink, or taste that distinguishes food cravings from hunger. While any of selection of foods may satisfy hunger, there is a specificity that must be matched to satisfy a food craving.[2] The strength of a craving is not a metric or equivalent of hunger and the notion that cravings are a response to nutritional and caloric deficits[3] has lost ground as it has become abundantly clear that there are a range of biological, cognitive, and emotional processes that trigger food cravings. Among them, are menstrual-related changes,[4] dysphoric mood states[5] as well as expectations and cognitions.[6] The craving experience can vary depending upon age, culture, and gender differences.[1]

Strong desires to eat may be evoked by cues such as the sight and smell of food, or stress, or hormonal fluctuations (cue-induced craving) as well as in the absence of such cues (tonic craving). These cravings explain 11% of the variance in eating-related outcomes surpassing any other single predictor of eating and weight gain.[7] Craving is a commonly used term in daily life as individuals face the dilemma of attempting to restrain their eating in an environment where there is no dearth of highly desirable foods. Cravings are frequently used to describe the reason why a food is consumed.[1] Most people are more likely to indulge in these cravings rather than restrain themselves.[6] Thus, an intervention that addresses cravings may be particularly helpful to individuals engaging in a relentless battle to curb overeating.

The corticolimbic brain areas involved in cognition, emotion, motivation, and decision-making interact with the hypothalamic and brain stem structures involved in the control of food intake and energy balance. Eating in the absence of nutritional need is evidence of a strong and overpowering control exerted by the corticolimbic structures.[8] Dopamine signaling plays a key role in translating motivation into action,[9] and opioid peptide transmission in the nucleus accumbens modulates the hedonic or pleasure impact of food.[10]

Phentermine is primarily a noradrenergic and perhaps dopaminergic sympathomimetic amine that acts as an appetite suppressant.[11] It was approved by the United States Food and

Drug Administration (FDA) for use in conjunction with lifestyle change efforts for short-term (several weeks) weight management. Serotonin (5-hydroxytriptamine, [5-HT]) is a neurotransmitter that regulates food intake and energy balance by acting on the central nervous system, with the key mediators being the 5-HT 2C receptors (5-HT2CR).[12] Further, 5-HT2CR have an established role in the regulation of forebrain dopaminergic systems[13–15] and should therefore affect behaviors motivated by food. Lorcaserin (Belviq®) is a highly selective 5-HT2CR agonist approved by the FDA as an adjunct to an energy restricted diet and increased physical activity for the long-term treatment of obesity and overweight in the presence of one or more weight-related comorbid conditions. When lorcaserin was approved for the treatment of obesity the FDA requested that the sponsoring company perform a safety study of phentermine used in combination with lorcaserin. This report describes the effect of lorcaserin alone and in combination with two doses of phentermine on perceptions of food cravings that was also investigated in the safety study done at the request of the FDA.[16]

Methods

Study Overview

This 12-week, randomized, double-blind, parallel-group, pilot safety study (Clinicaltrials.gov identification number: NCT01987427; Figure S1) was conducted at 12 sites in the United States, from October 2013 to September 2014, following Declaration of Helsinki guidelines. Institutional review boards reviewed and approved the protocol and all subjects provided written informed consent. The primary endpoint was the prevalence of serotonin related adverse events in the three groups and the secondary endpoint was weight loss and adverse events in the three groups. The results of the primary and secondary endpoints have been published.[16] The exploratory endpoint was the prevalence of food cravings during the treatment period.

Subjects

Eligible subjects were males and females aged 18–60 years, with a body mass index (BMI) ≥ 30 kg/m^2, or 27–29.9 kg/m^2 with one or more weight-related comorbidity (e.g., hypertension, dyslipidemia, sleep apnea). All subjects were ambulatory and able to participate in a moderate-intensity exercise program. Key exclusion criteria included recent treatment with monoamine oxidase inhibitors; recent or active history of depression or psychiatric disease requiring prescription medication; concomitant use of serotonin-norepinephrine reuptake inhibitors (SSRIs); use of fenfluramine, related derivatives, or other medications associated with increased risk of valvulopathy and pulmonary hypertension; history of cardiovascular disease within 3 months of screening; systolic blood pressure ≥150 or diastolic blood pressure ≥ 95 mmHg; valve replacement surgery; clinically significant diagnosed valvulopathy; diabetes mellitus; bariatric surgery; weight change in excess of five kg in the preceding three months; and pregnancy or lactation.

Randomization and Interventions

Subjects (n = 238) were assigned to treatments based on a computer-generated randomization scheme, reviewed and approved by an independent statistician. Subjects were

randomly assigned in a 1:1:1 ratio to receive Lorcaserin 10 mg twice daily (LOR BID) or Lorcaserin 10 mg twice + phentermine 15 mg once daily (LOR BID + PHEN QD), or Lorcaserin 10 mg twice + phentermine 15 mg twice daily (LOR BID + PHEN BID). As previously described,[16] subjects were screened in the two weeks prior to the baseline visit, following which assessments were made at baseline, and weeks 2, 4, 8, and 12. Adverse events (AEs), vital signs, concomitant medications, and body weight were assessed at each visit. A safety assessment via the telephone was conducted 3–4 weeks after subjects received their last study medication dose. All subjects received one-on-one counseling with a trained program counselor at each study visit, including instruction to exercise at moderate intensity for 30 minutes/day and reduce daily caloric intake to 600 kcal below their individual estimated daily energy requirement. Food cravings were assessed at baseline and weeks 4, 8, and 12.

