Effect of Lorcaserin Alone and in Combination with Phentermine on Food Cravings After 12-Week Treatment: A Randomized Substudy

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

Methods: Two hundred and thirty-five 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 to −0.55), −0.75 (−0.84 to −0.65), and −0.84 (−0.95 to −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 with LOR BID (P < 0.05).

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

Introduction

Food cravings refer to a motivational state in which 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. Though any selection of

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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 is a range of biological, cognitive, and emotional processes that trigger food cravings. Among them are menstrual-related changes (4), dysphoric mood states (5), and 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, stress, or hormonal fluctuations (cue-induced craving), as well as 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 challenge of attempting to restrain their eating in an environment in which 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-hydroxytryptamine [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). Furthermore, 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, which 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 identifier NCT01987427; Supporting Information 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 end point was the prevalence of serotonin-related adverse events in the three groups and the secondary end point was weight loss and adverse events in the three groups. The results of the primary and secondary end points have been published (16). The exploratory end point was the prevalence of food cravings during the treatment period.

### Subjects

Eligible subjects were males and females aged 18 to 60 years, with a body mass index (BMI) ≥ 30 kg/m² or 27 to 29.9 kg/m² with one or more weight-related comorbidities (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; 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 5 kg in the preceding 3 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 HCl 10 mg twice daily (LOR BID), lorcaserin HCl 10 mg twice + phentermine HCl 15 mg once daily (LOR BID + PHEN QD), or lorcaserin HCl 10 mg twice + phentermine HCl 15 mg twice daily (LOR BID + PHEN BID). As previously described (16), subjects were screened in the 2 weeks prior to the baseline visit, following which assessments were made at baseline and weeks 2, 4, 8, and 12. Adverse events, vital signs, concomitant medications, and body weight were assessed at each visit. A safety assessment via telephone was conducted 3 to 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 min/d 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 by using the Food Craving Inventory (FCI) and the Control of Eating Questionnaire (COEQ). The FCI is a validated questionnaire that asks about cravings for specific foods over the last 30 days. Subjects rate their cravings for specific foods by using a 5-point Likert scale. These foods are subsequently categorized as high fat, sweets, carbohydrates/starches, and fast-food fats (17). The 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...
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. Adapted from Smith SR, Garvey WT, Greenway FL, Zhou S, Fain R, Pilson R, Fujioka K, Aronne LJ. Coadministration of lorcaserin and phentermine for weight management: a 12-week, randomized, pilot safety study. Obesity (Silver Spring) 2017;25:857-865 (16). BID = twice daily; LOR = lorcaserin HCl 10 mg; PHEN = phentermine HCl 15 mg; QD = once daily. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline characteristics and demographics (full analysis population)a

|                      | LOR BID (n = 78) | LOR BID + PHEN QD (n = 78) | LOR BID + PHEN BID (n = 79) | Total (N = 235) |
|----------------------|------------------|---------------------------|----------------------------|----------------|
| Age, mean (SD), y    | 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)                  | 67 (30.7)      |
| 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 (82.4)                  | 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/m²| 38.4 (7.5)       | 38.0 (6.8)                | 38.5 (6.0)                 | 38.3 (6.8)     |
| Comorbid condition, n (%)b |          |                           |                            |                |
| 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), beats/min | 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) |

aAll randomized patients who received at least one dose of study drug.

bComorbid conditions self-reported as medical history and supported by medication use and/or baseline laboratory values. Some patients reported > 1 comorbid condition.

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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 10-cm visual analog scale, reported in millimeters, 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 postrandomization weight measurements) with last-observation-carried-forward imputation. To analyze the differences in food cravings between the groups, an analysis of covariance model was used to estimate how the ratings for each question on the FCI and COEQ changed 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
In total, 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. The study drug was not taken by 3 subjects; the remaining 235 comprised the full analysis set 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). Adverse events 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 (kilograms/percent) by using a mixed model repeated-measures analysis indicated significant improvements with the combination therapy versus 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 full analysis set 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 with 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 related to cravings in general as well as mood were significantly improved compared with the LOR BID group. Significantly greater reductions were demonstrated in the LOR BID + PHEN BID group compared with the LOR BID + PHEN QD group in the ratings for frequency and strength of food cravings, difficulty in resisting food cravings,
Comparison between the groups of the mean change from baseline in the scores for each question on the Control of Eating Questionnaire

