METABOLIC SYNDROME AND RELATED DISORDERS
Volume XX, Number XX, 2018

Pp. 1–5
DOI: 10.1089/met.2018.0075

Combination Therapies for Obesity

Michael Camilleri, MD, and Andres Acosta, MD, PhD

Abstract

The objective of this review is to examine advances in the development of combination therapies for the treatment of obesity beyond diet or lifestyle interventions. Experimental combination pharmacotherapies include combinations of pramlintide and phentermine as well as amylin and bupropion-naltrexone. Incretin and pancreatic hormones generally inhibit upper gastrointestinal motor functions, and combinations showing efficacy in obesity are coadministration of glucagon-like peptide-1 (GLP-1) with glucagon, a unimolecular dual incretin of PEGylated GLP-1/GIP coagonist, the combination of GLP-1 and PYY_{3-36}, and, in proof of concept studies, combined infusions of GLP-1, peptide YY, and oxyntomodulin. Among bariatric procedures, repeat intragastric balloon (IGB) treatments are more efficacious than IGB plus diet, and endoscopic intervention can enhance the effects of Roux-en-Y gastric bypass when weight regain occurs. A first trial has provided promising results with combination of IGB plus the GLP-1 analog, liraglutide, compared to the balloon alone. Thus, combination therapies for the treatment of obesity hold promise for introduction into clinical practice.

Keywords: obesity, pharmacotherapies, glucagon, GLP-1

Introduction

As the prevalence of obesity continues to rise, new management based on combined approaches are being developed. Central and peripheral mechanisms are involved in appetite regulation. Some of the currently approved medication combinations of naltrexone with bupropion and phentermine with topiramate are among the most efficacious pharmacologic therapies for weight loss,[1] and their effects appear to be exclusively central; however, their efficacy is countered by adverse effects which restrict dosage.

Peripheral mechanisms in appetite regulation include gastric emptying and accommodation, sensory mechanisms which convey symptoms of satiation to the brain, and peripherally released peptides and hormones. These provide feedback from nutrient activation of enteroendocrine and pancreatic cells to regulate metabolism (through incretin effects) or provide input to the highly organized hypothalamic circuitry and vagal nuclei, resulting in either orexigenic stimuli after fasting or an anorectic signal during meal ingestion.

Given the redundancy of appetite control mechanisms, there is an opportunity to use combination therapies, which could potentially enhance the efficacy of single therapies [*e.g.*, glucagon-like peptide-1 (GLP-1) analogs or agonists]; combination therapies are a logical, synergistic approach to replicate the multiple mechanisms that contribute to the benefits of bariatric surgery, including mechanical restriction of the gastric reservoir, alterations in the secretion of multiple gut hormones and, possibly, in the composition and secretion of bile acids, and, possibly, alterations of gut microbiota.

Figure 1 shows the brain–gut axis and the sites of actions of endogenous modifiers of appetite, as well as the predominant sites of actions of the current approved treatments for obesity: medications, devices, and bariatric procedures. The objective of this article is to review the advances in combination therapies in the treatment of obesity beyond diet or lifestyle interventions, using evidence typically obtained from studies in humans and experimental animal models of obesity.

Experimental Combination Pharmacotherapies

The attraction of combination therapies is that different mechanisms are targeted by the components of the combined therapy for obesity. The combined pharmacotherapy of pramlintide and phentermine was superior to pramlintide alone in humans[2]; thus, the mean reduction in body weight at 24 weeks was $\sim$10.5% with combination pramlintide with phentermine, in comparison to a mean reduction of

Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Mayo Clinic, Rochester, Minnesota.