Questionnaires

Food cravings were assessed using the Food Craving Inventory (FCI) and the Control of Eating Questionnaire (COEQ). The FCI is a validated questionnaire that asks about craving for specific foods over the last 30 days. Subjects rate their cravings for specific foods using a 5-point Likert scale. These foods are subsequently categorized as high fat, sweets, carbohydrates/starches and fast-food fats.[17] FCI measured the impact of the study intervention on cravings for high fats, sweets, carbohydrates/starches, fast-food fats and total cravings; therefore, decreases indicate less of a craving or desire for the food category. The COEQ is a validated questionnaire that asks more general questions about craving, including the prevalence and intensity of cravings, as well as the difficulty in resisting them.[18] The FCI and COEQ were measured at baseline, week 4, week 8, and week 12 (end of study). Each COEQ question was rated on a 10cm visual analog scale, reported in mm and each question was scored individually.

Statistical Analyses

Analyses of efficacy variables were performed on the modified intent-to-treat (MITT) population (all patients who received ≥1 dose of study drug and had both baseline and post-randomization weight measurements), with last-observation-carried-forward (LOCF) imputation. To analyze the differences in food cravings between the groups, analysis of covariance (ANCOVA) model was used to estimate how the ratings for each question on the FCI and COEQ change from baseline to week 12. The model included change from baseline as the response, treatment as a factor, and baseline BMI status as well as baseline scores as covariates. All values are expressed as least squares means ± standard error. Significance was set at $p < 0.05$.

Results

344 subjects were screened for inclusion in the study, of which 238 subjects were randomized to receive LOR BID, LOR BID+PHEN QD, or LOR BID+PHEN BID. Three subjects did not take the study drug; the remaining 235 comprised the full analysis set (FAS) population. Of the 235 patients treated, 44 (18.7%) dropped out of the study before week 12.

Safety and Body Weight Assessments

The results of the safety of the treatment and changes in body weight have been published.[16] Briefly, most withdrawals were from the LOR BID+PHEN BID group (n=79), of which 20 subjects (25.3%) did not complete the trial. The primary reason for non-completion was loss to follow-up, which occurred in 8.9% of the total population (21 of 235). AEs were cited as the reason for discontinuation by an additional 15 patients.

Mean weight loss ± standard deviation at week 12 in the MITT population was 3.5 ± 3.7 kg/3.3 ± 3.4%, 7.0 ± 6.0 kg/6.7 ± 5.4%, and 7.6 ± 4.7 kg/7.2 ± 4.6% for LOR BID, LOR BID+PHEN QD, and LOR BID+PHEN BID, respectively. Mean weight loss at week 12 in the Completers population was 4.0 ± 3.8 kg/3.8 ± 3.3%, 7.6 ± 6.1 kg/7.3 ± 5.4%, and 8.9 ± 4.3 kg/8.7±4.1% for LOR BID, LOR BID+PHEN QD, and LOR BID+PHEN BID, respectively (Figure 1). An exploratory analysis of change from baseline in body weight (kg/percent) using a mixed model repeated measures analysis indicated significant improvements with the combination therapy vs. LOR BID in both the MITT and Completer populations. Weight loss between the LOR BID + PHEN QD and LOR BID+PHEN BID groups was not significantly different. Baseline demographics and characteristics of the FAS population (Table 1) were similar between the groups.

Food Craving Inventory

There were significant reductions from baseline in all three groups across all subscales as well as the total score of the FCI. LOR BID + PHEN BID treatment reduced cravings for sweets and fast-food fats as well as the total score compared to LOR BID treatment, but the differences between the groups treated with LOR BID and LOR BID + PHEN QD, or LOR BID + PHEN BID and LOR BID + PHEN QD were not significantly different (Figure 2).

Control of Eating Questionnaire

At the end of the study, in all three groups, there were significant reductions from baseline in the ratings for hunger, frequency and strength of food cravings, difficulty in resisting food cravings, eating in response to craving, difficulty in controlling eating, and most of the questions relating to cravings for specific foods. In the LOR BID + PHEN BID group, ratings on all of the questions relating to cravings in general as well as mood were significantly improved compared to the LOR BID group. Significantly greater reductions were demonstrated in the LOR BID + PHEN BID group compared to the LOR BID + PHEN QD group in the ratings for frequency and strength of food cravings, difficulty in resisting food cravings, eating in response to craving, and difficulty in controlling eating. There was a significantly greater reduction in the LOR BID + PHEN QD group compared to the LOR BID group in the ratings for the frequency of food cravings and difficulty in controlling eating. Table 2 lists the comparisons between the groups for all of the 20 questions in the COEQ, whereas Figure 3 provides a comparison of selected questions. In the cravings for specific foods, there was a significant reduction from baseline in the assessment of craving for chocolate, other sweets, non-sweets, starchy foods, and dairy in all three groups. The reduction in craving for chocolate in the LOR BID + PHEN BID group was significantly lower compared to the LOR BID + PHEN QD group. In the LOR BID + PHEN BID group subjects reported significantly lower cravings for all of the foods except the craving for dairy

products, compared to the LOR BID group. There was a significantly greater reduction in the craving for non-sweets in the LOR BID + PHEN QD group compared to the LOR BID group (Figure 4).

