

Oral Presentations

12-OR Ileal Transposition Improves Glycemia in Streptozotocin Treated Rats. Wendt et al.

Diabetes is cured/improved in 85-95% of obese patients that undergo bariatric surgery. Recent data indicate that in addition to anatomical considerations, neurohormonal signals from the gut appears to mediate much of the improvements after bariatric surgery.

The authors did ileal transposition experiments in rats to see if there was a neurohormonal effect on weight. Distal ileal segment was transposed to the proximal small bowel just after the ligament of Treitz in SD rats treated with submaximal streptozotocin (these animals were not insulin resistant, were and not fat fed). Animals became diabetic, hyperphagic, polydipsic, and lost body weight prior to the ileal transposition. Rats were divided into two groups. Group 1 received ileal transposition and the Group 2 received a sham operation. After transposition food intake decreased, water intake decreased, animals demonstrated a decreased preference for high fat food. At 4 weeks post-op rats that had the ileal transposition showed decreases in fasting glucose levels and changes were observed even earlier. At 11 weeks post operatively the body weight were similar between the two groups but there were improvements in blood glucose, OGTT improvements in the ileal transposition animals; insulin levels were similar. Histologically Beta cells were more preserved in ileal transposition animals than in sham surgery animals. The similar body weights among the groups suggests a body-weight independent effect of transposition. Although not measured PYY and GLP-1 are made in L cells in terminal ileum. Increased nutrient load with the transposed ileum may be responsible for the observed effects – the so called “ileal brake”.

51-OR Supplemental Calcium in Overweight Out-Patients (SCOOP): A Randomize, Controlled Trial of the Effects of Calcium Supplementation on Body Weight and Body Composition. Yanovski et al.

Background: epidemiological and prospective cohort studies have indicated that BMI is inversely related to calcium intake. Theories include 1) low calcium intake results in PTH stimulation and elevated 1,25-dihydroxyvitamin D levels that result in increased adipocyte intracellular calcium levels that result in lower lipolysis and increase lipogenesis (Zemel) and 2) low dietary calcium results in less soap formation with dietary triglyceride in the gut so that more triglyceride is available for absorption. SCOOP is NIH sponsored study that investigates the effect calcium supplementation in 340 obese subjects 340 obese randomized to 750 mg calcium (as carbonate) BID or placebo for 2 yrs. Inclusion criteria allowed a BMI as low as 25; among the participants 37% were overweight and 63% were

obese participants. Baseline calcium intake was 882 mg and 23% had dietary calcium intakes less than 600 mg. Baseline calcium intake was inversely correlated with baseline BMI. 74% of the individuals completed the trial. Individuals with 25OHD levels <10 were supplemented with vitamin D. At the end of 2 yrs there were no differences in weight loss, no change in BMI and no change in body composition (DXA) between the two groups.

52-OR Bupropion and Zonisamide for the Treatment of Obesity. Greenway et al. (Orexigen).

