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Gastrointestinal Traits: Individualizing Therapy for Obesity with Drugs and Devices

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Abstract

Objectives—The objectives were to review the discrepancy between numbers of people requiring weight loss treatment and results, and to assess the potential effects of pharmacological treatments (recently approved for obesity) and endoscopically deployed devices on quantitative gastrointestinal traits in development for obesity treatment.

Methods—We conducted a review of relevant literature to achieve our objectives.

Results—The 2013 guidelines increased the number of adults recommended for weight loss treatment by 20.9% (116.0 million to 140.2 million). There is an imbalance between efficacy and costs of commercial weight loss programs and drug therapy (average weight loss ~5 kg). The number of bariatric procedures performed in the United States has doubled in the past decade. The efficacy of bariatric surgery is attributed to reduction in the volume of the stomach, nutrient malabsorption with some types of surgery, increased postprandial incretin responses, and activation of farnesoid X receptor mechanisms. These gastrointestinal and behavioral traits identify sub-phenotypes of obesity based on recent research.

Conclusions—The mechanisms or traits targeted by drug and device treatments include centrally mediated alterations of appetite or satiation, diversion of nutrients, and alteration of stomach capacity, gastric emptying, or incretin hormones. Future treatment may be individualized based on quantitative gastrointestinal and behavioral traits measured in obese patients.

Keywords

obesity; medical devices; pharmacotherapy; gastrointestinal traits; behavioral traits

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Introduction

Obesity is a complex chronic disease, which results from weight gain secondary to prolonged positive energy balance, that is, greater food intake over energy expenditure. The complexity of obesity goes beyond food intake, and this review does not address the hedonic aspects of energy intake or expenditure, or the strictly behavioral approaches to obesity therapy.

Compared with the 1998 guidelines, the 2013 guidelines (that were based on the National Health and Nutrition Examination Survey 2007-2012) increased the number of adults recommended for weight loss treatment by 20.9% from 116.0 million to 140.2 million, making 64.5% of non-pregnant, non-institutionalized U.S. adults candidates for weight loss treatment.[1,2] The 2013 guidelines recommended treatment for a larger proportion of overweight people having only one risk factor or having a large waist circumference. With these recommendations, up to 53.4% of adults could be considered for pharmacologic therapy in addition to life style therapy, and up to 14.7% could be considered for bariatric surgery.

A recent review of 45 studies (of which 39 were randomized, controlled trials) involving commercial weight loss programs based on diet and behavioral modification showed that, at 12 months, the commercial diets achieved greater weight loss than control/education and counseling: Weight Watchers by >2.6%, Jenny Craig >4.9%, and very-low-calorie programs (e. g. Medifast and OPTIFAST) >4.0% (latter with some attenuation of effect beyond 6 months).[3] These commercial programs incorporate group sessions (eg, Weight Watchers) or more expensive 1-on-1 counselling.

Despite the approval of novel pharmacological therapies for weight loss through medications that suppress patients' appetites and make them feel full, there is a perception that the public and physicians have not embraced the opportunity to use these medications. Factors leading to the decision not to use medications for obesity include the safety issues with past diet drugs, significant costs or co-pays, and physician propensity to wait a year or longer after approval of each new diet drug before prescribing it, to allow for unforeseen safety issues to emerge.[4]

There is also moderate overall average weight loss of 3 to 8 kg after at least 12 weeks of treatment with the novel pharmacological agents: lorcaserin, GLP-1 agonists, phentermine-topiramate and bupropion-naltrexone.[5-9] There is, thus, an imbalance between the perceived clinical need for weight loss, and the average efficacy and costs of commercial weight loss programs and drug therapy. There is a need for novel approaches to individualize therapy and enhance benefit to risk ratio with pharmacological approaches or therapeutic devices in development.

There has been significant progress in understanding the regulation of food intake by the brain gut axis and the central and peripheral regulation of appetite, and neural responses to macronutrients.[10,11] The key principles of obesity pathophysiology are illustrated in Figure 1. However, current therapy is still based on the assumption that one-treatment-fits-all in

obesity; this approach may explain the highly variable response to treatment with current pharmacological approaches.

