Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Intensive Behavioral Therapy for Obesity Combined with Liraglutide 3.0 mg: A Randomized Controlled Trial

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Objective: The Centers for Medicare and Medicaid Services (CMS) covers intensive behavioral therapy (IBT) for obesity. The efficacy, however, of the specific approach has never been evaluated in a randomized trial, as described here. The 1-year trial also assessed whether the addition to IBT of liraglutide 3.0 mg would significantly increase weight loss and whether the provision of meal replacements would add further benefit.

Methods: A total of 150 adults with obesity were randomly assigned to: IBT (IBT-alone), providing 21 counseling visits; IBT combined with liraglutide (IBT-liraglutide); or IBT-liraglutide combined for 12 weeks with a 1,000- to 1,200-kcal/d meal-replacement diet (Multicomponent). All participants received weekly IBT visits in month 1, every-other-week visits in months 2 to 6, and monthly sessions thereafter.

Results: Ninety-one percent of participants completed 1 year, at which time mean (± SEM) losses for IBT-alone, IBT-liraglutide, and Muticomponent participants were 6.1 ± 1.3%, 11.5 ± 1.3%, and 11.8 ± 1.3% of baseline weight, respectively. Fully 44.0%, 70.0%, and 74.0% of these participants lost ≥ 5% of weight, respectively. The liraglutide-treated groups were superior to IBT-alone on both outcomes. Weight loss in all three groups was associated with clinically meaningful improvements in cardiometabolic risk factors.

Conclusions: The findings demonstrate the efficacy of IBT for obesity and the potential benefit of adding pharmacotherapy to this approach.

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Introduction

Two nonsurgical interventions reliably induce a loss of 5% to 10% of initial body weight in persons with overweight or obesity (1). The first is a program of high-intensity lifestyle modification (i.e., diet, physical activity, and behavior therapy), delivered in 14 or more counseling contacts in 6 months (1,2). This is the frequency of individual or group counseling recommended by the Guidelines for the Management of Overweight and Obesity in Adults (2). It also is the frequency of brief (15 minutes) individual counseling covered by the Centers for Medicare and Medicaid Services (CMS) (3). The US Preventive Services Task Force recently reaffirmed its recommendation that clinicians screen all adults for obesity and offer those affected intensive behavioral counseling (4-6).

Medications for chronic weight management offer a second option for inducing a 5% or greater loss (7,8). The five medications currently approved by the Food and Drug Administration are recommended as an adjunct to a reduced-calorie diet and increased physical activity and have been shown to increase mean 1-year weight losses (compared with the same counseling with placebo) by an average of 2.6 to 8.8 kg, depending on the medication used (9). In industry-sponsored trials, weight loss medications typically have been combined with moderate-intensity lifestyle counseling (e.g., approximately monthly visits), potentially because of concerns that more intensive counseling could mask the comparative effects of medication (10). However, studies have shown that adding weight loss medication to high-intensity lifestyle modification produces mean losses that are approximately equal to the sum of the two separate interventions, suggesting additive benefits (11,12).

The present randomized controlled trial tested a treatment model for primary care practitioners (PCPs), including physicians and nurse practitioners (NPs), to provide intensive behavioral therapy (IBT) on the schedule covered by CMS: weekly, brief, in-person lifestyle counseling visits the first month, followed by every-other-week visits the next 5 months, approximating 14 to 15 contacts over 6 months (3).

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[This number of counseling visits is similar to that provided by registered dietitians in the first 6 months of the Diabetes Prevention Program (DPP) (13).] Patients who lose ≥ 3 kg at month 6 are eligible for additional monthly visits through month 12. The specific schedule and length (15 minutes) of counseling visits proposed by CMS has never been tested in a randomized controlled trial in which PCPs provided IBT, as required by CMS for coverage.

Mean 1-year weight losses achieved with this approach were compared with those of two other interventions that included the same background of IBT, provided by the same PCPs. Participants in a second group received IBT combined with liraglutide 3.0 mg/d, a glucagon-like peptide-1 receptor agonist approved for chronic weight management (7,14,15). A meta-analysis found that the addition of liraglutide 3.0 mg/d to approximately monthly lifestyle counseling increased weight loss by approximately 5.2 kg compared with the same counseling with placebo (9). Based on findings of the DPP, we anticipated that participants in the present study who received IBT-alone would lose a mean of 5% of baseline weight at 1 year, which would be approximately doubled by the addition of liraglutide 3.0 mg/d (9,13). Participants in a third group received IBT, liraglutide, and the addition, for 12 weeks, of a portion-controlled diet that provided 1,000 to 1,200 kcal/d. Meal replacements (including liquid shakes, meal bars, and prepared entrées) increase weight loss by approximately 3% to 5% in 12 weeks, compared with consumption of an isocaloric diet composed of conventional foods (16,17). This study assessed whether the provision of a portion-controlled diet would increase weight loss further when added to IBT plus liraglutide.

Methods

Trial design and setting

This was a single-site, open-label, parallel-group-design, randomized trial, conducted at The University of Pennsylvania, whose institutional review board approved the study protocol (ClinicalTrials.gov identifier NCT02911818). The trial was supported by an Investigator-Initiated Study award from Novo Nordisk. The company had no role in the design, execution, analysis, or reporting of the study, which was conceived by the first author. The last author analyzed the data, the first author wrote the initial draft of the manuscript, and all authors contributed to study implementation and the final draft. We used an open-label design to test IBT as it is delivered in clinical practice, without placebo. In addition, the efficacy of liraglutide 3.0 mg/d, compared with placebo, has been demonstrated in numerous double-blind, randomized trials (15,18,19), reducing the need for another such study.

Participants

Eligibility criteria included the following: ages 21 to 70 years; BMI of 30 to 55 kg/m^2; prior lifetime weight loss effort with diet and exercise (before considering antiobesity medication) (20); and agreement to participate for 1 year. Exclusion criteria included personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome; types 1 or 2 diabetes; renal, hepatic, or recent cardiovascular disease; blood pressure ≥ 160/100 mm Hg; medications that substantially affect body weight (e.g., corticosteroids); substance abuse; current major depression, suicidal ideation, or history of suicide attempts; bariatric surgery; use of weight loss medications or products, as well as weight loss ≥ 4.5 kg in past 3 months; and pregnancy/lactation. Antidepressant medications were permitted, except for those associated with marked weight gain (e.g., paroxetine) or loss (e.g., bupropion).