Discussion

Treatment with LOR BID, and the combination of LOR BID + PHEN QD or LOR BID + PHEN BID reduced subject's perceptions of food cravings compared to baseline, with the combination treatment providing greater reductions in a dose dependent manner. As previously reported, there was a similar pattern of weight loss in these groups counseled to reduce energy intake and increase physical activity, while being treated with the different doses of the medication.[16]

If food cravings were psychological manifestations of energy depletion reflected as a metabolic need and expressed as hunger, the reduction in energy intake during the treatment period would be expected to increase food cravings. However, in our study there was a reduction in food cravings despite energy restriction which is consistent with other studies whose findings were contrary to this expectation. In a survey evaluating food cravings in a large sample of undergraduate females, those who were currently on an energy restricted diet reported no more food cravings than non-dieters.[19] Although a weak association between dietary restraint and craving strength has been observed in a cross sectional study with female participants, the association of food cravings with emotional eating was by far of greater strength.[5]

In a comparison between subjects on a 1200 kilocalorie (kcal)/day balanced diet and a 420 kcal/day liquid diet for 12 weeks, despite an almost three fold greater weight loss on the 420 kcal/day liquid diet, the reduction in craving was greater as assessed by all the subscales of the FCI on the 420 kcal/day liquid diet compared to the 1200 kcal/day diet.[20] These studies underscore the difference between the physiologic need expressed as hunger, and food cravings. The results of a meta-analyses of studies evaluating food cravings during energy restriction concur with the reduction in cravings during calorie restriction.[21] Nevertheless, what appears to be of significant impact is that in our study, the dose response reduction elicited by the treatment suggests that lorcaserin in combination with phentermine can enhance the reduction in food cravings during energy restriction.

Pharmacologic interventions to address food cravings have also been explored in other studies. Bupropion, a dopamine reuptake inhibitor is approved for the treatment of depression and seasonal affective disorder, and as an aid in smoking cessation.[22,23] Naltrexone, an opioid receptor antagonist is approved for the treatment of alcohol and opioid dependence.[24,25] The combination treatment of naltrexone and bupropion showed improvements in control of eating assessed using the COEQ, in subjects placed on an energy restricted diet. Subjects in the group receiving the drug treatment reported reduced frequency and strength of food cravings compared to the group receiving the placebo. However, the FCI which assessed cravings for specific foods did not show any significant changes between the groups;[26–28] whereas LOR BID significantly reduced the total score as

well as the subscale scores on the FCI, from baseline in addition to reducing general and specific food cravings measured using the COEQ.

In a 12-week randomized controlled trial, the effect of phentermine and a meal replacement system along with nutritional counselling on weight loss and food cravings were compared with a group receiving the meal replacement and counseling along with a placebo.[29] A greater proportion of subjects in the phentermine group lost 5% or more of their body weight, and the craving for fats and sweets (evaluated using a variation of the FCI) reduced in the phentermine group, compared to the placebo group. The much smaller sample size in this study compared with the Phase III trial of naltrexone and bupropion that evaluated food cravings, suggests that phentermine may have a larger effect size on food cravings than the naltrexone/bupropion combination; but, it is only through a clinical trial making this comparison can any determination be made. Using neuroimaging techniques to map areas of the brain involved in the reward circuitry, it has been suggested that liraglutide a GLP-1 agonist approved by the FDA for long-treatment of obesity, may also reduce the appeal of food cues.[30]

The behavioral and neurobiological bases of obesity and substance abuse converge on several fronts.[31] For instance, cravings are associated with binge eating[32] as well drug addiction.[31] Lorcaserin has been investigated for its effects on smoking cessation and it has been shown to reduce nicotine seeking behaviors[33,34] In particular, lorcaserin prevents the nicotine-induced response to a rewarding stimuli.[33] Lorcaserin has also been shown to modulate impulsive behaviors.[35] In a clinical trial, subjects taking LOR BID in conjunction with an energy restricted diet for four weeks had decreased activation in attention-related areas of the brain, in response to food cues. Analyses of baseline predictors of success with administration of lorcaserin suggested that subjects who engaged in emotional eating were most likely to benefit from lorcaserin treatment.[36] Our study provides evidence for the effect of lorcaserin in combination with phentermine on the reward components of eating behavior. These aspects may be of particular relevance in eating disorders such as binge eating disorder where individuals widely experience food cravings and certainly bears investigation in future studies.

The strengths of this study included the randomized and double-blind nature of the trial; however, there were limitations. The study lacked a control group, and one could argue that part of the reduction in craving with the lorcaserin group was due to caloric restriction. The absence of measurements related to cravings once subjects were no longer on the medication following completion of the trial could also be considered a weakness, but was a function of superimposing the evaluation of craving as an exploratory endpoint on a pre-existing trial design. Another finding in the trial to note was the higher dropout rate in the LOR BID + PHEN BID group. The rates were 74.7%, retention in the LOR BID + PHEN BID compared to 87.2% and 82.1% in the LOR BID and LOR BID + PHEN QD respectively. A dose-dependent dropout rate for adverse events related to phentermine was also seen in trials of topiramate + phentermine and phentermine + lorcaserin.

