Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Effects of Liraglutide and Behavioral Weight Loss on Food Cravings, Eating Behaviors, and Eating Disorder Psychopathology

Ariana M. Chao [1,2], Thomas A. Wadden [2], Olivia A. Walsh[2], Kathryn A. Gruber[2], Naji Alamuddin[2], Robert I. Berkowitz[2,3], and Jena S. Tronieri[2]

Objective: This exploratory analysis examined the effects of intensive behavioral therapy (IBT) for obesity ("IBT-alone"), IBT plus liraglutide 3.0 mg/d ("IBT-liraglutide"), and IBT plus liraglutide 3.0 mg/d plus 12 weeks of a portion-controlled diet that provided 1,000 to 1,200 kcal/d ("Multicomponent") on changes in food cravings, eating behaviors, and eating disorder psychopathology at 24 and 52 weeks post randomization.
Methods: Adults with obesity (mean age = 47.6 ± 11.8 years and BMI = 38.4 ± 4.9 kg/m^2; 79.3% female; 54.0% non-Hispanic white; 44.7% black) were randomized to IBT-alone (n = 50), IBT-liraglutide (n = 50), or Multicomponent (n = 50).
Results: At weeks 24 and 52, liraglutide-treated groups reported significantly larger declines in weight concern relative to the IBT-alone group. At week 24, compared with IBT-alone, liraglutide-treated groups reported significantly greater reductions in dietary disinhibition, global eating disorder psychopathology, and shape concern. The Multicomponent group had significantly greater reductions in binge eating at week 24 relative to the IBT-alone group. However, differences among groups were no longer significant at week 52. Groups did not differ in total food cravings at week 24 or 52.
Conclusions: The combination of liraglutide and IBT was associated with greater short-term improvements in dietary disinhibition, global eating disorder psychopathology, and shape concern than IBT alone.

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Introduction

Glucagon-like peptide-1 (GLP-1) is secreted by the intestinal enteroendocrine cells in response to food intake (1). This incretin hormone helps to regulate food intake by slowing gastric emptying and inhibiting appetite centers in the brain (2). GLP-1 pathways have roles in both homeostatic and non-homeostatic food regulation (3). Liraglutide is a GLP-1 receptor agonist that has been approved by the US Food and Drug Administration and European Medicines Agency for use as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management. Liraglutide is associated with reduced ad libitum meal intake (4). It appears to act on the central nervous system to lower body weight by increasing satiety, with attendant reduction in calorie intake (4). In response to highly desirable foods, GLP receptor agonists decrease activation in areas of the brain associated with appetite and reward such as the parietal cortex, insula, putamen, and orbitofrontal cortex (5,6). This suggests that liraglutide may reduce food reward such as food cravings, an intense desire to consume a particular food (7). Liraglutide may also improve other aspects of appetite and eating behaviors such as hunger, dietary restraint, disinhibition, binge eating, and cognitive concerns related to eating, shape, and weight (5,6,8). Hunger is the susceptibility to eat in reaction to perceived physiological symptoms that indicate the need for food (9,10). Dietary restraint is the tendency to restrict food consumption to control body weight. Disinhibited eating is the propensity to overeat in response to different stimuli (10). Binge eating is the consumption of a large amount of food while feeling a loss of control over eating (11). However, little is known about the effects of liraglutide on appetite and eating behaviors.

We previously reported the primary results of a randomized controlled trial that examined the 1-year efficacy of intensive behavioral therapy (IBT), following the treatment schedule recommended

[1] Department of Biobehavioral Health Sciences, University of Pennsylvania School of Nursing, Philadelphia, Pennsylvania, USA. Correspondence: Ariana M. Chao (arichao@nursing.upenn.edu) [2] Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA [3] Department of Child and Adolescent Psychiatry and Behavioral Science, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA.

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by the Centers for Medicare and Medicaid Services ("IBT-alone"), compared with the same counseling combined with liraglutide 3.0 mg/d ("IBT-liraglutide") and with IBT-liraglutide combined for 12 weeks with a 1,000- to 1,200-kcal/d meal-replacement diet ("Multicomponent") (12). All participants received weekly IBT visits in month 1, every-other-week visits in months 2 to 6, and monthly sessions thereafter. Ninety-one percent of participants completed the 1-year trial at which time mean (SEM) weight losses for IBT-alone, IBT-liraglutide, and Multicomponent participants were 6.1% (1.3%), 11.5% (1.3%), and 11.8% (1.3%) of initial weight, respectively. Weight losses in the liraglutide-treated groups were significantly greater than the IBT-alone group. The present exploratory analysis examined the effects of liraglutide on changes in food cravings, eating behaviors, and eating disorder psychopathology at 24 and 52 weeks post randomization. We hypothesized that, compared with IBT alone, liraglutide-treated participants would report improvements in food cravings, dietary restraint, dietary disinhibition, hunger, eating disorder psychopathology, and binge eating.