A testable hypothesis is that actionable quantitative traits in obesity may constitute more specific therapeutic targets and may predict enhanced weight loss in individual patients with obesity. Recently, we have identified quantitative traits[12] that are regulated by the brain-gut axis, can be measured reliably in humans, and provide "actionable" approaches to control food intake. In a proof of concept, small, randomized, controlled trial, we demonstrated that phentermine-topiramate extended release resulted in significantly greater weight loss in patients who ingested >900 kcal at an *ad libitum* buffet meal.[12]

The objectives of this review are to examine "actionable" quantitative traits in the regulation of food intake in obesity; to identify pharmacological approaches that may be directed to these actionable traits in obesity; and to examine how the devices proposed for the treatment of obesity are directed to these traits, supporting the critical role of these actionable mechanisms in the treatment of obesity.

Food Intake: The Brain-Gut Axis

Food intake is regulated by a balance among appetite, satiation, and satiety, which is controlled by the brain-gut axis, whereby gastrointestinal signals inform brain centers about energy intake status (reviewed elsewhere[13]). Peripheral mechanisms in food intake regulation include the motor and sensory functions of the stomach such as the rate of emptying and gastric volume and accommodation, which result in signals of appetite in response to fasting and satiation in response to calorie and volume ingestion. In addition, the rich repertoire of peripherally released peptides and hormones (such as ghrelin, motilin, cholecystokinin, GLP-1, peptide YY and oxyntomodulin) provides feedback from the arrival of nutrients in different regions of the gut from where they are released to exert effects on satiation or regulate metabolism through their incretin effects. Ultimately, these peripheral factors provide input to the highly organized hypothalamic and vagal centers to influence energy intake during meal ingestion and the return of appetite and hunger during fasting. These peripheral mechanisms are discussed in greater detail elsewhere.[10]

Hypothalamic centers, involving several peptide receptors, also control food intake. The arcuate nucleus receives input from brainstem (eg, vagal) nuclei and from circulating hormones through an incomplete blood brain barrier. Neurons in the arcuate nucleus are either orexigenic [eg, contain neuropeptide Y via Y1 receptors or agouti-related peptide (AgRP)] or anorexigenic [eg, contain pro-opiomelanocortin (POMC)], cocaine- and amphetamine-related transcript (CART)]. POMC is a precursor of α melanocyte stimulating hormone (α-MSH). Ultimately, other regions of the hypothalamus (the paraventricular nucleus and lateral hypothalamus) and higher centers (such as amygdala, limbic system and cerebral cortex) are stimulated to influence the same hypothalamic nuclei to change feeding behavior.

Gastric Determinants of Postprandial Symptoms and Satiation

Satiation is the sense of feeling full during a meal, which induces meal termination; satiety is the degree of fullness that persists until the consumption of a subsequent meal after a period of fasting[14,15] and regulates meal frequency, which is also influenced by learned habits. Satiation is appraised by the volume to fullness and maximum tolerated volume of Ensure nutrient drink (1 kcal/mL) ingested at a rate of 30 kcal/minute.[16] Satiety is appraised by the total calorie intake at an ad libitum buffet meal[17] after a standard period of fasting (eg, 4 hours) and a standard prior meal (eg, a 300 kcal liquid breakfast meal).

Studies based on hundreds of patients with dyspepsia convincingly showed that gastric motor functions (such as emptying and accommodation) and gastric sensation are important determinants of intra-prandial and postprandial symptoms.[18] In studies conducted in patients with functional dyspepsia and in obese patients (in response to pharmacological perturbations) in a laboratory setting, it was demonstrated that, apart from body mass index (BMI), age, and gender, the following factors account for about 50% of the variance in postprandial symptoms such as bloating and satiation: smaller fasting gastric volume, accelerated gastric emptying at 1 hour, and delayed gastric emptying at 4 hours.[19,20]

These studies provided data to consider a role of the stomach and other gastrointestinal factors in association with brain centers such as the hypothalamus and vagal nuclei in the control of calorie intake. Some prior studies had indicated there were abnormalities of function, such as increased gastric volume, but these were only demonstrated in patients with binge eating disorder.[21] Thus, the functions of the stomach in particular have not been systematically evaluated in overweight or obese patients until relatively recently.