Conclusions

Lorcaserin at 20mg/day may enhance the reduction in food cravings when subjects are placed on an energy restricted diet; however, lorcaserin at 20mg/dayin combination with phentermine at 15 mg/day or 30mg/day reduces food cravings in a dose dependent manner. Phentermine has previously been shown to reduce food cravings when administered alone as has the combination of bupropion and naltrexone, as well as liraglutide. Thus, anti-obesity medications appear to influence the motivational drive to eat or reward-induced eating; however, the relative contributions of these medications in addressing physiologic hunger and reward mechanisms, the long-term effects as well as the subsets of the population that may respond more favorably than others have yet to be determined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known about the subject

- Lorcaserin, (LOR) a selective 5-HT_{2c} receptor agonist, is approved for weight management as an adjunct to a reduced-calorie diet and increased physical activity.
- LOR in combination with phentermine 15 mg once (QD) or twice (BID) a day gives additive weight loss.

What this study adds

- LOR 10 mg BID may reduce craving during energy restriction, but LOR BID in combination with phentermine 15mg QD or BID, reduces cravings in a dose dependent manner.

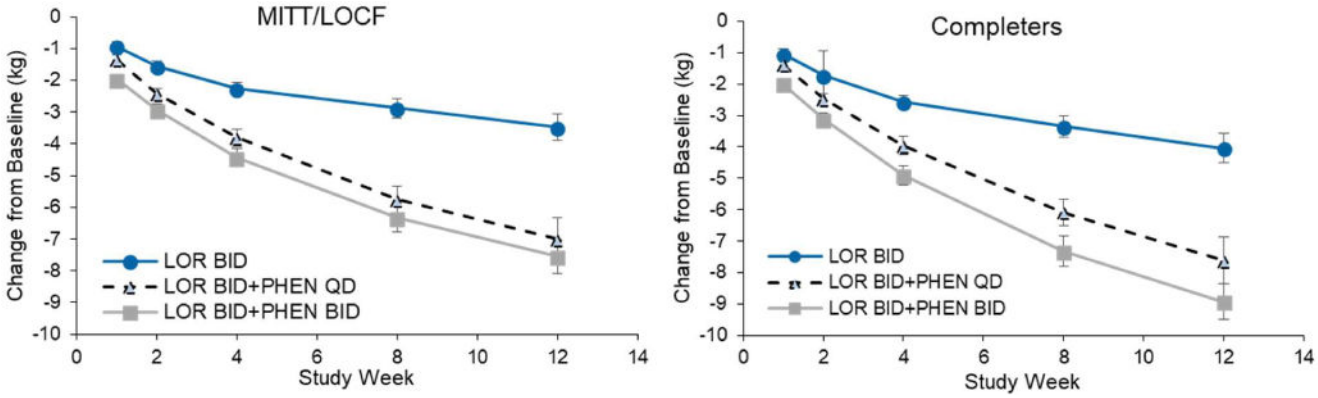

Figure 1.

Change from baseline in body weight in (A) modified intent to treat with last observation carried forward (MITT/LOCF) and (B) Completer groups. Originally published in Obesity (2017) 25, 857–65.