Methods

This was a secondary analysis of a single-site, open-label, parallel-group design randomized trial (12). Participants were 150 adults with obesity. Major inclusion criteria were as follows: aged 21 to 70 years, BMI 30 to 55 kg/m^2, and prior lifetime weight loss effort with diet and exercise. Exclusion criteria included the following: having a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2; having type 1 or 2 diabetes; having renal, hepatic, or recent cardiovascular disease; taking medications that substantially affect body weight; having current major depression, suicidal ideation, or a history of suicide attempts; having had bariatric surgery; being pregnant and/or lactating; or losing ≥4.5 kg in the past 3 months.

Procedures

Participants were recruited by print and radio announcements and referrals from primary care practices. Applicants completed a phone screen with a research coordinator. Those who appeared eligible completed an in-person screening visit with a psychologist who obtained applicants' written informed consent and assessed their eating, physical activity, and mood (13). Eligible participants completed a medical history, physical examination, electrocardiogram, and blood draw with a study physician or nurse practitioner. Eligible participants were then scheduled for their randomization visit.

Interventions: common components

All participants received 21 sessions of IBT, delivered by a physician, nurse practitioner, or registered dietitian. Sessions were structured, lasted 15 minutes, and were delivered as 4 weekly visits, then 10 every-other-week sessions, followed by 7 visits every 4 weeks. Participants who weighed < 113.6 kg were prescribed a diet of 1,200 to 1,499 kcal/d of conventional foods, and those who weighed ≥ 113.6 kg were prescribed 1,500 to 1,800 kcal/d. Approximately 15% to 20% of kilocalories were from protein, 20% to 35% from fat, and the remainder from carbohydrates. Participants were instructed to record their food and calorie intake daily. They were encouraged to engage in low- to moderate-intensity physical activity 5 days per week, gradually building to ≥ 225 min/wk from weeks 25 to 52.

IBT-alone. Participants in this group received the intervention as described.

IBT-liraglutide. These participants received the IBT program, but starting at week 1, they also were prescribed liraglutide 3.0 mg/d as a once-daily, self-administered, subcutaneous injection. As recommended, the medication was initiated at 0.6 mg/d for 1 week and increased by 0.6 mg/d in weekly intervals until 3.0 mg/d was achieved.

Multicomponent. These participants received the same treatment as those in IBT-liraglutide except that, at week 4, they were prescribed a 12-week, 1,000- to 1,200-kcal/d diet that provided four servings daily of a liquid shake (Health Management Resources, Boston, Massachusetts; 160 kcal per shake) and an evening meal of a frozen food entrée (250-300 kcal), with a serving of fruit and salad.

Measures

Questionnaires were administered at baseline, week 24, and week 52. The total frequency of food cravings was assessed using the Food-Craving Inventory (14), which asks participants to rate their cravings for particular foods in the past month. The Cronbach α was 0.91 for the scale. The Eating Inventory was used to evaluate cognitive dietary restraint, dietary disinhibition, and hunger (9). The Cronbach α for the scales was 0.73, 0.72, and 0.80, respectively. Eating disorder psychopathology was measured using the Eating Disorder Examination Questionnaire (EDE-Q), which assesses core eating disorder behaviors and attitudes over the previous 28 days (11). The measure forms a global score and four subscales: dietary restraint, eating concern, weight concern, and shape concern. In this sample, the Cronbach α for the global score was 0.86, and for the dietary restraint, eating concern, weight concern, and shape concern subscales, it was 0.75, 0.73, 0.76, and 0.54, respectively. For global and subscale scores, a score of ≥4 is considered in the clinical range (15,16). The EDE-Q also measures binge eating, defined as consumption of an unusually large amount of food given the circumstances while feeling a sense of loss of control over eating.