Procedures

Participants were recruited by print and radio announcements and referrals from the medical center's affiliated primary care practices. Applicants completed a telephone screen with a research coordinator. Those who appeared eligible completed an in-person screening visit with a psychologist, who fully described the trial's nature and requirements, obtained applicants' written informed consent, and assessed their eating and physical activity (21), as well as mood (22). Eligible participants next met with a study physician or NP who completed a medical history, physical examination, electrocardiogram, and blood draw. Participants were informed of laboratory results within 72 hours and, if still eligible, were scheduled for their randomization visit.

Randomization

Participants were randomly assigned to interventions, in equal numbers, using a computer-generated algorithm, operated by the study statistician (JST). Randomization used varying block sizes (i.e., 3, 6, or 9). The first randomization visit was on September 21, 2016, and the last outcome assessment was completed on May 23, 2018.

Interventions: common components

Participants in all three groups received the same 21 sessions of IBT, delivered on the schedule recommended by CMS: 4 initial weekly visits, followed by 10 every-other-week sessions (through month 6), followed by 7 additional visits, delivered every 4 weeks, through month 12. Departing from the CMS protocol, all participants were provided counseling in the second 6 months, regardless of whether they had lost ≥ 3 kg at month 6. (This was done principally for statistical purposes, to maintain an approximately equal number of participants in the three groups at the primary outcome assessment at month 12.) Counseling sessions lasted 15 minutes and were delivered following a detailed protocol (23), adapted from the DPP (13). Participants who weighed < 113.6 kg (250 lb) were prescribed a diet of 1,200 to 1,499 kcal/d, composed of conventional foods, with approximately 15% to 20% kcal from protein, 20% to 35% from fat, and the remainder from carbohydrate. Participants who weighed ≥ 113.6 kg were prescribed 1,500 to 1,800 kcal/d. Participants were instructed to record their food and calorie intake daily, using applications (e.g., MyFitnessPal) or paper diaries (24). They were provided lists of breakfast, lunch, and dinner options (of conventional foods) to be used, as in prior studies (13,25), if they had trouble selecting their meals. Participants were instructed to engage in low- to moderate-intensity physical activity (principally walking) 5 d/wk, gradually building to ≥ 180 min/wk by week 24 (24). This increased to ≥ 225 min/wk from weeks 25 to 52, consistent with targets for weight loss maintenance (25). Treatment sessions included examining participants' weight change since the last visit, reviewing calorie intake and physical activity for the most recent week, and discussing a new topic from the behavior-change curriculum (23). All participants also had seven brief (5 min) medical visits over the year (i.e., weeks 1, 4, 8, 16, 24, 40, and 52) to review vital signs and any health concerns. These visits were included principally to monitor liraglutide-treated participants but also were provided to the IBT-alone participants to maintain consistency of treatment contact.

IBT-alone. Participants in this group received the intervention as described above. No supplemental treatment was provided.

IBT-liraglutide. These participants received the same program of lifestyle counseling as those in IBT-alone. However, starting at week 1, they also were prescribed liraglutide as a once-daily, self-administered subcutaneous injection (14). A study physician or NP taught participants to inject in their abdomen, thigh, or upper arm. To reduce the likelihood of gastrointestinal symptoms (e.g., nausea), 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. Medical staff helped participants develop a medication schedule to facilitate adherence.

Multicomponent. These participants received the same treatment as those in IBT-liraglutide, with one exception. At week 4, they were prescribed, for 12 weeks, a 1,000- to 1,200-kcal/d diet that provided four servings daily of a liquid shake (Health Management Resources, 160 kcal per shake) and an evening meal of a frozen food entrée (250-300 kcal), with a serving of fruit and salad (24). As with liraglutide, all Health Management Resources products were provided free of charge; participants were responsible for purchasing frozen food entrées and other foods.

Interventionists

IBT was delivered by a physician and two NPs, as well as by two registered dietitians (RDs) who worked incident to the PCPs, as permitted by CMS (26). (Incident coverage requires PCPs to be physically present in the primary care setting at the time when ancillary providers, such as RDs, deliver in-person counseling.) One NP and one RD had previously provided IBT; the three other clinicians had not but had offered weight management advice. Before treatment, all interventionists received 4 to 6 hours of instruction in delivering IBT and were

TABLE 1 Participants' characteristics at randomization

	IBT-alone (*n* = 50)	IBT-liraglutide (*n* = 50)	Multicomponent (*n* = 50)	Total (*N* = 150)
Sex (female), *n* (%)	39 (78%)	42 (84%)	38 (76%)	119 (79.3%)
Race, *n* (%)				
Black	22 (44%)	23 (46%)	22 (44%)	67 (44.7%)
White	27 (54%)	27 (54%)	27 (54%)	81 (54.0%)
Multiracial or other	1 (2%)	0 (0%)	1 (2%)	2 (1.3%)
Ethnicity (Hispanic), *n* (%)	3 (2%)	3 (6%)	4 (8%)	10 (6.7%)
Age (y)	49.5 ± 11.0	45.2 ± 12.3	48.0 ± 11.9	47.6 ± 11.8
Weight (kg)	105.8 ± 14.7	107.8 ± 17.9	111.7 ± 19.4	108.4 ± 17.5
Height (cm)	166.8 ± 7.3	167.3 ± 8.8	169.5 ± 9.1	167.8 ± 8.5
BMI (kg/m^2)	38.0 ± 4.3	38.5 ± 5.4	38.8 ± 5.0	38.4 ± 4.9
Waist circumference (cm)	116.7 ± 11.6	116.7 ± 10.4	120.1 ± 11.8	117.8 ± 11.3
Systolic BP (mm Hg)	139.1 ± 14.6	135.2 ± 12.3	138.7 ± 13.1	137.7 ± 13.4
Diastolic BP (mm Hg)	77.5 ± 9.7^{ab}	73.9 ± 7.6^{a}	78.4 ± 10.5^{b}	76.6 ± 9.5
Heart rate (BPM)	82.0 ± 14.2	79.3 ± 12.7	81.8 ± 15.5	81.0 ± 14.2
Total cholesterol (mg/dL)	197.2 ± 33.3	192.6 ± 35.2	188.1 ± 38.1	192.6 ± 35.5
HDL cholesterol (mg/dL)*	59.3 ± 14.8	60.0 ± 14.1	53.6 ± 13.0	57.6 ± 14.2
LDL cholesterol (mg/dL)	116.6 ± 30.2	112.2 ± 29.5	112.8 ± 32.0	113.9 ± 30.5
Triglycerides (mg/dL)	106.4 ± 43.6	102.1 ± 56.1	108.6 ± 52.6	105.7 ± 50.8
C-Reactive protein (mg/L)	5.9 ± 6.0	6.5 ± 5.7	7.9 ± 9.2	6.8 ± 7.1
Hemoglobin A_{1c}	5.7 ± 0.3	5.6 ± 0.3	5.7 ± 0.4	5.7 ± 0.3
Fasting glucose (mg/dL)	90.8 ± 10.2	88.3 ± 8.1	89.0 ± 8.4	89.4 ± 8.9
Fasting insulin	9.9 ± 5.7	9.2 ± 5.3	9.5 ± 5.5	9.5 ± 5.5
HOMA-IR	2.3 ± 1.6	2.0 ± 1.2	2.1 ± 1.2	2.1 ± 1.3
Depression symptoms (PHQ-9)	4.9 ± 3.6	4.4 ± 4.0	5.4 ± 4.0	4.8 ± 3.9
Short Form 36				
Physical component summary	46.7 ± 7.7^{a}	50.6 ± 5.7^{b}	47.6 ± 8.6^{a,b}	48.3 ± 7.5
Mental component summary	50.9 ± 7.6	49.9 ± 10.1	46.6 ± 9.8	49.1 ± 9.4