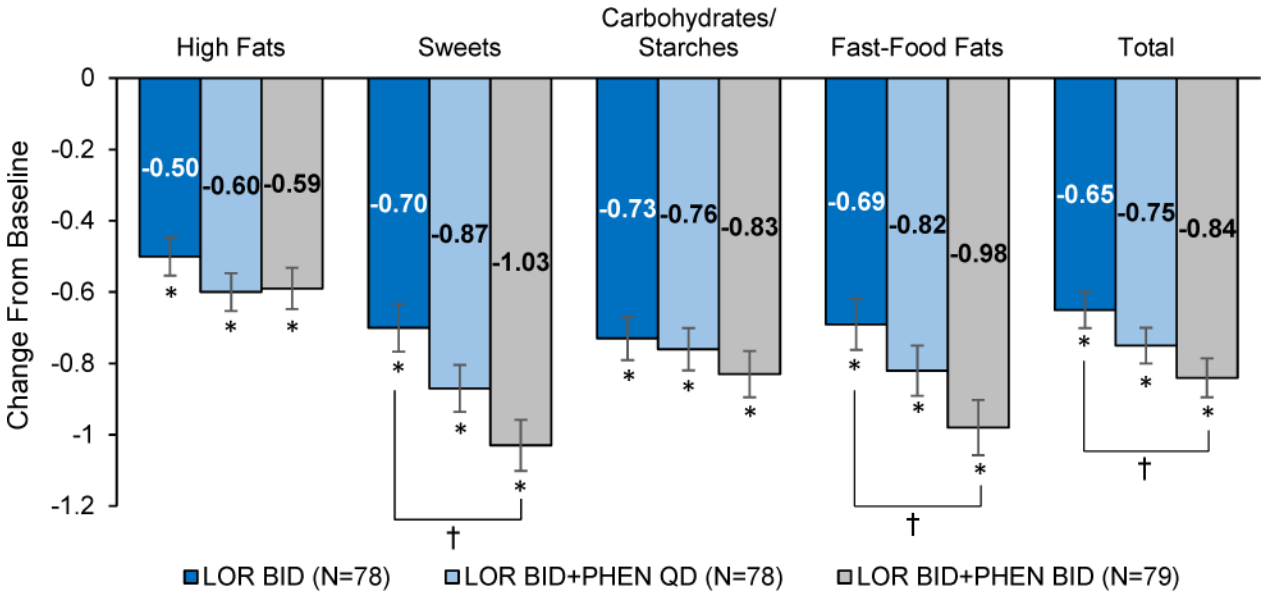

Figure 2.

Change from baseline at week 12 in the Food Craving Inventory (FCI) subscales and in the total score. *p<0.0001 for FCI score change from baseline at Week 12. †p<0.01 between treatment groups. Data presented are the LS mean change from baseline ± SEM. BID=twice daily; LOR=lorcaserin HCl 10 mg; LS=least squares; PHEN=phentermine HCl 15 mg; QD=once daily; SEM=standard error of the mean.

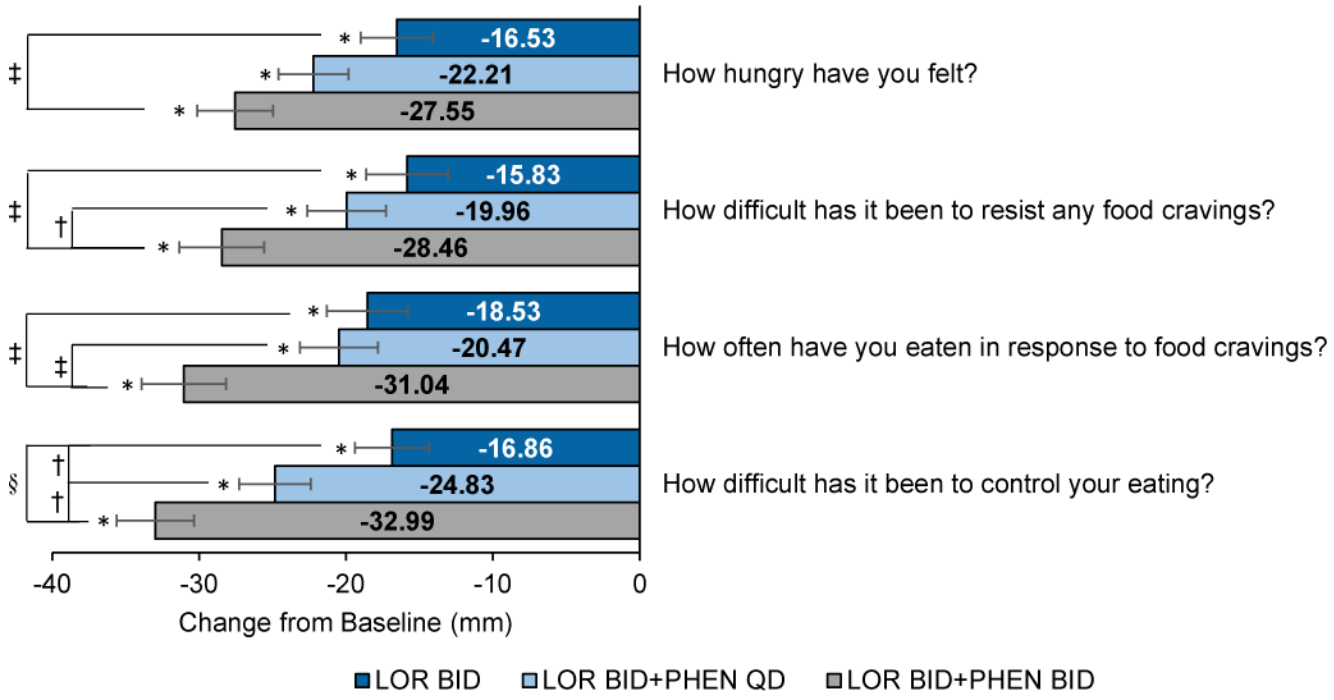

Figure 3.

Change from baseline at week 12 in selected questions from the Control of Eating Questionnaire (COEQ). *$p<0.0001$ for COEQ response change from baseline at Week 12. †$p<0.05$ between treatment groups. ‡$p<0.01$ between treatment groups. §$p<0.0001$ between treatment groups. Data presented are the LS mean change from baseline ± SEM. BID=twice daily; LOR=lorcaserin HCl 10 mg; LS=least squares; PHEN=phentermine HCl 15 mg; QD=once daily; SEM=standard error of the mean.