This is a proof of concept study that was done based upon preclinical data that indicate zonisamide and bupropion synergistically act to increase firing of POMC neurons (α MSH), decrease food intake, and loss of weight as well as clinical trial data that has demonstrated weight loss in obese subjects when each agent is used alone. 5 clinical sites recruited subjects into two similar clinical protocols (OT 101 and OT 102). Subjects were age 18-60, with BMI between 30 and 40. OT 101 and OT 102 were run in tandem at the same sites (8 sites for 101 study, 5 sites for 102 study). After enrollment into OT101 was completed, enrollment into OT 102 began. OT 101 evaluated the weight loss effect of Bupropion SR and Naltrexone: placebo vs. naltrexone vs. bupropion vs combination naltrexone and bupropion for 16 weeks (the data for OT 101 was presented in a poster – see 406-P below). The OT 102 study randomized 118 subjects to Zonisamide 400 mg daily or combination Zonisamide 400 mg daily and Bupropion SR 150 mg BID for 16 weeks. The Bupropion and placebo groups from OT 101 were used in the analysis as control arms for the OT 102 study. The Bupropion arm from OT 101 and Zonisamide and combination Zonisamide/Bupropion arms from OT 102 were all extended to 24 weeks. At week 24 subjects in the Zonisamide and combination Zonisamide/Bupropion arms were re-randomized to either 200 mg Zonisamide daily or 400 mg Zonisamide daily for an additional 24 weeks (48 weeks total); Bupropion was continued at the same dose. Discontinuation rates at 16 weeks were 27% for Bupropion, 31% for Zonisamide, 47% for combination Zonisamide and Bupropion, and 32% for placebo. At 16 and 24 weeks weight loss from baseline was Bupropion 3.7% and 3.6%; Zonisamide 5.7% and 6.5%; combination Bupropion-Zonisamide 8.3 and 9.2%; placebo 0.7% and 0.4% (intergroup comparisons [Bupropion and Zonisamide to combination] were significant at 16 and 24 weeks $p < .001 - < .026$). 50% of subjects on the combination of Zonisamide and Bupropion had at least a 10% weight loss at 16 or 24 weeks. At 48 weeks weight loss from baseline was Zonisamide 200 mg 3.1%, Zonisamide 400 mg 9.3%, Zonisamide 200 plus Bupropion 8.4%, Zonisamide 400 plus Bupropion 12%. The most common AEs were insomnia (20% in combination group), nausea (18.6% in combination group) and fatigue (10% in combination group). There were no statistically significant changes in lipids.

53-OR Pramlintide Treatment for Obesity Elicited Progressive Weight Loss When Used with a Structured Lifestyle Intervention Program: a Randomized Controlled Trial. (Amylin study). Aronne et al.

Pramlintide and intensive lifestyle intervention (LEARN program) effect on weight loss was studied in obese non-diabetic subjects. The trial investigated the dose response of BID and TID dosing with pramlintide for 16 weeks after a 1 week placebo lead in. 408 subjects were randomized to one of 7 arms. 1) placebo, 2) pram 120 mcg BID, 3) pram 240 BID, 4) pram 360 BID, 5) pram 120 TID, 6) pram 240 TID, 7) pram 360 TID. Pramlintide was given by subcutaneous injection 15 minutes prior to meals. The BID arms injected prebreakfast and predinner with pram and placebo at lunch. Discontinuation rates were approximately 35% across arms; only at the highest doses were there increased drop outs due to AEs. The BID regimen demonstrated a clear dose response with maximal weight loss from baseline of 6.1 kg at the 360 mcg dose compared to 2.6 kg in placebo. In the TID arms there was not a clear dose response as all treatment arms gave a similar effect (approximately 6%). 44-50% of subjects achieved at least 5% weight loss in the treatment arms vs 28% in the placebo group. The categorical weight loss analysis was also presented by plotting percent weight change for each individual categorized by arm in a histogram. A shift to the left in the 5% and 10% weight loss thresholds indicated better results for subjects on treatment. Nausea was not a major contributor to weight loss as even those subjects without nausea had similar degrees of weight loss; nausea was the most common AE (9-29% of subjects).

55-OR A 24-Week Randomized Controlled Trial of VI-0521, a Combination Weight Loss Therapy, in Obese Adults. Gadde et al (Vivus).

This was a 24 week study of VI-0521 (Qnexa, topiramate/phentermine) vs topiramate vs phentermine vs placebo in 200 obese individuals (50 subjects per group with a overall total of 41 men – randomization was stratified by gender). Doses of both topiramate and phentermine were not disclosed due to “safety” and “proprietary” reasons. The drugs were administered as identical capsules in two bottles (A and B). Subjects were 18-60 yrs old, BMI 30-50, without history of kidney stone (kidney stones are a known topiramate AE). Subjects entered a 4 week dose escalation phase followed by a treatment phase for a 24 week study period (no run in). Subjects were instructed in a 500 kcal deficit diet and were encouraged to engage in physical activity. The primary endpoint was change in baseline weight at the end of the study. Secondary endpoints included waist circumference, blood pressure, and lipids. The Hospital Anxiety Depression scale (HAD) been used to identify and monitor for depression (The HAD has been used in other studies presented at the meeting). 79% (158) completed the study with the following breakdown VI-0521 92%, topiramate 80%, phentermine 76%, placebo 62%. There were 4 early withdrawals from the VI-0521 group. The table shows the Intention-To-Treat (ITT) analysis and the Complete analysis.