Values shown are *n* (%) or means ± standard deviation. For diastolic blood pressure and the Short Form 36(27), physical component summary score, values with different superscripts (^{a} vs. ^{b}) differ significantly from each other at $P < 0.05$. (Values that share a superscript do not differ significantly.)
*There was a significant omnibus effect for HDL cholesterol ($P = 0.04$), but no two treatment groups differed significantly in pairwise comparisons using Tukey tests.
BP, blood pressure; BPM, beats per minute; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; PHQ-9, Patient Health Questionnaire 9.

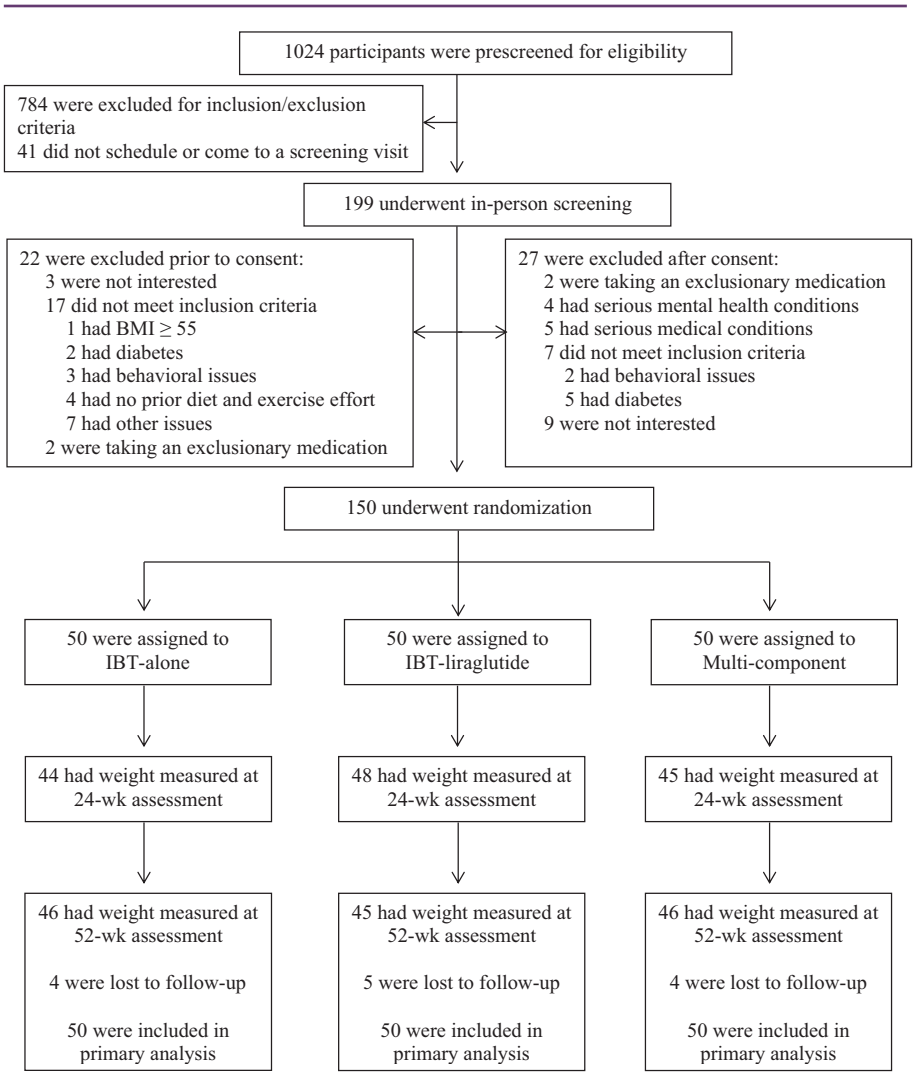

Figure 1 CONSORT diagram showing screening, randomization, and assessment of study participants. Weight was measured at week 52 on 137 of 150 (91.3%) participants, and all participants were included in the intention-to-treat analyses.

certified after satisfactorily conducting two role-play visits (23,24). Monthly individual supervision of 30 to 60 minutes was provided thereafter. Interventionists counseled the same participants at each visit. The physician and two NPs treated a total of 90 participants, and the RDs treated the remaining 60.

Outcomes

The study's primary outcome was mean percentage reduction in baseline body weight at week 52. Weight was measured by certified staff at randomization and weeks 24 and 52 using a digital scale (Tanita BWB-800). (It also was measured for clinical purposes at all IBT visits to provide participants feedback on their progress.) Waist circumference and blood pressure, as well as fasting glucose, insulin, triglycerides, C-reactive protein, and lipids, were measured on the same three occasions, using standardized methods described previously (23,24). Quality of life (27) and symptoms of depression (28) also were assessed.

Statistical analyses

Preliminary analyses examined baseline differences between randomized groups on demographic and other variables. Mean percentage reduction in baseline weight at week 52 in the intention-to-treat population was compared using repeated-measures, linear mixed-effects models (for continuous outcomes). With 50 participants per treatment arm, the study had 80% power to detect a 4.5-percentage point difference in weight change between IBT-alone and IBT-liraglutide and between IBT-alone and Multicomponent, the study's two primary a priori comparisons. Holm's procedure (29) was used to adjust for multiple comparisons and to identify differences in at least one of the two contrasts at $P=0.025$. The percentages of participants who lost ≥ 5%, ≥ 10%, and ≥ 15% of baseline weight were analyzed using logistic regression; participants who did not complete the assessments were categorized as not having achieved the categorical losses. These and other secondary outcomes, including changes in body weight at week 24, were examined using $P<0.05$.