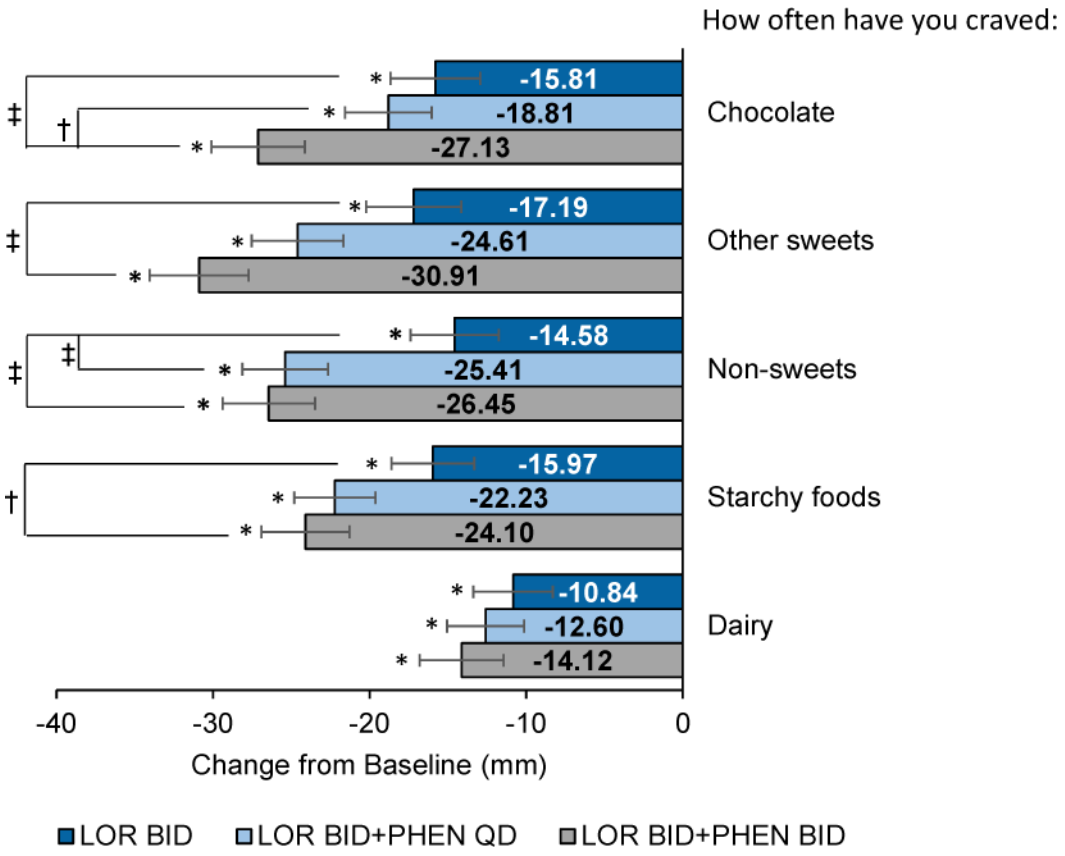

Figure 4.

Change from baseline at week 12 in the Control of Eating Questionnaire (COEQ) relating to specific types of foods. *p<0.0001 for COEQ response change from baseline at Week 12. †p<0.05 between treatment groups. ‡p<0.01 between treatment groups. Data presented are the LS mean change from baseline ± SEM. BID=twice daily; LOR=lorcaserin HCl 10 mg; LS=least squares; PHEN=phentermine HCl 15 mg; QD=once daily; SEM=standard error of the mean.

Table 1

Baseline characteristics and demographics (full analysis population)[a]

Demographics	LOR BID (N=78)	LOR BID+ PHEN QD (N=78)	LOR BID+ PHEN BID (N=79)	Total (N=235)
Age, mean (SD), years	42.5 (11.0)	44.8 (11.1)	41.2 (11.7)	42.8 (11.3)
Sex, n (%)				
Male	10 (12.8)	8 (10.3)	17 (21.5)	35 (14.9)
Female	68 (87.2)	70 (89.7)	62 (78.5)	200 (85.1)
Race, n (%)				
White	46 (59.0)	50 (64.1)	44 (55.7)	140 (59.6)
Black or African American	29 (37.2)	26 (33.3)	32 (40.5)	87 (37.0)
Asian	0	1 (1.3)	0	1 (0.4)
American Indian or Alaska Native	1 (1.3)	1 (1.3)	1 (1.3)	3 (1.3)
Native Hawaiian or Other Pacific Islander	0	0	1 (1.3)	1 (0.4)
Other	2 (2.6)	0	1 (1.3)	3 (1.3)
Ethnicity, n (%)				
Hispanic or Latino	11 (14.1)	7 (9.0)	6 (7.6)	24 (10.2)
Not Hispanic or Latino	67 (85.9)	71 (91.0)	73 (92.4)	211 (89.8)
Weight, mean (SD), kg	105.3 (21.0)	105.0 (23.4)	106.6 (19.7)	105.7 (21.3)
BMI, mean (SD), kg/m^2	38.4 (7.5)	38.0 (6.8)	38.5 (6.0)	38.3 (6.8)
Comorbid condition[b], n (%)				
Hypertension	13 (16.7)	18 (23.1)	16 (20.3)	47 (20.0)
Dyslipidemia	19 (24.4)	20 (25.6)	11 (13.9)	50 (21.3)
Sleep apnea	3 (3.8)	3 (3.8)	0	6 (2.6)
Impaired glucose tolerance	2 (2.6)	0	0	2 (0.9)
Blood pressure, mean (SD), mmHg				
Systolic	122.5 (12.4)	119.9 (13.6)	122.1 (12.0)	121.5 (12.7)
Diastolic	77.8 (8.3)	78.7 (8.3)	79.3 (8.2)	78.6 (8.2)
Heart rate, mean (SD), bpm	71.9 (9.5)	73.1 (9.5)	72.2 (10.7)	72.4 (9.9)
Waist circumference, mean (SD), cm	112.2 (13.8)	112.2 (15.1)	114.0 (12.0)	112.8 (13.7)
Hip circumference, mean (SD), cm	124.1 (14.3)	123.7 (14.3)	125.4 (12.8)	124.4 (13.8)
Waist/hip ratio, mean (SD)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)

[a] All randomized patients who received at least one dose of the study drug.