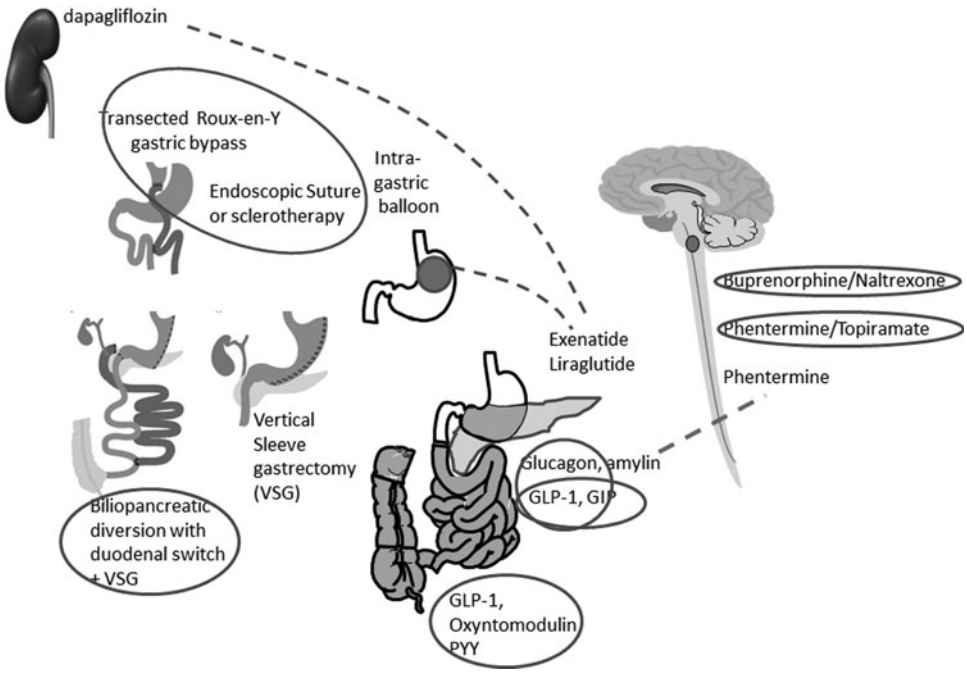

FIG. 1. Individual and combined therapeutic approaches in obesity.

~2.5% with pramlintide alone. In addition, the combination of amylin and bupropion-naltrexone on food intake and body weight was interactive in rodent models.[3] A third example is provided by the effects on weight loss in patients with type 2 diabetes mellitus of exenatide once weekly plus daily dapagliflozin [an inhibitor of the sodium/glucose cotransporter 2 (SGLT2) in renal tubular epithelium], and exenatide once weekly or dapagliflozin daily added to metformin monotherapy.

Among the overall population, weight loss was significantly greater after 28 weeks for patients receiving exenatide once weekly plus dapagliflozin (average weight loss 3.55 kg) compared to the same treatments individually (average weight loss of 2.0 kg with daily dapagliflozin and 1.5 kg with exenatide once weekly).[4] There were greater reductions in body mass index (BMI) observed in all BMI groups, including normal weight and overweight patients, with combination treatment compared with either treatment alone.[5] Exenatide once weekly plus dapagliflozin was superior to placebo in a separate 24-week trial,[6] and results were sustained over 1 year of treatment.[7]

Such sustained weight loss over 1 year is noteworthy and emphasizes the goal of long-term weight loss in the assessment of the utility of efficacy of combination therapies over single therapies. The additional weight loss with dapagliflozin may have resulted from calorie loss through glycosuria.[4] Such combinations may also have synergistic (although yet unproved) salutary effects on cardiovascular disease. However, it is important to specify that, as yet, these combinations have only been tested for efficacy in patients with diabetes and not in the broader context of obesity.

Gut Hormone or Incretin Combinations

The incretins are hormones that are released after eating and augment the secretion of insulin from pancreatic beta cells. Incretins and pancreatic hormones generally inhibit upper gastrointestinal motor function [*e.g.*, amylin, glucagon, glucose-stimulated insulinotropic peptide (GIP), GLP-1, and peptide tyrosine tyrosine (PYY)] or secretion (*e.g.*, oxyntomodulin). In addition, many of these hormones also exert central effects that reduce appetite and some (*e.g.*, GLP-1 analogs or GLP-1 receptor agonists) are efficacious in the treatment of obesity.[1]

Several combined incretins and hormones have been tested. Typically, human trials have been preceded by proof-of-concept studies in experimental animals. For example, a coagonist targeting rectors of a hormone (glucagon) and the incretin (GLP-1) in diet-induced obese mice resulted in reduction of body weight, loss of body fat from decreased food intake, and increased energy expenditure.[8] Coadministration of GLP-1 with glucagon in humans resulted in increased energy expenditure[9] and a reduction in food intake by an average 13%[10]; whereas, glucagon or GLP-1, given individually at subanorectic doses, did not significantly reduce food intake. The effect of the combination on resting energy expenditure is attributable to the effects of the hormone glucagon; there was no significant change in resting energy expenditure during GLP-1 infusion.