| Week | Question | Mean | SE | P value | Mean | SE | P value | Mean | SE | P value | Mean | SE | P value |
|------|----------|------|----|---------|------|----|---------|------|----|---------|------|----|---------|
| 4    | How hungry have you felt? | -0.9 ± 0.7 | 0.28 | 0.005 | -0.9 ± 0.7 | 0.29 | 0.003 | -0.9 ± 0.7 | 0.29 | 0.002 | -0.9 ± 0.7 | 0.29 | 0.002 |
| 8    | How full have you felt? | 0.7 ± 0.7 | 0.24 | 0.002 | 0.7 ± 0.7 | 0.24 | 0.002 | 0.7 ± 0.7 | 0.24 | 0.002 | 0.7 ± 0.7 | 0.24 | 0.002 |
| 12   | How strong was your desire to eat sweet foods? | 6.7 ± 3.6 | 0.29 | 0.000 | 6.7 ± 3.6 | 0.29 | 0.000 | 6.7 ± 3.6 | 0.29 | 0.000 | 6.7 ± 3.6 | 0.29 | 0.000 |
| 4    | How happy have you felt? | 3.1 ± 0.7 | 0.28 | 0.005 | 3.1 ± 0.7 | 0.29 | 0.003 | 3.1 ± 0.7 | 0.29 | 0.002 | 3.1 ± 0.7 | 0.29 | 0.002 |
| 8    | How anxious have you felt? | 3.7 ± 3.6 | 0.29 | 0.000 | 3.7 ± 3.6 | 0.29 | 0.000 | 3.7 ± 3.6 | 0.29 | 0.000 | 3.7 ± 3.6 | 0.29 | 0.000 |
| 12   | How strong was your desire to eat savory foods? | 3.7 ± 3.6 | 0.29 | 0.000 | 3.7 ± 3.6 | 0.29 | 0.000 | 3.7 ± 3.6 | 0.29 | 0.000 | 3.7 ± 3.6 | 0.29 | 0.000 |
| 4    | How often have you eaten in response to food cravings? | 2.2 ± 0.7 | 0.28 | 0.005 | 2.2 ± 0.7 | 0.29 | 0.003 | 2.2 ± 0.7 | 0.29 | 0.002 | 2.2 ± 0.7 | 0.29 | 0.002 |
| 8    | How strong was your desire to eat chocolate flavored foods? | 3.3 ± 3.6 | 0.29 | 0.000 | 3.3 ± 3.6 | 0.29 | 0.000 | 3.3 ± 3.6 | 0.29 | 0.000 | 3.3 ± 3.6 | 0.29 | 0.000 |
| 12   | How often have you eaten in response to food cravings for other sweet foods? | 3.3 ± 3.6 | 0.29 | 0.000 | 3.3 ± 3.6 | 0.29 | 0.000 | 3.3 ± 3.6 | 0.29 | 0.000 | 3.3 ± 3.6 | 0.29 | 0.000 |

TABLE 2: Comparison between the groups of the mean change from baseline in the scores for each question on the Control of Eating Questionnaire.
TABLE 2. (continued).

| Week 4 | Week 8 | Week 12 |
|--------|--------|---------|
| 2 vs. 1 | 3 vs. 1 | 3 vs. 2 |

| Question | Mean | SE | P value | Mean | SE | P value | Mean | SE | P value |
|----------|------|----|---------|------|----|---------|------|----|---------|
| 17 How often do you have cravings for savory foods? | -7.3 ± 3.5 | 0.003 | 0.001 | -3.3 ± 3.5 | 0.001 | 0.001 |
| 18 How often do you have cravings for sweet foods? | -6.6 ± 3.3 | 0.001 | 0.001 | -9.9 ± 3.3 | 0.001 | 0.001 |
| 19 Generally, how difficult has it been to control your eating? | -4.2 ± 3.8 | 0.001 | 0.001 | -13.4 ± 3.9 | 0.001 | 0.001 |

Discussion

Treatment with LOR BID and the combination of LOR BID + PHEN QD or LOR BID + PHEN BID reduced subjects’ perceptions of food cravings compared with 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 that were 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 nondieters (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 1,200 kcal/d balanced diet and a 420 kcal/d liquid diet for 12 weeks, despite an almost three-fold greater weight loss on the 420 kcal/d liquid diet, the reduction in craving was greater as assessed by all the subscales of the FCI (20). These studies have underscored 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 eating in response to craving, and difficulty in controlling eating. There was a significantly greater reduction in the LOR BID + PHEN QD group compared with 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 cravings for chocolate in the LOR BID + PHEN BID group was significantly lower compared with 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 with the LOR BID group. There was a significantly greater reduction in the craving for non-sweets in the LOR BID + PHEN QD group compared with the LOR BID group (Figure 4).
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 the control of eating assessed by 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 with 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); however, 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 by using the COEQ.

In a 12-week randomized controlled trial, the effect of phentermine and a meal replacement system along with nutritional counseling 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 by using a variation of the FCI) reduced in the phentermine group compared with 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 on food cravings than the naltrexone/bupropion combination; however, it is only through a clinical trial making this comparison can any determination be made. By 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-term 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 4 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

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 < 0.0001 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. [Color figure can be viewed at wileyonlinelibrary.com]

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. [Color figure can be viewed at wileyonlinelibrary.com]
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, in which 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 it was a function of superimposing the evaluation of craving as an exploratory end point 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 with 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.

Conclusion

Lorcaserin at 20 mg/d may enhance the reduction in food cravings when subjects are placed on an energy-restricted diet; however, lorcaserin at 20 mg/d in combination with phentermine at 15 mg/d or 30 mg/d 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, antiobesities 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, and the subsets of the population that may respond more favorably than others have yet to be determined.

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