[b] Comorbid conditions were self-reported as medical history and supported by medication use and/or baseline laboratory values. Some patients reported ≥ 1 comorbid condition.

BID=twice daily; BMI=body mass index; LOR=lorcaserin HCl 10 mg; PHEN=immediate-release phentermine HCl 15 mg; QD=once daily, SD=standard deviation. Originally published in Obesity (2017) 25, 857–65. Originally published in Obesity (2017) 25, 857–65.

Table 2

Comparison between the groups of the mean change from baseline in the scores for each of the questions on the Control of Eating Questionnaire

	Question	Week 4						Week 8						Week 12					
		2 v. 1		3 v. 1		3 v. 2		2 v. 1		3 v. 1		3 v. 2		2 v. 1		3 v. 1		3 v. 2	
		Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value
1	How hungry have you felt?	−0.9 ± 3.1	0.768	−7.6 ± 3.1	**0.015**	−6.7 ± 3.1	**0.031**	−4.3 ± 3.3	0.204	−9.0 ± 3.5	**0.010**	−4.7 ± 3.3	0.155	−5.7 ± 3.3	0.090	−11.0 ± 3.4	**0.002**	−5.3 ± 3.4	0.114
2	How full have you felt?	0.7 ± 3.1	0.824	7.4 ± 3.1	**0.019**	6.7 ± 3.1	**0.030**	2.2 ± 3.3	0.503	8.6 ± 3.4	**0.011**	6.4 ± 3.2	**0.046**	0.5 ± 3.1	0.878	5.9 ± 3.2	0.070	5.4 ± 3.1	0.085
3	How strong was your desire to eat sweet foods?	−5.0 ± 3.6	0.163	−11.4 ± 3.6	**0.002**	−6.4 ± 3.6	0.075	−1.9 ± 3.6	0.597	−9.0 ± 3.7	**0.016**	−7.1 ± 3.6	**0.049**	−2.7 ± 4.0	0.504	−12.6 ± 4.1	**0.003**	−9.9 ± 4.0	**0.015**
4	How strong was your desire to eat savoury foods?	−6.1 ± 3.6	0.090	−7.3 ± 3.6	**0.044**	−1.2 ± 3.6	0.737	3.8 ± 3.5	0.280	−5.6 ± 3.6	0.125	−9.4 ± 3.5	**0.007**	−10.1 ± 4.0	**0.013**	−13.5 ± 4.1	**0.001**	−3.5 ± 4.0	0.389
5	How happy have you felt?	3.8 ± 3.0	0.209	4.8 ± 3.0	0.112	1.0 ± 3.0	0.734	0.3 ± 3.5	0.935	3.2 ± 3.6	0.372	2.9 ± 3.5	0.398	4.1 ± 3.5	0.240	7.9 ± 3.6	**0.029**	3.8 ± 3.5	0.286
6	How anxious have you felt?	−2.2 ± 3.7	0.554	−1.8 ± 3.7	0.628	0.4 ± 3.7	0.914	−2.6 ± 3.8	0.484	−7.6 ± 3.9	0.053	−4.9 ± 3.7	0.189	−7.5 ± 3.9	0.057	−9.1 ± 4.1	**0.026**	−1.6 ± 4.0	0.685
7	How alert have you felt?	4.1 ± 3.0	0.170	6.7 ± 3.0	**0.028**	2.6 ± 3.0	0.393	0.9 ± 3.3	0.795	6.3 ± 3.4	0.070	5.4 ± 3.3	0.104	3.2 ± 3.0	0.280	8.6 ± 3.1	**0.006**	5.4 ± 3.0	0.078
8	How contented have you felt?	2.2 ± 2.6	0.407	5.9 ± 2.7	**0.029**	3.7 ± 2.6	0.167	−2.9 ± 3.2	0.363	1.8 ± 3.3	0.599	4.7 ± 3.2	0.148	2.2 ± 3.2	0.500	9.7 ± 3.3	**0.004**	7.5 ± 3.2	**0.021**
9	During the last 7 days how often have you had food cravings?	−0.6 ± 3.5	0.869	−8.5 ± 3.4	**0.014**	−8.0 ± 3.4	**0.022**	−1.9 ± 3.4	0.589	−6.5 ± 3.5	0.068	−4.6 ± 3.4	0.181	−8.3 ± 4.0	**0.038**	−16.3 ± 4.1	**<.0001**	−8.0 ± 4.0	**0.048**
10	How strong have any food cravings been?	−2.5 ± 3.4	0.458	−8.6 ± 3.4	**0.013**	−6.1 ± 3.4	0.077	0.4 ± 3.5	0.900	−5.7 ± 3.6	0.121	−6.1 ± 3.5	0.086	−6.7 ± 3.8	0.080	−15.2 ± 3.9	**<.0001**	−8.5 ± 3.8	**0.028**
11	How difficult has it been to resist any food cravings?	−2.2 ± 3.5	0.532	−7.1 ± 3.5	**0.046**	−4.9 ± 3.5	0.167	−2.4 ± 3.6	0.500	−7.2 ± 3.7	0.054	−4.7 ± 3.6	0.186	−4.1 ± 3.8	0.274	−12.6 ± 3.9	**0.001**	−8.5 ± 3.8	**0.026**
12	How often have you eaten in response to food cravings?	−2.7 ± 3.1	0.377	−8.4 ± 3.0	**0.007**	−5.6 ± 3.0	0.065	−2.0 ± 2.9	0.489	−8.4 ± 3.0	**0.006**	−6.3 ± 2.9	**0.031**	−1.9 ± 3.7	0.604	−12.5 ± 3.8	**0.001**	−10.6 ± 3.7	**0.005**
13	How often have you had cravings for chocolate and chocolate flavoured foods?	−9.0 ± 3.4	**0.008**	−16.4 ± 3.4	**<.0001**	−7.4 ± 3.4	**0.029**	−4.7 ± 3.3	0.163	−9.7 ± 3.4	**0.005**	−5.0 ± 3.3	0.131	−3.0 ± 3.9	0.441	−11.3 ± 4.0	**0.005**	−8.3 ± 3.9	**0.034**