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	VI-0521	Topiramate	Phentermine	Placebo	P
<i>Weight loss (kg)</i>					
<i>ITT</i>	-11.4	-6.6	-5.3	-2.2	<.0001
<i>Completer</i>	-11.8	-7.2	-6.1	-3.2	
<i>% weight loss</i>					
<i>ITT</i>	-10.7	-6.3	-4.6	-2.1	<.0001
<i>Completer</i>	-11.1	-6.9	-5.5	-2.8	<.0001
<i>Categorical loss</i>					
<i>5% or more</i>	82%	50%	38%	14%	
<i>10% or more</i>	50%	16%	14%	8%	
<i>15% or more</i>	20%				

Graphical presentation of percent weight loss overtime indicated separation between groups as early as 4 weeks and no plateauing of effect in the VI-0521 group at study end (24 weeks). Waist circumference and BP decreased more in the VI-0521 group than in the other treatment arms. Lipids showed non statistically significant trends toward improvement. Total cholesterol decreased 10%, LDL decreased 5.9%, TG decreased 16.2% in VI-0521 group. There were no changes in HDL. 2D echocardiograms done at beginning and end of study showed no valvular or pulmonary artery pressure changes.

56-OR Clinically Significant Weight Reduction in Subjects with Type 2 Diabetes Treated with Exenatide. Qu et al (Lilly and Amylin).

Weight gain is often associated with improved metabolic control in Type 2 Diabetics. This report details the prevention of weight gain associated with the improved metabolic control of diabetes with exenatide in diabetics not adequately managed on metformin and sulfonylurea. This is a post-hoc analysis of a larger exenatide study. This was a 26 week open label treatment of type 2 diabetics treated with metformin/sulfonylurea that were randomized to either addition of glargine insulin (titrateable) or exenatide (283 per group). BMI at baseline was 31.3. 80% of exenatide and 90.3% of glargine patients completed the study. Both groups had similar decrements in HgbA1c by 1% from a baseline of 8.2%. At study end there was a 1.8 kg increase in weight in the glargine group and a 2.3 kg decrease in weight in the exenatide group. 24 blood glucose levels showed lower preprandial values in glargine arm and lower postprandial values in exenatide arm. 5% or greater weight loss occurred in 22% of exenatide subjects compared to 2.6% of glargine subjects. For 10% or greater weight loss these values were 4.3% and 0.4% respectively. 15% of glargine treated subjects gained 5% or more of baseline weight compared to 0.7% receiving exenatide. Hypoglycemia was similar in both groups and was infrequent.

57-OR Effect of NPY5R Antagonist on Weight Regain after VLCD-Induced Weight Loss. Erondy et al (Merck).

MK-0557 is an antagonist of NPY 5 receptor and has been evaluated in studies as long as 1 year with little effect on weight loss in obese individuals. In a 52 week study of more than 1600 subjects, MK-0557 treated individuals lost a mean of 7.5 pounds vs. 4 pounds for placebo subjects. There is now interest in determining if NPY5R antagonism may be effective in minimizing weight regain after weight loss. MK-0557 therapy following a VLCD (very low calorie diet) was examined to determine the effect of drug on maintaining weight. 502 subjects age 18-65, BMI 30-43 received a VLCD (800 kcal/d) with meal replacements for 6 weeks after which time those who lost at least 6% of their baseline weight were randomized to MK-0557 or placebo for 1 yr. 177 subjects were randomized to placebo and 182 were randomized to MK-0557 (1mg/day). 131 in placebo and 127 in MK-0557 groups completed the study. 80% of subjects were female. At the end of the VLCD the mean weight loss was 9.1 kg. Weight loss continued in placebo and MK-0557 group through the 12 week time point of the weight maintenance period. After the 12 week point both groups started to gain weight. At study end there was a 1.6 kg difference (3.1 kg placebo vs. 1.5 kg MK-0557) in weight gain after the start of the maintenance phase; ITT or completer analysis demonstrated similar magnitude of effect that was statistically significant. The authors concluded that the magnitude of the effect however was not clinically meaningful. There were no statistically significant changes in secondary endpoints of lipids, blood pressure, or waist circumference. In general MK-0557 was well tolerated. MK-0557 development may have been abandoned.