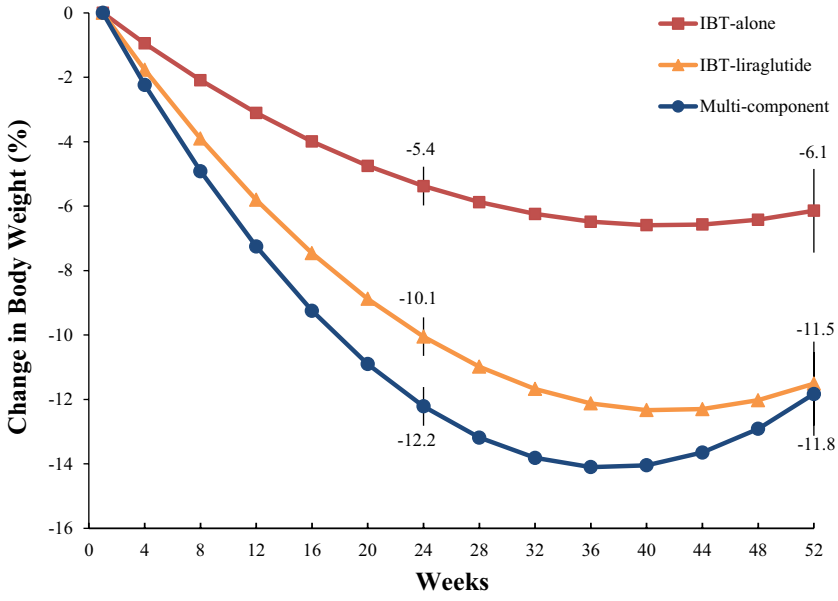

Figure 2 Estimated mean percentage reduction in baseline weight over 52 weeks in the intention-to-treat-population ($N = 150$, with 50 participants in each treatment group). *P* values for pairwise comparisons at week 24 and week 52 are shown in Table 2.

TABLE 2 Estimated mean percent reduction in baseline weight, weight loss (kg), and change in BMI at weeks 24 and 52 in the intention-to-treat population ($N = 150$)

				P value		
	IBT-alone ($n = 50$)	IBT-liraglutide ($n = 50$)	Multicomponent ($n = 50$)	IBT-liraglutide vs. IBT-alone	Multicomponent vs. IBT-alone	Multicomponent vs. IBT-liraglutide
Change in weight (%)						
Week 24	−5.4 ± 0.6	−10.1 ± 0.6	−12.2 ± 0.6	<0.001	<0.001	0.017
Week 52	−6.1 ± 1.3	−11.5 ± 1.3	−11.8 ± 1.3	0.005	0.003	0.863
Change in weight (kg)						
Week 24	−5.8 ± 0.8	−10.6 ± 0.8	−13.6 ± 0.8	<0.001	<0.001	0.007
Week 52	−6.6 ± 1.3	−12.2 ± 1.3	−13.3 ± 1.3	0.004	0.001	0.561
Change in BMI						
Week 24	−2.0 ± 0.3	−3.8 ± 0.3	−4.7 ± 0.3	<0.001	<0.001	0.016
Week 52	−2.3 ± 0.5	−4.3 ± 0.5	−4.6 ± 0.5	0.003	0.001	0.687

Values shown are estimated marginal means (± standard error of the mean) for the intention-to-treat population ($N = 150$).

Results

Participants' baseline characteristics

Participants were 119 (79.3%) women and 31 men (total $N = 150$) with a mean (± standard deviation) age of 47.6 ± 11.8 years, weight of 108.4 ± 17.5 kg, and BMI of 38.4 ± 4.9 (Table 1). Ninety-eight percent had completed high school or more; 54.0% self-identified as non-Hispanic white, 44.7% identified as black, and 6.7% as Hispanic. Groups differed significantly at baseline on only physical-related quality of life, which was controlled for in relevant analyses (Table 1).

Retention

Figure 1 shows the progression of participants through the study. More than 91% of participants provided a 52-week measurement of weight. Missed visits at this time resulted from 13 individuals who were lost to follow-up.

Weight loss

At week 52, the IBT-alone, IBT-liraglutide, and Multicomponent groups achieved mean (± standard error of the mean [SEM]) reductions in baseline weight of 6.1 ± 1.3%, 11.5 ± 1.3%, and 11.8 ± 1.3%, respectively (Figure 2 and Table 2). Both liraglutide-treated groups lost significantly more weight than IBT-alone. The IBT-liraglutide and Multicomponent interventions did not differ significantly at week 52 but did differ at week 24, when losses were 10.1 ± 0.6% and 12.2 ± 0.6%, respectively (Table 2).

Categorical weight losses. At week 52, 44% of IBT-alone participants lost ≥ 5% of baseline weight, 26% lost ≥ 10%, and 12% lost ≥ 15% (Figure 3). (The categories are overlapping, such that the 44% who lost ≥ 5% includes those who lost ≥ 10% and ≥ 15%.) Among participants in each of the liraglutide-treated groups, 70% or more lost ≥ 5% of baseline weight, 46% or more lost ≥ 10%, and ≥ 28% lost ≥ 15% of baseline weight (Figure 3). Significantly more IBT-liraglutide and Multicomponent participants met the 5% and 10% categorical weight losses than did those who received IBT-alone. Significantly more Multicomponent than IBT-alone participants also achieved the 15% weight loss criterion. The IBT-liraglutide and Multicomponent groups did not differ significantly on any of the categorical losses at week 52 or at week 24 (Figure 3).

Weight loss ≥ 3 kg. At week 24, 56% of IBT-alone participants lost ≥ 3 kg, the CMS criterion for receiving additional monthly counseling through week 52. Significantly more IBT-liraglutide (86%; $P = 0.002$) and Multicomponent participants (90%; $P < 0.001$) met this criterion than did those who received IBT-alone (with no significant differences between the two liraglutide-treated groups). At 1 year, 52%, 78%, and 82% of participants in the three groups, respectively, lost ≥ 3 kg, with the same pattern of significant differences between groups. Of the 22 IBT-alone participants (44%) who did not lose ≥ 3 kg at week 24, 3 participants did so at week 52, with the additional counseling visits provided between months 7 and 12. Five participants, however, who had lost ≥ 3 kg at week 24 did not maintain this loss at week 52.