Statistical analyses

Baseline differences between treatment condition on demographic and other variables were examined using ANOVA and χ^2 tests. Percentage reduction in food cravings, eating behaviors, and eating disorder psychopathology at weeks 24 and 52 in the intention-to-treat population was compared using repeated-measures linear mixed-effects models. Differences between groups in changes in outcomes were compared using least squares means. Effect sizes were also calculated for between-group differences using Cohen's d with values of d = 0.2, 0.5, and 0.8 corresponding to small, medium, and large effects, respectively (17). A power analysis was conducted for the parent study (12); however, no a priori power analysis was conducted for these exploratory analyses. Statistical significance was considered as a two-sided $P < 0.05$.

Results

Participants' baseline characteristics

Participant characteristics have been reported previously (Table 1) (12). At baseline, as measured by the EDE-Q, 8.3% of the sample scored in the clinically significant range for global eating disorder psychopathology

TABLE 1 Baseline characteristics for the total sample and by treatment group

	Total (*N* = 150)	IBT-alone (*n* = 50)	IBT-liraglutide (*n* = 50)	Multicomponent (*n* = 50)	*P* value
Age, y	47.6 ± 11.8	49.5 ± 11.0	45.2 ± 12.3	48.0 ± 11.9	0.19
Sex (female)	119 (79.3%)	39 (78.0%)	42 (84.0%)	38 (76.0%)	0.59
Ethnicity					
Hispanic/Latino	10 (6.7%)	3 (6.0%)	3 (6.0%)	4 (8.0%)	0.90
Race, N (%)					
White	81 (54.0%)	27 (54.0%)	27 (54.0%)	27 (54.0%)	0.67
Black	67 (44.7%)	22 (44.0%)	23 (46.0%)	22 (44.0%)	
Multiracial or other	2 (1.3%)	1 (2.0%)	0 (0%)	1 (2.0%)	
BMI, kg/m^2	38.4 ± 4.9	38.0 ± 4.3	38.5 ± 5.4	38.5 ± 5.0	0.70
Weight, kg	108.4 ± 17.5	105.8 ± 14.7	107.8 ± 17.9	111.7 ± 19.4	0.23
Total food cravings	2.5 ± 0.6	2.5 ± 0.5	2.4 ± 0.6	2.5 ± 0.6	0.40
Cognitive dietary restraint	10.3 ± 3.8	9.9 ± 3.5	10.8 ± 4.1	10.1 ± 3.9	0.45
Dietary disinhibition	9.5 ± 3.2	9.6 ± 3.0	9.1 ± 3.6	9.8 ± 3.0	0.52
Hunger	6.2 ± 3.5	6.4 ± 3.2	6.3 ± 3.6	6.1 ± 3.8	0.92
Eating disorder psychopathology					
Global score	2.7 ± 0.9	2.8 ± 0.9	2.5 ± 0.9	2.9 ± 0.8	0.13
Dietary restraint	1.8 ± 1.3	1.7 ± 1.4	1.6 ± 1.3	2.0 ± 1.3	0.49
Eating concern	1.4 ± 1.2	1.4 ± 1.2	1.2 ± 1.0	1.6 ± 1.3	0.26
Shape concern	3.9 ± 1.1	4.0 ± 1.2	3.6 ± 1.2	4.1 ± 1.0	0.13
Weight concern	3.2 ± 0.9	3.2 ± 0.9	3.0 ± 0.8	3.3 ± 0.9	0.41
Binge eating, episodes in past 28 days	3.9 ± 6.4	3.6 ± 5.6	3.0 ± 5.5	5.1 ± 7.8	0.25
Binge eating, ≥ 1 episode in past 28 days	77 (52.0%)	24 (49.0%)	22 (44.0%)	31 (63.3%)	0.14
Binge eating, ≥ 4 episodes in past 28 days	49 (33.1%)	16 (32.7%)	13 (26.0%)	20 (40.8%)	0.29

Data given as *N* (%) or mean ± SD. Total *N*'s range from 147 to 150 (with subgroup *n*'s ranging from 48 to 50) because of missing values.

and 10.3% for dietary restraint, 3.2% for eating concern, 53.8% for shape concern, and 18.6% for weight concern. At this time, 52.0% of the sample endorsed at least 1 episode of binge eating in the past 28 days, and 33.1% of the sample reported ≥4 episodes in the past 28 days. Baseline scores did not differ significantly among treatment groups (Table 1).