Poster Presentations

170-P Discovery of a Novel CB-1 Inverse Antagonist for the Treatment of Obesity. Fong et al. (Merck).

Preclinical data showing MK-0364 “inverse agonist” activity at the CB-1 receptor which appears to inhibit the binding of synthetic ligands and endogenous endocannabinoids in CHO cells expressing the CB-1 receptor. Studies in DIO rats showed that animals treated with MK-0364 rats lost up to 30% of baseline weight over 2 week study period at 3 mg/kg. DIO Fat mass also declined. The pharmacology of MK-0364 is complex; it binds specifically to the CB1 receptor, has agonist activity but blocks the activity of endocannabinoid and synthetic CB1 receptor agonist ligands (agonist-antagonist). Evidence that it inhibited constitutive activity of the CB-1 receptor, validating the concept of an “inverse agonist”, was not presented. The compound is apparently in Phase II clinical development.

283-P Pharmacokinetics of a CB1 Receptor Inverse Agonist in Healthy Male Subjects. Addy et al. (Merck).

This was a Phase I study of MK-0364 PK up to 600 mg as a single doses in a total of 24 subjects (18 active and 6 placebo)

PK was dose proportional to 150 mg and moderately less dose proportional at higher doses. There as an increased AUC and Cmax with food. T1/2 48-65 hrs. MK-0364 is a “inverse agonist” for the CB1 receptor (see 170-P) and has an active metabolite with a T1/2 and 45-66 hours and an AUC that is 2-3 fold greater than the parent compound. Based on binding data, the metabolite appears to be 7 fold less potent than the parent. MK-0364 was well tolerated.

406-P Opioid Antagonists Synergize with Bupropion to Cause Weight Loss. Cowley et al. (Orexigen).

Preclinical and clinical data on combination of Naltrexone and Bupropion was presented. Opioid mu receptors inhibit POMC neurons in the arcuate nucleus; Naltrexone, an opioid antagonist, releases this inhibition increasing POMC activity and appears to have a synergistic effect with bupropion. The clinical study data for the proof of concept study (OT 101) was presented in this poster and had been presented earlier this year at the ADA meeting. 217 subjects with BMI 30-40 were randomized at 8 sites to bupropion 150 mg (SR) BID, naltrexone 50mg qd, combination of bupropion 150 mg BID and naltrexone 50 mg qd or placebo. The study was designed as a 16 week treatment period but was extended to 24 weeks for the bupropion and bupropion/naltrexone combination arms. At week 24 mean weight loss from baseline in the completer analysis was bupropion -4.1%, naltrexone -2.2%, placebo -0.9% and combination bupropion/naltrexone -6.5% (p all significant vs. combination). In the ITT analysis the values were bupropion -3.5%, naltrexone -2.0%, combination naltrexone/bupropion -4.7% and placebo -1.0% (all significant vs combination). There was a plateau of weight loss in the bupropion group at 16 weeks but the combination arm did reach a plateau even at 24 weeks. In the categorical analysis those with at least a 5% weight loss from baseline were bupropion 35%, naltrexone 21%, combination naltrexone/bupropion 54%, placebo 10% (all significant vs combination); and for at least a 10% weight loss from baseline bupropion 10%, naltrexone 0%, combination naltrexone/bupropion 18% and placebo 5% (combination was not significantly different from placebo). The most common adverse event was nausea.

514-P NPY5R Antagonism Does Not Augment the Weight Loss Efficacy of Sibutramine or Orlistat. Erondy et al (Merck).