In contrast, there was significant increase in resting energy expenditure by a mean of 146.99 kcal/day during glucagon infusion and a mean 146.26 kcal/day during GLP-1/glucagon combined infusion. However, glucagon inevitably results in hyperglycemia; the addition of GLP-1 reduces the hyperglycemia due to its insulinotropic effect.[9]

Similarly, a unimolecular dual agonist of the (incretin hormone) GLP and GIP receptors of PEGylated GLP-1/GIP coagonist maximized metabolic benefits in rodents, monkeys, and humans.[11]

The combination of GLP-1 and PYY_{3-36} has been shown to have a synergistic effect in two human studies. In a double-blind, four-arm, crossover, randomized study, 25 male participants received placebo, GLP-1, PYY_{3-36}, or

GLP-1 plus PYY_{3-36}. The coinfusion of GLP-1 and PYY_{3-36} produced a reduction of 30.4% of food intake compared to placebo and more than the sum of each independently, suggesting a synergistic effect.[12] A subsequent experimental study tested acute continuous subcutaneous infusion for 10.5 hrs/day of GLP-1, peptide YY, and oxyntomodulin [summarized as GOP], at doses that replicated the postprandial concentrations observed after Roux-en-Y gastric bypass (RYGB). Oxyntomodulin analogs have significant potential due to the inherent affinity of oxyntomodulin to both glucagon and GLP-1 receptors.

In a single-blinded, randomized, placebo-controlled, crossover study, GOP was shown to be safe and effective in reducing food intake (mean reduction 32%) without significantly altering resting energy expenditure.[13] On the contrary, not all gut hormones show synergistic effects; for example, PYY and pancreatic polypeptide did not reduce food intake in rodents or in16 fasted, lean, healthy human volunteers (6 men and 10 women).[14]

It is clearly important to assess longer-term effects of combination therapies with hormones and incretins, and such studies are eagerly awaited.

Combination Therapies Involving Devices or Bariatric Surgery

Repeat intragastric balloon treatments compared to balloon plus diet

After intragastric balloon (IGB) placement, two groups were randomized to either repeat placement of IGB or diet. Six months later, the balloon was removed. Weight over the next 2 years continued to be lower in the sequential balloon treatment group compared with the balloon-diet group, as shown by the mean percent of excess body weight loss of 51.9% ± 24.6% in the sequential balloon group and 25.1% ± 26.2% in the balloon-diet group.[15]

RYGB combined with dietitian support postsurgery

Two studies have assessed the additional value of dietary counseling compared to standard care after RYGB. In one study, 84 individuals who underwent bariatric surgery were randomly assigned to receive either dietary counseling or standard postoperative care for the first 4 months after surgery. There were no differences in the percent of weight loss over the subsequent 24 months.[16]

In a second study, 302 patients in the surgeon follow-up group and 268 in the joint surgeon-dietitian follow-up group had no differences in weight loss over 3, 6, or 12 months, but there were improved thiamine and triglyceride control and lower diet-related complications with dietitian support.[17]

Conversely, other studies have demonstrated the benefit of combined lifestyle intervention-medical management with RYGB in achieving, in patients with poorly controlled diabetes, the composite goal of HbA1c less than 7.0%, low-density lipoprotein cholesterol less than 100 mg/dL, and systolic blood pressure less than 130 mmHg, and the weight loss was approximately threefold higher at 3 years in the combined RYGB-lifestyle modification group compared to the unoperated group.[18] In addition, follow-up of the same cohorts showed that, at 5 years, participants in the RYGB group had a mean weight loss of 21.8% compared with 9.6% in lifestyle–medical management group, although the mean weight loss in RYGB group fell from 26.1% to 21.8% at 5 years whereas the lifestyle–medical management group mean weight loss increased from 7.8% at 1 year to 9.6% at 5 years.[19]

Endoscopic enhancement of effects of RYGB when weight regain occurs

In patients with RYGB, weight plateau or regain may be associated with an increase in the size of the gastric pouch or the outlet that is the anastomosis with the Roux jejunal limb. The mechanisms for the increase in the size of the gastric pouch are unclear; thus, it is conceivable that the change in the gastric pouch may be a cause or, potentially, an effect of the excessive food intake in the postprandial period. Nevertheless, endoscopic suturing, including purse-string suturing, or sclerotherapy are able to reduce the size of the outlet and restore weight loss.[20–23]

Combined bariatric endoscopy with pharmacotherapy

One study compared the effects of an IGB in 64 patients compared to a combination of balloon plus liraglutide, up to 1.8 mg/day, in 44 patients.[24] At baseline, there were no group differences in BMI. The mean weight loss after balloon removal was 8.3 kg greater in the balloon plus liraglutide group than in the balloon alone group, and the advantage was still significantly greater 6 months post-balloon removal in the group receiving liraglutide.[24] The authors conducted multivariate analysis and concluded that the advantage may not be significant; the study needs to be replicated.