Quantitative Gastrointestinal and Behavioral Traits in Obesity

In a study involving 507 overweight, obese, or normal-weight participants,[12] obesity was associated with larger fasting gastric volume, accelerated gastric emptying of solids and liquids, lower postprandial levels of one of the satiation-associated hormones, peptide tyrosine tyrosine (PYY), and higher volume of liquid calories ingested to achieve comfortable postprandial fullness and larger calorie intake in a buffet meal. Principal component analysis identified latent dimensions that accounted for approximately 81% of the variation among overweight and obese subjects, including satiety or satiation (21%), gastric motility (14%), behavioral factors (13%), and gastric sensorimotor factors (11%) (Fig. 2).

It was proposed that these quantitative traits may be specifically targeted by approved pharmacotherapy. Thus, the combination of phentermine and topiramate extended released caused significant weight loss, slowed gastric emptying, and decreased calorie intake; importantly, a baseline abnormal satiety test in the form of an ad libitum meal significantly predicted weight loss response to phentermine and topiramate extended released.[12]

These data suggested that quantitative traits are associated with high body mass index or high waist circumference; they can distinguish different obesity phenotypes and may serve as traits to individualize pharmacotherapy for obesity.

Lessons Learned from Bariatric Surgery

The number of bariatric procedures performed in the United States has virtually doubled in the last decade to about 180,000 operations per year, and the most frequently performed operations are Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy.[22] At present, the best evidence for the validity of quantitative gastrointestinal and behavioral traits of obesity as "actionable" traits is based on the efficacy of bariatric surgery. Specifically, with partial gastrectomy in the RYGB procedure or vertical sleeve gastrectomy, there is early reduction in the volume of the stomach, induction of early satiation, and increased postprandial AUC GLP-1 response. These are 3 of the actionable quantitative traits because they are associated with obesity.[12] In addition, some bariatric procedures divert nutrients and result in malabsorption, such as RYGB and biliopancreatic diversion with duodenal switch. These procedures also are associated with correction of glycemia even before the benefits of weight loss, and these effects are in part attributed to the earlier and higher postprandial incretin responses,[23] to activation of farnesoid X receptor mediated mechanisms,[24] and to changes in bile acids and microbiome.[25]

In addition to effects on weight, the long-term effects of bariatric surgery on health status and morbidity related to obesity are well documented and include long-term remission of type 2 diabetes mellitus (T2DM) with micro- and macro-vascular adverse events,[26] more efficient than usual care in the prevention of T2DM in obese persons,[27] better diabetes control with RYGB than medical care,[28] better 3-year outcomes (such as HbA1c, BMI, number of medications for diabetes) with RYGB and vertical sleeve gastrectomy compared with intensive medical therapy for diabetes,[29] lower unadjusted cumulative incidence of fatal and total cardiovascular events,[30] improvement of cardiovascular risk factors with bilio-pancreatic diversion,[31] reduced cancer incidence particularly in women, diabetics, and smokers,[32] and reduced transminases proportionate to weight loss in patients with non-alcoholic steatohepatitis.[33]

The objectives of non-surgical weight loss therapies should include impact on the comorbidity of obesity in addition to effects on body weight.

Traits Associated with Food Intake, Postprandial Symptoms, and Obesity

Prior studies identified quantitative traits that are associated with postprandial symptoms and food intake. One example is intragastric pressure,[34] but this requires invasive measurement with an intragastric manometric or barostatic sensor device. Our prospective studies[12] identified the following quantitative traits in the brain-gut axis that are involved in food intake regulation and represent latent dimensions that contribute to the obesity trait, based on a principal components analysis (Fig. 2):

1) Appetite: Individuals with obesity have reported increased appetite (measured by visual analog scores or higher fasting plasma ghrelin levels);

2) Enlarged fasting gastric volume [measured by single photon emission computed tomography (SPECT)];

3) Reduced gastric accommodation (by SPECT, after a 300 kcal liquid nutrient meal);

4) Accelerated gastric emptying of solids and liquids (by scintigraphy of a dual radiolabeled meal);

5) Decreased satiation (assessed as an increased calorie intake to sensation of fullness by a laboratory-based test measuring liquid nutrient intake at constant rate of 30 mL/min);

6) Decreased satiety (assessed as an increased calories intake by ad-libitum meal 4 hours after standard breakfast);

7) Decreased peak postprandial GLP-1;

8) Eating behaviors and affect, based on validated questionnaires.