Changes by treatment condition

Food cravings. From randomization to week 24 and week 52, all groups had significant declines in total food cravings (all $P<0.001$; Table 2). At week 52, the IBT-alone group had a mean decline of 0.4 (SE 0.1) points for total food cravings, which was similar to IBT-liraglutide (0.4 [0.1]; $P=0.75$) and Multicomponent (0.5 [0.1]; $P=0.55$).

Eating behaviors. At week 24, the IBT-alone group had a mean decline of 1.7 (SE 0.5) points in dietary disinhibition, which was significantly less than the Multicomponent group (3.2 [0.4]; $P=0.03$; Cohen's d = 0.32; Table 2). IBT-alone and IBT-liraglutide groups did not differ significantly at week 24 (2.9 [SE 0.4]; $P=0.08$). At week 52, the differences between the IBT-alone group and the IBT-liraglutide and Multicomponent groups were not significant ($P=0.11$; $P=0.051$). At week 52, hunger declined by 1.8 (SE 0.5) points in the IBT-alone group, which was not significantly different from the decline of 3.0 (0.5) points in the IBT-liraglutide group ($P=0.09$) or the decline of 3.0 (0.5) points in the Multicomponent ($P=0.11$) group. Each group had significant improvement in cognitive dietary restraint from baseline to week 24, which was sustained to week 52 (all $P<0.001$). At week 52, improvement in cognitive restraint was not significantly different between the IBT-alone group and IBT-liraglutide ($P=0.67$) or Multicomponent ($P=0.80$) groups.

Eating disorder psychopathology. All groups had statistically significant declines in global eating disorder psychopathology and subscale scores from randomization to week 24 and randomization to week 52 (all $P<0.05$; Table 2). At week 24, the IBT-alone group had a mean decline of 0.3 (SE 0.1) points for global eating disorder psychopathology, which was significantly less than the IBT-liraglutide group (0.7 [0.1]; $P=0.03$; Cohen's d = 0.31) and the Multicomponent group (0.8 [0.1]; $P=0.01$; Cohen's d = 0.42). At week 52, the differences among groups were no longer significant. At weeks 24 and 52, the IBT-alone group had mean declines of 0.5 (SE 0.2) and 0.7 (SE 0.1) points, respectively, in weight concern, which were significantly smaller changes than those of the IBT-liraglutide group ($P=0.01$, 0.03; Cohen's d = 0.40, 0.32), which had reductions of 1.1 (0.1) and 1.1 (0.1) points, respectively, and the Multicomponent group ($P=0.002$, 0.01; Cohen's d = 0.45, 0.37), which had declines of 1.1 (0.1) and 1.2 (0.1) points, respectively. At week 24, relative to IBT-alone, the Multicomponent group had significantly larger declines in eating concern ($P=0.02$; Cohen's d = 0.34). At week 24, change in shape concern was lower in the IBT-alone group than in IBT-liraglutide ($P=0.02$; Cohen's d = 0.35) and Multicomponent ($P=0.02$; Cohen's d = 0.36) groups. At week 52, changes in eating and shape concerns did not differ among groups. Dietary restraint did not differ among groups at week 24 or 52.

TABLE 2 Changes in weight, food cravings, eating behaviors, and eating disorder psychopathology at weeks 24 and 52, as measured from randomization