Attendance and effect of interventionist

Participants in the IBT-alone, IBT-liraglutide, and Multicomponent interventions attended a mean (± standard deviation) of 72.4 ± 35.1%, 91.2 ± 16.8%, and 89.0 ± 22.6% of 21 scheduled counseling visits, respectively. Attendance was significantly lower in IBT-alone than in the two other groups ($P = 0.011$ and $P = 0.016$, respectively), which did not differ significantly from each other. Figure 4 shows that, in each of the three treatment groups, greater visit attendance was generally associated with greater weight loss. For example, participants in the IBT-alone group who attended 100% of treatment visits lost a mean of 9.7% of initial weight, compared with 3.5% for those who attended an average of 54% of possible visits.

Analyses across the three treatment groups revealed no significant differences in mean (± SEM) 52-week weight losses among participants treated by the physician/NPs versus the RDs (9.8 ± 1.0% vs. 9.9 ± 1.3%, respectively). Mean weight losses also did not differ significantly between the two experienced and three novice interventionists (10.2 ± 1.5% vs. 9.7 ± 1.0%, respectively).

Changes in cardiometabolic risk factors and quality of life

All three interventions produced clinically meaningful improvements at week 52 in systolic and diastolic blood pressure, low-density lipoprotein cholesterol, triglycerides, and depression, although differences between groups were not statistically significant (Table 3). By contrast, significantly greater improvements were observed in one or both of the liraglutide-treated groups in 52-week changes in waist circumference, high-density lipoprotein cholesterol, C-reactive protein, fasting glucose, hemoglobin A_{1c}, and mental health (28). The IBT-liraglutide group, compared with IBT-alone, had a significantly smaller decrease in heart rate at week 24 but not at week 52.

Adverse events

Cases of nausea, constipation, upper respiratory infection, and gastroenteritis were 10 or more percentage points higher in both liraglutide-treated groups than in IBT-alone (Table 4). A total of six serious adverse events were reported including asthma, bile duct stones, gastroenteritis, pneumonia, and wound infection, all of which resolved fully.

Discussion

This study has two principal findings, the first of which was that 21 brief sessions of IBT, delivered by PCPs, induced clinically meaningful weight loss at 1 year. The second was that the addition to IBT of liraglutide 3.0 mg/d nearly doubled the mean weight loss produced by behavioral counseling alone. These results have important implications for the management of obesity in primary care practice, as recommended by the US Preventive Services Task Force (4,5).

This is the first randomized controlled trial of which we are aware to test the efficacy of IBT for obesity, as largely modeled on the treatment approach covered by CMS. Participants in the IBT-alone group lost a mean 6.1% of baseline weight at 1 year, and 44% lost ≥ 5% of body weight, a common criterion of clinically meaningful weight loss (2). Participants who attended all counseling visits lost an average of 9.7% of baseline weight, compared with 3.5% for those with lower attendance (i.e., those who attended 54.0% of possible visits), confirming the positive relationship between these variables reported in prior observational studies of IBT (30,31).

The frequency and duration of treatment visits proposed by CMS were based largely on findings of systematic reviews of randomized trials (32,33), many of which included group behavioral weight loss counseling of 60 to 90 minutes, often considered the standard of care (2). Few interventions, whether for groups or individuals, provided visits < 30 minutes, raising questions about CMS' proposed 15-minute sessions. However, CMS' recommendation of frequent visits in the first 6 months (i.e., 14-15 sessions) is consistent with findings of systematic reviews (32) and treatment guidelines (2) and resembles the 16 sessions of individual counseling provided in the first 6 months of the DPP (13). Participants in that study lost a mean of approximately 7 kg at both 6 and 12 months, results only marginally better than those from the present study (i.e., 5.8 and 6.6 kg at weeks 24 and 52, respectively), which used an abbreviated version of the DPP protocol, previously implemented in a primary care setting (23,34). CMS does not provide or recommend a specific weight loss