	Question	Week 4						Week 8						Week 12					
		2 v. 1		3 v. 1		3 v. 2		2 v. 1		3 v. 1		3 v. 2		2 v. 1		3 v. 1		3 v. 2	
		Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value
14	How often have you had cravings for other sweet foods	−1.0 ± 3.3	0.755	−9.4 ± 3.3	**0.005**	−8.3 ± 3.3	**0.013**	−3.9 ± 3.4	0.248	−8.8 ± 3.5	**0.012**	−4.9 ± 3.3	0.146	−7.4 ± 4.1	0.073	−13.7 ± 4.2	**0.001**	−6.3 ± 4.1	0.129
15	How often have you had cravings for fruit or fruit juice?	0.8 ± 3.9	0.836	4.6 ± 3.9	0.239	3.8 ± 3.9	0.333	3.9 ± 4.3	0.369	0.9 ± 4.4	0.845	−3.0 ± 4.3	0.491	−0.5 ± 3.7	0.903	−0.5 ± 3.9	0.891	−0.1 ± 3.8	0.984
16	How often have you had cravings for dairy foods?	−4.2 ± 3.7	0.259	−4.1 ± 3.7	0.277	0.2 ± 3.7	0.966	0.7 ± 3.9	0.853	−3.2 ± 4.1	0.425	−4.0 ± 3.9	0.316	−1.8 ± 3.4	0.609	−3.3 ± 3.6	0.360	−1.5 ± 3.5	0.664
17	How often have you had cravings for starchy foods?	−0.9 ± 3.5	0.800	−4.4 ± 3.5	0.212	−3.5 ± 3.5	0.317	−1.7 ± 3.6	0.638	−1.7 ± 3.6	0.638	−4.3 ± 3.6	0.234	−6.3 ± 3.6	0.083	−8.1 ± 3.7	**0.030**	−1.9 ± 3.7	0.611
18	How often have you had cravings for savoury foods?	−7.3 ± 3.5	**0.038**	−7.8 ± 3.5	**0.028**	−0.4 ± 3.5	0.906	−2.5 ± 3.6	0.496	−12.7 ± 3.7	**0.001**	−10.2 ± 3.6	**0.005**	−10.8 ± 3.8	**0.005**	−11.9 ± 3.9	**0.003**	−1.0 ± 3.9	0.788
19	Generally, how difficult has it been to control your eating?	−6.6 ± 3.3	**0.045**	−9.9 ± 3.3	**0.003**	−3.3 ± 3.2	0.309	−5.9 ± 3.3	0.074	−12.6 ± 3.4	**< 0.001**	−6.7 ± 3.2	**0.040**	−8.0 ± 3.4	**0.021**	−16.1 ± 3.5	**< 0.001**	−8.2 ± 3.4	**0.018**
20	How difficult has it been to resist nominated food?	−4.2 ± 3.8	0.278	−13.4 ± 3.9	**0.001**	−9.2 ± 3.8	**0.017**	−0.8 ± 4.0	0.849	−12.4 ± 4.1	**0.003**	−11.6 ± 4.0	**0.004**	−5.5 ± 4.1	0.177	−16.4 ± 4.2	**< 0.001**	−10.9 ± 4.1	**0.009**

1 = lorcaserin 10mg twice daily (LOR BID), 2 = lorcaserin with with phentermine, 15mg/day (LOR BID + PHEN QD), 3 = lorcaserin with phentermine 15mg twice daily (LOR BID + PHEN BID) Significance was set at $p < 0.05$ and the figures in bold font represent the statistically significant changes