weight loss was observed (mean ΔBMI SDS -1.09 ± 1.00), in one patient BMI stabilization (ΔBMI SDS +0.03), and in two patients an increase in BMI SDS was seen (mean ΔBMI SDS +0.32 ± 0.05). Of nine children with acquired HO and measurement of REE before and during treatment, a mean REE increase of +15.3% ± 10.5 was observed. In three out of five patients with genetic obesity, initially weight loss was observed resulting in BMI stabilization at end of follow-up due to weight regain (mean ΔBMI SDS -0.08 ± 0.19). In these patients, no difference in REE before and during treatment was observed. In two patients an increase in BMI SDS was seen (mean ΔBMI SDS +0.29 ± 0.25). However, one patient discontinued treatment after one month, due to hypertension. Thirteen out of 18 children (72.2%) reported improvement of either their hyperphagia, energy level, and/or behavior. No serious side effects were reported.
Conclusion: In children and adolescents with acquired HO, treatment with dextroamphetamine may significantly lower BMI, reduce hyperphagia and improve activity level. In genetic HO, these effects were less pronounced. Future studies in a larger cohort and with randomized controlled designs are needed to support these results.

Adipose Tissue, Appetite, and Obesity
WHAT'S NEW IN WEIGHT MANAGEMENT THROUGH THE LIFESPAN?

Once-Weekly Exenatide Enhances Weight Loss Maintenance in Adolescents with Severe Obesity: A Randomized, Placebo-Controlled Trial

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Background: In adolescents with severe obesity, long-term weight loss maintenance using lifestyle therapy alone is hampered by numerous biological adaptations favoring weight regain such as increased appetite and sense of food palatability and decreased satiety and resting energy expenditure. Anti-obesity pharmacotherapy may have a role in mitigating some of these physiological adaptations, thereby enhancing weight loss maintenance. We conducted a randomized, double-blind, placebo-controlled clinical trial to evaluate the effect of the glucagon-like peptide-1 receptor agonist (GLP-1RA) exenatide extended release (XR) on the maintenance of BMI reduction and improvements in cardiometabolic risk factors induced by short-term meal replacement therapy (MRT) among adolescents with severe obesity. **Methods:** One-hundred adolescents ages 12 to <18 years with BMI ≥120% of the 95th percentile engaged in an MRT intervention consisting of pre-portioned meals averaging 1,400 kcals/day with a goal of reducing BMI by ≥5% within eight weeks. Participants achieving this goal were randomized 1:1 to either exenatide XR (2 mg/week subcutaneously) + lifestyle therapy or matching placebo + lifestyle therapy for a subsequent 52 weeks. The primary outcome was mean percent change in BMI from randomization (post-MRT) to 52 weeks. Secondary outcomes included changes in body fat (DXA) and cardiometabolic risk factors. **Results:** Sixty-six participants (mean age 16±1.5 years; 47% female; mean BMI 36.9±4.4 kg/m^2) achieved ≥5% BMI reduction with MRT and were randomized; 56 (85%) completed the 52-week visit. From randomization (post-MRT) to 52-weeks, the exenatide and placebo group mean BMI increased 4.6% and 10.1%, respectively. The prespecified intention-to-treat, last observation carried forward primary analysis demonstrated a placebo-subtracted exenatide treatment effect of -4.1% (95% CI -8.6 to 0.5, p=0.078). The per-protocol analysis (excluding participants with major protocol deviations) demonstrated a placebo-subtracted exenatide treatment effect of -5.7% (95% CI -10.9 to -0.6, p=0.030). The placebo-subtracted exenatide treatment effect on total body fat was -3.0 kg (95% CI -6.7 to 0.7, p=0.108), systolic blood pressure -3.2 mmHg (95% CI -7.0 to 0.7, p=0.107), and triglycerides to HDL ratio -0.6 (95% CI -1.2 to 0.0, p=0.050). Exenatide was generally well-tolerated and the adverse event profile was similar to previous reports of GLP-1RAs. **Conclusion:** The steep trajectory of weight regain following short-term MRT, particularly in the placebo group, underscores the challenge many adolescents encounter in maintaining weight loss over time. GLP-1RA treatment with once-weekly exenatide appears to partly mitigate the propensity toward weight regain after initial dietary-induced weight loss among adolescents with severe obesity.

Adipose Tissue, Appetite, and Obesity
WHAT'S NEW IN WEIGHT MANAGEMENT THROUGH THE LIFESPAN?