Combined Endobarrier® and pharmacotherapy

Endobarrier in 21 grade 1 obese type 2 diabetic patients with poor metabolic control was associated with significant weight decrease (mean ~15% of total body weight) and moderate reduction (mean 0.6%) in HbA1c at 12 months.[25] There were no significant changes in GLP-1 concentrations. It is, therefore, intriguing that the combination of Endobarrier with the GLP-1 analog, liraglutide, and 1.8 mg/day resulted in greater weight loss (mean 11.3 kg) compared to liraglutide treatment alone (mean 4.5 kg), and this suggests that the effect of liraglutide augments weight loss by adding a central effect on appetite to the peripheral mechanisms induced by the Endobarrier.[26]

Selection of Combination Therapies for Obesity

While new combination pharmacotherapies will require formal trials, we anticipate implementation of pharmaceutical augmentation of weight loss after bariatric surgery or endoscopy, particularly when the magnitude of weight loss has not resulted in the planned weight loss, or when weight is regained. It remains to be determined which combinations will be more effective, and it is conceivable that the selection of combination therapies for obesity may be advantageous by knowing the underlying obesity phenotype.[27] Assuming that there will be an increase in the use of IGB treatments, we may speculate on combination treatments based on the following phenotypes in obese patients: accelerated gastric emptying with liraglutide; low satiation or satiety with centrally acting

agents (buprenorphine-naltrexone or phentermine-topiramate) or satiety hormones/incretins (*e.g.*, PYY); and low resting energy expenditure with glucagon.

Conclusions

There are promising combination therapies on the threshold for introduction into clinical practice. Formal controlled trials are needed, and understanding the effects on obesity related pathophysiology represents an opportunity for devising such combination approaches for the treatment of obesity.

Acknowledgments

Dr. Camilleri is supported by NIH grant R01-DK67071. The work was supported by Endoscopy and Physiology Core Laboratory, CTSA grant number UL1-TR002377 from the National Center for Advancing Translational Sciences (NCATS), a component of National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH.

Authors' Contributions

M. Camilleri and A. Acosta: both conducted literature review and coauthored the article.

Author Disclosure Statement

Novo Nordisk provided liraglutide for trials in Dr. Camilleri's laboratory within the past 2 years. Dr. Acosta declares no conflicts of interest.