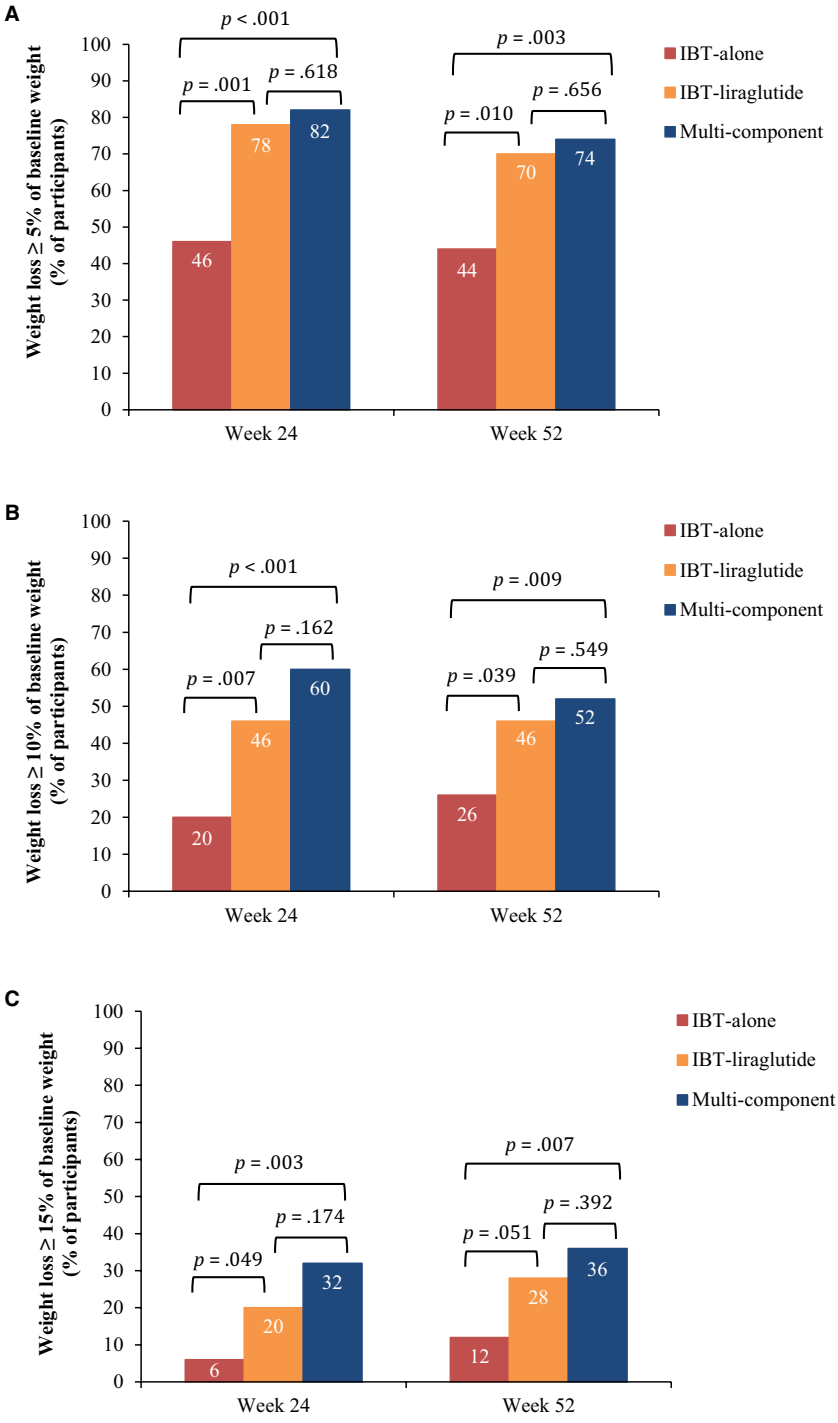

Figure 3 (A) Percentage of participants in each group in the intention-to-treat population ($N = 150$) who lost 5% or more of baseline weight at week 24 and week 52. (Participants with missing weights were assumed not to have met the categorical loss.) (B,C) Percentages of participants who lost ≥ 10% and ≥ 15% of baseline weight, respectively. Percentages are cumulative; the percentage of participants, for example, who lost ≥ 5% of baseline weight includes the percentage who lost 10% or more.

protocol, instead encouraging clinicians to follow a more general 5-A approach to diet and activity modification (i.e., assess, advise, agree, assist, and arrange) (4,35). We believe that the use of a structured behavioral weight loss protocol (e.g, DPP) will increase the likelihood of clinically meaningful weight reduction with CMS-covered IBT (35), a hypothesis that needs to be tested.

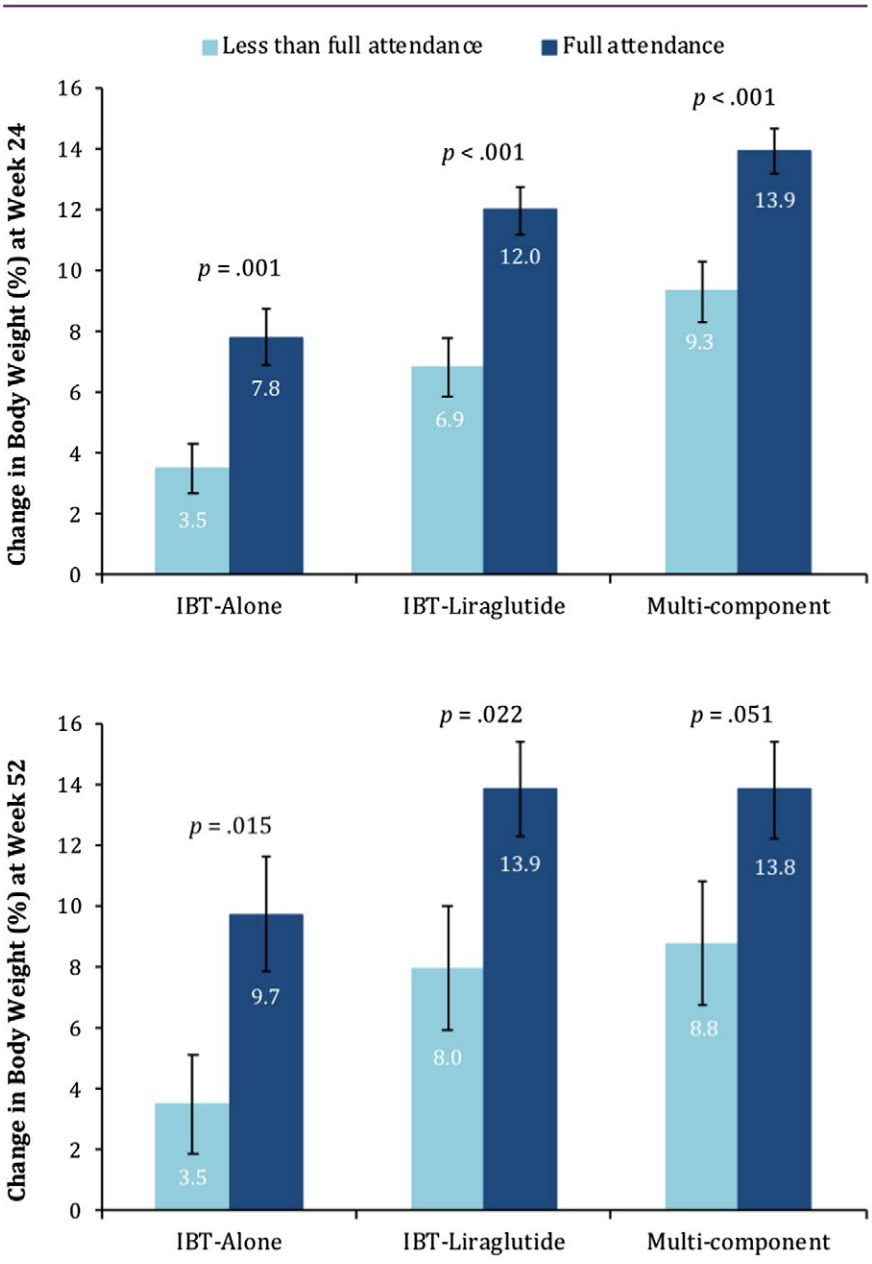

Figure 4 Mean weight losses for the three groups in the intention-to-treat population ($N = 150$) at weeks 24 and 52 based on attendance of IBT visits. Forty percent ($n = 20$) of IBT-alone, 60% ($n = 30$) of IBT-liraglutide, and 58% ($n = 29$) of Multicomponent participants attended all 21 treatment visits ($P = 0.09$ for difference among groups). The remaining 71 participants who did not have "full attendance" completed a mean of 14.0 ± 6.6 visits (66.7 ± 31.2% of possible visits). Among participants without full attendance, the 30 IBT-alone participants attended a mean of 11.3 ± 7.3 visits (54.0 ± 34.7%), the 20 IBT-liraglutide participants attended 16.4 ± 4.3 sessions (78.1 ± 20.6%), and the 21 Multicomponent participants attended 15.5 ± 6.1 sessions (73.9 ± 28.9%). Among these participants, the IBT-alone group differed significantly in attendance from the IBT-liraglutide group ($P = 0.017$) but did not differ significantly from the Multicomponent group ($P = 0.053$).