The MK-0557 NPY5R antagonist in combination with sibutramine or orlistat (see also 57-OR) was investigated. 497 subjects with BMI 30-43 were randomized to placebo, sibutramine (10 mg qd), orlistat (120 mg TID), MK-0557 (1 mg qd) plus sibutramine (10 mg qd) or MK-0557 plus orlistat (120 mg TID). Treatment continued for 1 year in conjunction with a low calorie diet and exercise. 69-80% of subjects completed the study. The addition of MK-0557 did not augment the

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weight loss seen with sibutramine or orlistat monotherapy. Mean weight loss for sibutramine was 5.9 kg, for orlistat -4.9 kg. The weight loss difference between MK-0557 plus sibutramine and sibutramine alone was 0.1 kg and between MK-0557 plus orlistat and orlistat alone was 0.9 kg (both non-significant)

517-P Effects of Exenatide and Twice-Daily Biphasic Insulin Aspart on Body Weight and Cardiovascular Risk Factors in Patients with Type 2 Diabetes. Festy et al (Amylin/Lilly).

Exenatide vs. premixed aspart insulin (70/30) was studied in type 2 diabetics failing metformin and sulfonylurea therapy (see 56-OR). Diabetic subjects entered into this study had a baseline BMI of 30.4 and a HgbA1c of 8.6%; they were randomized to 52 weeks of exenatide or premixed aspart (titrated to fasting blood glucose of <126 and postprandial of <180). 253 received exenatide and 248 received aspart. Exenatide treatment resulted in a decrease in HgbA1c of 1.04% and aspart treatment was associated with a decrease of 0.89%. This difference was of borderline statistical significance. Exenatide was associated with weight loss of 2.5 Kg and aspart was associated with a weight gain of 2.9 kg ($p < .001$). Exenatide resulted in significant reductions in systolic (approx 4.2 mmHg) and diastolic (approx 2 mmHg) blood pressure. Standard mixed meal tolerance tests were modestly better in exenatide treated subjects. HDL levels were increased more in the aspart group than the exenatide group (.06 mmol/L $p < .001$) but not in the aspart group. There were no other significant differences in lipid levels. LDL particle size increased in the exenatide group (0.3 nm, $p < .001$) but didn't change in the aspart group.

635-P through 638-P

Phase I data for S-2367 was reported. S-2367 is a NPY5R antagonist being developed by Shionogi. Studies were done in healthy overweight and obese men and women. Escalating multiple dose studies were conducted through 3200 mg daily for as long as 14 days. 637-P reported the results of an oral fat load in fed individuals and demonstrated that S-2367 treatment decreased AUC of triglyceride as measured by retinol that was used as a tracer. Although not presented the author indicated that insulin levels were decreased in this study.

Symposia

The afternoon session of October 23 included two symposia on the brain gut axis in feeding, satiety, nutrient sensing and weight. GLP-1 had a central role in most of the 4 talks. Andrew Young from Amylin discussed the effects and mechanism of action of exenatide on weight loss in studies in type 2 diabetics. He presented some data with respect to a long acting formulation of exenatide (weekly injection) that suggests robust weight loss in type 2 diabetics (4 kg at 15 weeks) relative to the currently available formulation. It appears that this formulation is in clinical trials for obesity. Remy Burcelin from Toulouse (INSERM) presented his data showing that GLP-1 controls insulin secretion (incretin effect) through a central mechanism. Patricia Brubaker (Toronto) presented data that the enteroendocrine L cells in the distal ileum responsible for GLP-1 secretion (and co-secreted PYY) are innervated by cholinergic neurons and respond to luminal

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nutrient stimuli, cholinergic stimuli and circulatory stimuli. The GLP-1 secretion appears to have two phases – the initial phase is rapid and mediated by vagal efferent input and the delayed phase is mediated through luminal contents. The early rapid rise in GLP-1 can be abolished by vagotomy. The cholinergic input is mediated via M1 muscarinic receptors. Interestingly she showed that bethanechol, a non-selective muscarinic agonist, increased GLP-1 secretion in rodents. Pirenzapine a selective M1 antagonist blocked GLP-1 secretion. Atropine has also been shown to block glucose stimulated GLP-1 secretion.

NAASO The Obesity Society Annual Scientific Meeting was held in Boston October 20-24, 2006. Additional details, including abstracts have been published in Obesity 14(9) Supp A1-A318, 2006 and are available on request. Additional information about the meeting is available at www.naaso.org. NAASO has indicated that official recordings of oral presentations and symposia will be available on their website shortly after the conclusion of the meeting.

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