Weight Loss Maintenance With Once-Weekly Semaglutide 2.4 MG in Adults With Overweight or Obesity Reaching Maintenance Dose (STEP 4)

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Background: In people with overweight or obesity, long-term maintenance of weight loss is challenging. Subcutaneous (s.c.) semaglutide, a glucagon-like peptide-1 analogue, has shown clinically-relevant weight loss in a phase 2 trial in people with obesity. STEP 4 investigated the impact of continued semaglutide 2.4 mg treatment, vs switching to placebo, on maintenance of weight loss in participants who reached 2.4 mg of semaglutide during a run-in period.
Methods: This was a 68-week withdrawal trial (NCT03548987) in 902 subjects aged ≥18 years with body mass index (BMI) ≥30 kg/m^2 (or BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity), without diabetes. Following a 20 week run-in period, 803 subjects who reached the maintenance dose of once-weekly (OW) s.c. semaglutide 2.4 mg were randomized 2:1 to continue treatment with semaglutide 2.4 mg or switch to placebo for 48 weeks, both as adjunct to lifestyle intervention. The primary endpoint was percentage change in body weight between randomization (week 20) and week 68. Confirmatory secondary endpoints included change in waist circumference and systolic blood pressure. Two estimands were defined: treatment policy and trial product; results are presented for the treatment policy estimand, unless stated otherwise.
Results: Mean body weight (±SD) was 107.2 ±22.7 kg at week 0 and 96.1 ±22.6 kg at randomization (week 20; mean change -10.6%). Randomized participants were mostly female (79%) and white (84%); mean age was 46 years and mean BMI was 34.4 kg/m^2. Between weeks 20–68, estimated mean body weight change was −7.9% vs +6.9% for semaglutide 2.4 mg vs placebo (estimated treatment difference [ETD]: −14.8%; 95% confidence interval [CI]: −16.0, −13.5; p<0.0001), and -8.8% vs 6.5%, respectively, for the trial product estimand (ETD: -15.3%; 95% CI: -16.5, -14.1; p<0.0001). For participants randomized to continue semaglutide, the estimated change in body weight from week 0–68 was -17.4% (-18.2% for trial product estimand). Continued semaglutide treatment (weeks 20–68) led to clinically-relevant improvements in waist circumference, systolic blood pressure, BMI, HbA_{1c}, FPG, and lipids (total cholesterol, LDL, VLDL, and triglycerides) vs switching to placebo (p<0.0001 for all). During the run-in period, 5.3% of participants discontinued treatment due to adverse events; during the randomized period, 2.4% (semaglutide) and 2.2% (placebo) discontinued. Nausea, diarrhea and constipation (mostly transient and mild-to-moderate) were the most frequent adverse events with semaglutide.
Conclusion: In adults with overweight or obesity, continued treatment after dose escalation with OW s.c. semaglutide 2.4 mg until week 68 led to clinically-relevant weight loss, while switching to placebo led to significant weight regain; these data underscore the chronicity and relapsing nature of obesity, and the need for continued treatment.

Adipose Tissue, Appetite, and Obesity

WHAT'S NEW IN WEIGHT MANAGEMENT THROUGH THE LIFESPAN?

Weight Loss, Improved Body Composition and Fat Distribution by Tesomet in Acquired Hypothalamic Obesity

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Background: Structural damage to the hypothalamus often results in hypothalamic obesity characterized by rapid and severe weight-gain with increased risk of cardiovascular and metabolic morbidity and mortality. Currently, there are no approved or effective pharmacological treatments and conventional weight management remains largely ineffective. **Objective:** This RCT investigated safety and efficacy of Tesomet (co-administration of 0.5mg tesofensine and 50mg metoprolol) in hypopituitary patients with acquired hypothalamic obesity. **Methods:** Twenty-one (16 females) hypopituitary adults with hypothalamic obesity were randomized to Tesomet or placebo (2:1) for 24 weeks (NCT03845075). Subjects also received diet and lifestyle counselling. Primary endpoint was safety evaluated by change in heart rate, blood pressure and adverse events. Secondary endpoints included changes in anthropometric measures, body composition, corrected QT-interval and arrythmias. **Results:** Subjects had a median (range) age of 50 (25; 70) years and 90% had a BMI ≥30 kg/m^2. Almost half (48%) had a history of craniopharyngioma, 86% had undergone pituitary/hypothalamic surgery, and 52% had irradiation therapy. All received one or more anterior pituitary hormone replacements; 52% had diabetes insipidus. In total, 18/21 subjects completed the study, one without investigational treatment. Three serious adverse events (SAE) were recorded in 2 subjects randomized to Tesomet. Adverse events were otherwise mostly mild (58%), frequently reported were sleep disturbances (62%), dry mouth (46%) and dizziness (46%), known side effects of tesofensine or metoprolol. Four subjects, two in each group, discontinued treatment. Tesomet discontinuation was secondary to anxiety (n=1) or dry mouth (n=1). No significant differences in heart rate or blood pressure were observed between the two groups. At week 24, compared to placebo (weight-loss: -0.3%), Tesomet treatment resulted in additional mean weight-loss of -6.3% (95CI [-11.3%; -1.3%], p=0.017); increase in the proportion of patients achieving >5% reduction in body weight (Tesomet 8; Placebo 1, OR 11.2 [1.0; 120.4], p=0.046); and reduction in waist circumference of -5.7cm ([-11.5; 0.1], p=0.054). Tesomet-induced weight loss was primarily correlated to a reduction in mean (SD) fat mass -5.3kg (5.3) (r^2=0.9, P=0001) and to lesser extent a reduction in lean tissue mass -2.9kg (1.9) (r^2=0.4, P=0.03). Treatment did not affect corrected