References

1. Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: A systematic review and meta-analysis. *JAMA* 2016;315:2424–2434.
2. Aronne LJ, Halseth AE, Burns CM, et al. Enhanced weight loss following coadministration of pramlintide with sibutramine or phentermine in a multicenter trial. *Obesity* 2010; 18:1739–1746.
3. Clapper JR, Athanacio J, Wittmer C, et al. Effects of amylin and bupropion/naltrexone on food intake and body weight are interactive in rodent models. *Eur J Pharmacol* 2013;698:292–298.
4. Frías JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): A 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol* 2016;4:1004–1016.
5. Jabbour SA, Frías JP, Guja C, et al. Effects of exenatide once weekly plus dapagliflozin, exenatide once weekly, or dapagliflozin, added to metformin monotherapy, on body weight, systolic blood pressure, and triglycerides in patients with type 2 diabetes in the DURATION-8 study. *Diabetes Obes Metab* 2018;20:1515–1519.
6. Lundkvist P, Sjöström CD, Amini S, et al. Dapagliflozin once-daily and exenatide once-weekly dual therapy: A 24-week randomized, placebo-controlled, phase II study examining effects on body weight and prediabetes in obese adults without diabetes. *Diab Obes Metab* 2017;19:49–60.
7. Lundkvist P, Pereira MJ, Katsogiannos P, et al. Dapagliflozin once daily plus exenatide once weekly in obese adults without diabetes: Sustained reductions in body weight, glycaemia and blood pressure over 1 year. *Diabetes Obes Metab* 2017;19:1276–1288.
8. Day JW, Ottaway N, Patterson JT, et al. A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. *Nat Chem Biol* 2009;5:749–757.
9. Tan TM, Field BC, McCullough KA, et al. Coadministration of glucagon-like peptide-1 during glucagon infusion in humans results in increased energy expenditure and amelioration of hyperglycemia. *Diabetes* 2013;62: 1131–1138.
10. Cegla J, Troke RC, Jones B, et al. Coinfusion of low-dose GLP-1 and glucagon in man results in a reduction in food intake. *Diabetes* 2014, 63:3711–3720.
11. Finan B, Ma T, Ottaway N, et al. Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. *Sci Transl Med* 2013;5:209ra151.
12. Schmidt JB, Gregersen NT, Pedersen SD, et al. Effects of PYY3-36 and GLP-1 on energy intake, energy expenditure, and appetite in overweight men. *Am J Physiol Endocrinol Metab* 2014;306:E1248–E1256.
13. Tan T, Behary P, Tharakan G, et al. The effect of a subcutaneous infusion of GLP-1, OXM, and PYY on energy intake and expenditure in obese volunteers. *J Clin Endocrinol Metab* 2017;102:2364–2372.
14. Neary NM, McGowan BM, Monteiro MP, et al. No evidence of an additive inhibitory feeding effect following PP and PYY 3–36 administration. *Int J Obes (Lond)* 2008;32: 1438–1440.
15. Genco A, Cipriano M, Bacci V, et al. Intragastric balloon followed by diet vs intragastric balloon followed by another balloon: A prospective study on 100 patients. *Obes Surg* 2010;20:1496–1500.
16. Sarwer DB, Moore RH, Spitzer JC, et al. A pilot study investigating the efficacy of postoperative dietary counseling to improve outcomes after bariatric surgery. *Surg Obes Relat Dis* 2012;8:561–568.
17. Garg T, Birge K, Rosas U, et al. A postoperative nutritional consult improves bariatric surgery outcomes. *Surg Obes Relat Dis* 2016;12:1052–1056.
18. Ikramuddin S, Korner J, Lee WJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: The Diabetes Surgery Study randomized clinical trial. *JAMA* 2013;309:2240–2249.
19. Ikramuddin S, Korner J, Lee WJ, et al. Lifestyle intervention and medical management with vs without Roux-en-Y gastric bypass and control of hemoglobin A1c, LDL cholesterol, and systolic blood pressure at 5 years in the diabetes surgery study. *JAMA* 2018;319:266–278.
20. Thompson CC, Chand B, Chen YK, et al. Endoscopic suturing for transoral outlet reduction increases weight loss after Roux-en-Y gastric bypass surgery. *Gastroenterology* 2013;145:129–137, e3.
21. Kumar N, Thompson CC. Transoral outlet reduction for weight regain after gastric bypass: Long-term follow-up. *Gastrointest Endosc* 2016;83:776–779.
22. Riva P, Perretta S, Swanstrom L. Weight regain following RYGB can be effectively treated using a combination of endoscopic suturing and sclerotherapy. *Surg Endosc* 2017; 31:1891–1895.
23. Jirapinyo P, Kröner PT, Thompson CC. Purse-string transoral outlet reduction (TORe) is effective at inducing weight

loss and improvement in metabolic comorbidities after Roux-en-Y gastric bypass. *Endoscopy* 2018;50:371–377.
24. Mosli MM, Elyas M. Does combining liraglutide with intragastric balloon insertion improve sustained weight reduction? *Saudi J Gastroenterol* 2017;23:117–122.
25. Vilarrasa N, de Gordejuela AG, Casajoana A, et al. Endobarrier® in grade I obese patients with long-standing type 2 diabetes: Role of gastrointestinal hormones in glucose metabolism. *Obes Surg* 2017;27:569–577.
26. Sen Gupta P, Drummond RS, Lugg ST, et al. One year efficacy, safety and tolerability outcomes of endoscopic duodenal exclusion using endobarrier as an adjunct to glucagon-like peptide-1 (GLP-1) therapy in suboptimally controlled type 2 diabetes: A randomised controlled trial. Presented at the Endocrine Society's 98th Annual Mtg., April 1–4, 2016, Boston, MA, Presentation Number: SAT-690.
27. Acosta A, Camilleri M, Shin A, et al. Quantitative gastrointestinal and psychological traits associated with obesity and response to weight-loss therapy. *Gastroenterology* 2015;148:537–546, e4.

Address correspondence to:
Michael Camilleri, MD
Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER)
Mayo Clinic
Charlton Building, Rm. 8-110
200 First Street SW
Rochester, MN 55905

E-mail: camilleri.michael@mayo.edu