The addition to IBT of liraglutide 3.0 mg/d increased mean 1-year weight loss from 6.1% to 11.5% of initial weight, confirming the additive effects of behavior therapy and pharmacotherapy for obesity (11,12). Fully 70% of IBT-liraglutide participants lost ≥ 5% of baseline weight, and 46% lost ≥ 10%, values higher than those in trials of liraglutide 3.0 mg/d combined with less intensive counseling (9,15). The greater weight loss in these participants, compared with IBT-alone, translated into significantly greater 1-year improvements in waist circumference, high-density lipoprotein cholesterol, and mental health (27). Significantly greater improvements also were observed in glucose

TABLE 3 Changes in CVD risk factors and other secondary outcomes at weeks 24 and 52, as measured from randomization

	IBT-alone (*n* = 50)	IBT-liraglutide (*n* = 50)	Multicomponent (*n* = 50)	Total (*N* = 150)
Systolic BP (mm Hg)				
Week 24	−13.6 ± 2.1	−12.0 ± 2.1	−15.4 ± 2.1	−13.7 ± 1.2***
Week 52	−14.1 ± 2.1	−13.3 ± 2.1	−15.3 ± 2.1	−14.2 ± 1.2***
Diastolic BP (mm Hg)				
Week 24	−3.2 ± 1.2	−3.4 ± 1.2	−4.5 ± 1.2	−3.7 ± 0.7***
Week 52	−3.0 ± 1.2	−2.9 ± 1.2	−3.5 ± 1.2	−3.2 ± 0.7***
Heart rate (BPM)				
Week 24	−9.5 ± 2.0[a]	−3.6 ± 2.0[b]	−5.5 ± 2.0[ab]	−6.1 ± 1.2
Week 52	−7.4 ± 2.0	−5.3 ± 2.0	−9.7 ± 2.0	−7.5 ± 1.2***
Waist circumference (cm)				
Week 24	−5.2 ± 1.1[a]	−9.9 ± 1.1[b]	−12.9 ± 1.1[b]	−9.3 ± 0.7
Week 52	−6.5 ± 1.3[a]	−11.1 ± 1.3[b]	−12.6 ± 1.3[b]	−10.1 ± 0.8
Total cholesterol (mg/dL)				
Week 24	−12.2 ± 3.6	−13.9 ± 3.5	−16.8 ± 3.6	−14.3 ± 2.0***
Week 52	−7.0 ± 3.5	−9.7 ± 3.6	−10.0 ± 3.5	−8.9 ± 2.0***
HDL cholesterol (mg/dL)				
Week 24	−2.5 ± 1.3	−1.2 ± 1.2	−1.1 ± 1.3	−1.6 ± 0.7*
Week 52	−1.3 ± 1.3[a]	3.0 ± 1.3[b]	2.0 ± 1.3[a,b]	1.2 ± 0.7
LDL cholesterol (mg/dL)				
Week 24	−8.7 ± 3.1	−9.3 ± 3.0	−11.9 ± 3.0	−10.0 ± 1.8***
Week 52	−3.3 ± 3.1	−9.6 ± 3.1	−9.4 ± 3.1	−7.4 ± 1.8***
Triglycerides (mg/dL)				
Week 24	−4.6 ± 5.8	−14.9 ± 5.6	−15.5 ± 5.7	−11.8 ± 3.3***
Week 52	−16.3 ± 5.7	−21.3 ± 5.8	−14.4 ± 5.7	−17.3 ± 3.3***
C-Reactive protein (mg/L)				
Week 24	−0.7 ± 0.7	−1.2 ± 0.7	−2.5 ± 0.7	−1.4 ± 0.4
Week 52	−0.4 ± 0.7[a]	−2.0 ± 0.7[a,b]	−3.0 ± 0.7[b]	−1.8 ± 0.4
HbA_{1c}				
Week 24	−0.3 ± 0.04[a]	−0.4 ± 0.03[b]	−0.5 ± 0.03[b]	−0.4 ± 0.02
Week 52	−0.3 ± 0.03[a]	−0.5 ± 0.03[b]	−0.6 ± 0.03[b]	−0.5 ± 0.02
Fasting glucose (mg/dL)				
Week 24	−1.9 ± 1.3[a]	−4.4 ± 1.3[a,b]	−6.6 ± 1.3[b]	−4.3 ± 0.8
Week 52	0.01 ± 1.3[a]	−5.2 ± 1.3[b]	−5.7 ± 1.3[b]	−3.6 ± 0.8
Fasting insulin				
Week 24	−1.9 ± 0.7	−0.8 ± 0.7	−0.9 ± 0.7	−1.2 ± 0.4**
Week 52	−1.5 ± 0.8	−1.1 ± 0.8	−1.5 ± 0.8	−1.4 ± 0.5**
HOMA-IR				
Week 24	−0.5 ± 0.2	−0.3 ± 0.2	−0.3 ± 0.2	−0.4 ± 0.1**
Week 52	−0.4 ± 0.2	−0.3 ± 0.2	−0.4 ± 0.2	−0.4 ± 0.1**
Depression symptoms (PHQ-9)				
Week 24	−1.5 ± 0.6	−3.0 ± 0.6	−2.9 ± 0.6	−2.6 ± 0.3***
Week 52	−1.8 ± 0.6	−1.9 ± 0.6	−1.5 ± 0.6	−1.8 ± 0.4***

TABLE 3. *Continued*

	IBT-alone (*n* = 50)	IBT-liraglutide (*n* = 50)	Multicomponent (*n* = 50)	Total (*N* = 150)
Short Form 36				
Physical component summary				
Week 24	4.8 ± 1.0	2.3 ± 1.0	4.4 ± 1.0	4.0 ± 0.6
Week 52	4.4 ± 1.0	2.1 ± 1.0	3.4 ± 1.0	3.4 ± 0.6
Mental component summary				
Week 24	0.8 ± 1.3[a]	4.4 ± 1.3[a,b]	6.9 ± 1.3[b]	4.3 ± 0.8
Week 52	0.8 ± 1.3[a]	4.5 ± 1.3[b]	6.4 ± 1.3[b]	4.1 ± 0.8