	Mean ± SE			Cohen's d		
Characteristic	IBT-alone ($n=50$)	IBT-liraglutide ($n=50$)	Multicomponent ($n=50$)	IBT-alone vs. IBT-liraglutide	IBT-alone vs. Multicomponent	IBT-liraglutide vs. Multicomponent
Change in weight (%)						
Week 24	−5.4 ± 0.6[a,**]	−10.1 ± 0.6[b,**]	−12.2 ± 0.6[c,**]	0.76	1.11	0.36
Week 52	−6.1 ± 1.3[a,**]	−11.5 ± 1.3[b,**]	−11.8 ± 1.3[b,**]	0.49	0.52	0.03
Total food cravings						
Week 24	−0.5 ± 0.1**	−0.5 ± 0.8**	−0.4 ± 0.1**	0.04	0.07	0.11
Week 52	−0.4 ± 0.1**	−0.4 ± 0.1**	−0.5 ± 0.1**	0.04	0.08	0.04
Cognitive dietary restraint						
Week 24	+4.4 ± 0.7**	+5.0 ± 0.6**	+5.3 ± 0.6**	0.10	0.15	0.05
Week 52	+4.1 ± 0.6**	+3.8 ± 0.6**	+4.4 ± 0.6**	0.06	0.04	0.10
Dietary disinhibition						
Week 24	−1.7 ± 0.5[a,**]	−2.9 ± 0.4[a,b,**]	−3.2 ± 0.4[b,**]	0.25	0.32	0.07
Week 52	−1.8 ± 0.4**	−2.9 ± 0.4**	−3.1 ± 0.5**	0.23	0.28	0.05
Hunger						
Week 24	−2.0 ± 0.6**	−2.9 ± 0.5**	−3.0 ± 0.5**	0.18	0.21	0.03
Week 52	−1.8 ± 0.5**	−3.0 ± 0.5**	−3.0 ± 0.5**	0.26	0.25	0.01
Eating disorder psychopathology						
Global score						
Week 24	−0.3 ± 0.1[a]	−0.7 ± 0.1[b,**]	−0.8 ± 0.1[b,**]	0.31	0.42	0.10
Week 52	−0.4 ± 0.1*	−0.6 ± 0.1**	−0.8 ± 0.1**	0.16	0.29	0.14
Dietary restraint						
Week 24	+1.1 ± 0.2**	+1.3 ± 0.2**	+0.9 ± 0.2**	0.05	0.11	0.17
Week 52	+1.0 ± 0.2**	+1.2 ± 0.2**	+0.8 ± 0.2*	0.09	0.10	0.19
Eating concern						
Week 24	−0.3 ± 0.2[a,*]	−0.7 ± 0.2[a,**]	−0.9 ± 0.2[b,**]	0.26	0.34	0.08
Week 52	−0.5 ± 0.2*	−0.5 ± 0.2*	−0.7 ± 0.2**	0.01	0.10	0.10
Shape concern						
Week 24	−0.9 ± 0.2[a,**]	−1.6 ± 0.2[b,**]	−1.6 ± 0.2[b,**]	0.35	0.36	0.01
Week 52	−1.1 ± 0.2**	−1.5 ± 0.2**	−1.7 ± 0.2**	0.22	0.29	0.07
Weight concern						
Week 24	−0.5 ± 0.2[a,**]	−1.1 ± 0.1[b,**]	−1.1 ± 0.1[b,**]	0.40	0.45	0.05
Week 52	−0.7 ± 0.1[a,**]	−1.1 ± 0.1[b,**]	−1.2 ± 0.1[b,**]	0.32	0.37	0.04
Binge eating episodes						
Week 24	−1.3 ± 0.9[a]	−2.4 ± 0.8[a,b,*]	−3.8 ± 0.8[b,**]	0.13	0.31	0.18
Week 52	−2.3 ± 0.8*	−1.8 ± 0.8*	−3.1 ± 0.8**	0.06	0.11	0.16

For each variable,three treatment groups compared using pairwise comparisons. Significant differences between groups at $P<0.05$ are denoted by different superscripts (e.g., a vs. b) between the values. For comparison of each variable, absence of any superscripts indicates no significant differences among groups.
*$P<0.05$ for within-group changes over time.
**$P<0.001$ for within-group changes over time.

At week 24, the IBT-liraglutide group had a significant within-group mean decline of 2.4 (SE 0.8) binge eating episodes ($P=0.01$), and the Multicomponent group declined by 3.8 (0.8) ($P<0.001$). The IBT-alone group had a mean decline of 1.3 (SE 0.9) binge eating episodes ($P=0.12$). The Multicomponent group had greater decreases in the number of binge eating episodes than the IBT-alone group ($P=0.04$; Cohen's d = 0.31). At week 52, all groups had significant decreases in the number of binge eating episodes (all $P<0.05$). However, the IBT-alone group did not differ in changes compared with IBT-liraglutide ($P=0.71$) or Multicomponent ($P=0.48$). Among those with ≥ 1 episodes of binge eating at baseline, at week 24, the IBT-alone group had declines of 3.4 (1.5) binge eating episodes, which did not differ significantly from IBT-liraglutide (5.8 [1.5]; $P=0.27$) or Multicomponent (6.2 [1.3]; $P=0.15$). At week 52, all groups had significant within-group declines in binge eating (all $P<0.001$). The IBT-alone group had declines of 4.9 (1.4), which did not differ from the decline of 5.1 (1.5) in the IBT-liraglutide group ($P=0.91$) or 5.1 (1.3) in the Multicomponent group ($P=0.91$). Among those with ≥4 episodes of binge eating at baseline, at week 24, the IBT-alone group had a decline of 5.0 (2.0) binge eating episodes, which did not differ significantly from IBT-liraglutide (9.2 [2.2];

$P=0.16$) or Multicomponent (−9.1 [1.8]; $P=0.13$). At week 52, the IBT-alone group had declines of 7.1 (2.0) binge eating episodes, which were similar to IBT-liraglutide (−7.8 [2.1]; $P=0.79$) and Multicomponent (−7.2 [1.8]; $P=0.96$).