Values shown are means ± SE. For each variable, the three treatment groups were compared using pairwise comparisons. Scores at randomization were included as covariate in these models to control for initial differences among groups. Significant differences between groups at $P<0.05$ are denoted by different superscripts ([a] vs. [b]) between values. For example, at week 24, the 9.5-BPM decrease in heart rate for IBT-alone was significantly greater than the 3.6-BPM decrease in IBT-liraglutide. This is shown by the "a" superscript with –9.5 ± 2.0[a], compared with the b superscript for –3.6 ± 2.0[b]. Values that share a superscript do not differ significantly. For example, neither the IBT-alone nor IBT-liraglutide group differed significantly from the 5.5-BPM decrease in the Multicomponent group, which is marked "ab". For the comparison of each variable, the absence of any superscript letters indicates that there were no significant differences among groups. In those cases, changes over time in the total sample ($N = 150$) that were statistically significant are indicated using $^{*}P<0.05$, $^{**}P<0.01$, and $^{***}P<0.001$.
BP, blood pressure; BPM, beats per minute; CVD, cardiovascular disease; HbA_{1c}, hemoglobin A_{1C}; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; PHQ-9, Patient Health Questionnaire 9.

TABLE 4 Adverse events with incidence of 5% or more of patients in any treatment group, as well as all serious adverse events

	IBT-alone (*n* = 50)		IBT-liraglutide (*n* = 50)		Multicomponent (*n* = 50)	
	n (%)	Events, *n*	*n* (%)	Events, *n*	*n* (%)	Events, *n*
All adverse events	30 (60%)	63	45 (90%)	164	47 (94%)	171
Adverse events ≥ 5% in any treatment group	21 (42%)	39	42 (84%)	119	44 (88%)	128
Nausea	4 (8%)	4	18 (36%)	21	13 (26%)	17
Constipation	1 (2%)	2	15 (30%)	16	17 (34%)	21
Upper respiratory infection	8 (16%)	8	16 (32%)	18	14 (28%)	18
Musculoskeletal injury	6 (12%)	7	6 (12%)	6	12 (24%)	12
Gastroenteritis	2 (4%)	2	10 (20%)	12	8 (16%)	8
Diarrhea	2 (4%)	2	6 (12%)	9	7 (14%)	7
Vomiting	3 (6%)	3	6 (12%)	8	5 (10%)	6
Gastroesophageal reflux disorder	2 (4%)	2	2 (4%)	2	6 (12%)	9
Injection site irritation	0	0	5 (10%)	5	6 (12%)	6
Fatigue	0	0	4 (8%)	4	5 (10%)	6
Sinusitis	3 (6%)	3	2 (4%)	2	5 (10%)	5
Knee pain	2 (4%)	2	2 (4%)	2	4 (8%)	4
Lower back pain	2 (4%)	2	1 (2%)	1	4 (8%)	5
Abdominal pain	0	0	4 (8%)	4	2 (4%)	2
Headache	1 (2%)	1	3 (6%)	3	1 (2%)	1
Tonsillopharyngitis	1 (2%)	1	3 (6%)	3	0	0
Depressed mood	0	0	3 (6%)	3	1 (2%)	1
All serious adverse events	2 (4%)	2	0	0	3 (6%)	4
Asthma exacerbation	1 (2%)	1	0	0	0	0
Bile duct stone	0	0	0	0	1 (2%)	1
Gastroenteritis	0	0	0	0	1 (2%)	2
Pneumonia	0	0	0	0	1 (2%)	1
Wound infection	1 (2%)	1	0	0	0	0

The table shows the number of participants who had an event, *n* (%), and the total number of events reported, Events, *n*.

and hemoglobin A_{1c}, results that likely were attributable to liraglutide's independent effects on glucose metabolism (14). Liraglutide was generally well tolerated, with adverse events similar to those reported previously (9,14,15).

The addition of a 12-week meal-replacement diet to IBT-liraglutide significantly increased weight loss at week 24, but not by as much as expected (36), and the benefit was not maintained at week 52. We previously showed in a randomized trial that the combination of the weight loss medication sibutramine and high-intensity group behavioral weight loss counseling, delivered with a 1,200- to 1,500-kcal/d diet of conventional foods, produced a 10.4% reduction in initial weight at 1 year. The addition of a 1,000-kcal/d meal-replacement diet to this regimen for the first 16 weeks increased mean 1-year weight loss to 16.5% (36). Participants in the meal-replacement group challenged each other, by their large weekly weight losses, to adhere strictly to the 1,000-kcal/d diet. Our clinical impression is that the individual counseling in the present study did not facilitate the same robust adherence to the meal-replacement diet as did the social support and healthy competition engendered by group counseling (36).

This study's strengths include high participant engagement and retention rates. Potential limitations include the absence of a usual-care group, which was not included because of consistent evidence that it would yield a 1-year weight loss of 1% to 2% (23,37). The study also did not include principally older adults (≥65 years), as covered by the Medicare benefit, and the trial was not conducted in a primary care setting. In addition, by design, participants were provided 21 sessions of IBT regardless of whether they lost≥3 kg at month 6. The favorable results from this well-controlled efficacy study await replication in larger pragmatic trials that include greater numbers of older adults (i.e., the target for CMS) and are conducted in primary care settings.

The present findings show that physicians and NPs can provide effective IBT for obesity, facilitating weight losses comparable to those produced by RDs. Further study, however, is needed to determine the minimum instruction that PCPs in nonspecialty practices would require to provide such care and at what financial and personal costs to their already busy practice schedules (38). Most physicians do not have the training, time, or financial incentive to provide intensive behavioral counseling (38). CMS allows ancillary health professionals (e.g., RDs) to provide IBT if working incident to PCPs. However, PCPs must be physically present when ancillary counseling is provided (3,26). Such restrictions likely have contributed to IBT's low use rate (<1%) among eligible CMS beneficiaries (39). We encourage CMS to change the model by which IBT is delivered to include RDs, health counselors, and other trained interventionists (2) as eligible primary providers. This modification, as well as covering group treatment and validated telephone and digitally delivered counseling (2,40), could greatly increase access to IBT while substantially reducing the cost of this important care.**O**

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A deidentified data set will be made available to external investigators (upon request to the first author), once the research team has completed its analysis and reporting of secondary findings from the study. This is expected to be approximately 2 years after the publication of this report.

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