Discussion

In this study, relative to IBT alone, liraglutide combined with IBT was associated with greater short-term improvements in dietary disinhibition, global eating disorder psychopathology, and shape and weight concerns, though effect sizes were small. Liraglutide-treated groups also had longer-term improvement in weight concern compared with those in the IBT-alone group. These results add to the literature suggesting the short-term benefits of liraglutide on appetite and eating behavior that contribute to weight loss (18). In addition, the results show that use of this weight loss medication did not adversely affect eating-disordered thoughts or concerns.

Scores on appetite measures plateaued from week 24 to 52, and differences between groups were no longer significant for dietary disinhibition, global eating disorder psychopathology, and shape and weight concerns at week 52. Several explanations may underlie the tendency of improvements in subjective appetite and eating behaviors to plateau or deteriorate. Anorexigenic hormones such as leptin decrease and orexigenic hormones such as ghrelin increase following weight loss, which may contribute to greater perceptions of hunger (19). Studies have also suggested that the effects of long-acting GLP-1 agonists on gastric emptying may diminish over time because of tolerance and tachyphylaxis (20,21), which may have resulted in diminished perceptions of appetite control after 24 weeks of treatment. Obesogenic social and environmental factors, such as the abundance of highly palatable foods, may also "wear down" on the neural effects of liraglutide on hedonic reward pathways and may increase the desire to consume energy-rich foods. However, studies are needed to test these hypotheses. Despite the attenuation of the effects of the interventions on appetite and eating behaviors after 24 weeks, participants treated with liraglutide continued to have greater weight losses at week 52. This supports that the medication continued to have beneficial effects on weight loss despite perceived subjective appetite. Further examination is needed to examine whether objective measures of appetite (e.g., food intake, food selection) continue to improve long term and to explore other mechanisms and mediators related to liraglutide's potential beneficial effects on long-term weight control.

In the short term, relative to IBT alone, both liraglutide-treated groups reported larger improvements in dietary disinhibition, and Multicomponent had larger reductions in binge eating. The present findings are supported by a preclinical study that showed that liraglutide suppressed feeding behavior via inhibitory processes (22), as well as by a previous 12-week pilot study that demonstrated the benefits of liraglutide on binge eating behaviors (23). Taken together, these findings suggest that the effects of liraglutide on satiety, disinhibition, and food reward may potentially be beneficial for reducing episodes of binge eating. However, a fully powered randomized controlled trial is necessary to test this effect as the present study was underpowered to detect differences in changes in binge eating behavior. In addition, binge eating was assessed using self-report, which tends to lead to overestimation of binge eating episodes compared with interview-based methods (11).

This study has several strengths, including the excellent retention rate. However, there are several limitations. The study did not include a placebo group, and participants and staff were not masked to treatment assignment. In addition, we were unable to assess whether liraglutide would produce changes in appetite-related measures independent of the greater weight loss that was observed in the liraglutide-treated groups compared with IBT alone. Overall, the number of individuals with clinically significant eating disorder scores was low, which may limit generalizability. The sample was predominantly female, few participants were Hispanic, and participants were excluded if they had type 2 diabetes, which may also limit generalizability. The Cronbach α for the EDE-Q shape concern subscale was low. Results from this scale should be interpreted cautiously.

In summary, the combination of liraglutide and IBT was associated with improved dietary disinhibition, binge eating, and eating disorder psychopathology at 24 weeks, but results diminished over time. Additional studies are needed to investigate the mechanisms underlying the long-term weight losses seen with liraglutide.

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A deidentified data set, including participant data and data dictionaries that underlie the results reported in this article (text, tables, figures, and appendices), will be made available to external investigators who provide a methodologically sound proposal to the first author and once the research team has completed its analysis and reporting of secondary findings from the study. Proposals should be directed to arichao@nursing.upenn.edu. To gain access, data requestors will need to sign a data access agreement. The study protocol will also be made available (upon request to the first author). This is expected to be approximately 2 years after the publication of this report and end 5 years following article publication.

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