In our patient cohort, these gastrointestinal "actionable" traits were largely independent of the behavioral traits. Indeed, among 169 patients with obesity, there were single trait abnormalities in subsets of the patients: 22 patients with exclusive acceleration of gastric emptying (GE $T_{1/2}$ <85 minutes), 29 patients with fasting gastric volume >300 mL, and 24 patients with abnormal satiation (based on volume to fullness >800 mL [kcal] or >800 kcal ingested at buffet meal).[12] In addition, 15 patients had large gastric volume and abnormal satiation/satiety, and another 15 patients had accelerated gastric emptying and abnormal satiation/satiety. Thus, in almost two-thirds of obese patients in our cohort, there was either unique or a combination of two alterations in quantitative traits that could constitute targets for therapy,

What Pharmacotherapies Might Be Directed at Different "Actionable" Obesity Traits?

Different "actionable" obesity traits have been identified based on quantifiable traits that differ in obesity compared with normal weight. These lead to hypotheses that can be tested in therapeutic trials and which should appraise patients with the abnormal function specified compared with patients with normal function.

a. Patients with accelerated gastric emptying: The class of amylin agonists (eg, pramlintide[35]) or GLP-1 agonists (eg, liraglutide, exenatide) might be preferred for this group of patients, as they retard gastric emptying.[36-38]

b. Patients with enlarged gastric volume: Ghrelin or motilin agonists may be preferred as they reduce gastric accommodation[39,40]; however, ghrelin agonists may not be the preferred class of medications because they increase appetite.[41] The opioid antagonist, naltrexone, reduces gastric accommodation[42]; however, it is unclear whether the combination bupropion/naltrexone sustained released has any effect on gastric volume and accommodation. In contrast, GLP-1 agonists, which enhance gastric volume and postprandial accommodation,[36] may not be the preferred medications for patients with enlarged gastric volume.

c. Patients with prominent psychological/depression scores: These patients may be amenable to treatment with centrally acting medications that may also impact affect, such as lorcaserin (a selective serotonin 5-HT_{2C} agonist which activates hypothalamic centers to reduce food intake) or the combination of bupropion and

naltrexone. The mechanisms of action of these medications are not completely understood; however, they have proven efficacious in reducing body weight. Bupropion appears to reduce food intake by acting on adrenergic and dopaminergic receptors in the hypothalamus, whereas naltrexone is an opioid receptor antagonist with minimal effect on weight loss that might block inhibitory influences of opioid receptors activated by the β-endorphin that is released in the hypothalamus and stimulates feeding.[43] Although lorcaserin and bupropion/naltrexone may have an effect on satiation, their main effects may be mediated through higher brain centers that regulate feeding behavior and cravings.

d. Patients with low levels of satiation or satiety: Centrally acting medications that act on the hypothalamic nuclei of satiation, such as phentermine/topiramate ER, may be the drugs selected for patients with low levels of satiation or satiety who tend to consume more calories. Phentermine acts to reduce appetite through increasing norepinephrine in the hypothalamus, and topiramate may reduce appetite through its effect on γ-aminobutyric acid (GABA) receptors. Interestingly, phentermine/topiramate ER produced a decrease of 160 kcal in a satiety test, and individuals with abnormal satiation (who consumed more than 800 kcal before reaching “usual fullness” or 1400 kcal before reporting “maximal tolerated volume”) lost twice as much weight in a pilot 2-week trial compared with obese individuals with normal satiation.[12]

Novel Devices Proposed in Obesity Treatment and their Potential Effects on Gastrointestinal Traits Associated with Obesity

In general, the devices proposed or in development for treatment of obesity can be grouped into 3 categories: those that divert nutrients, those that occupy space in the stomach, and those that alter gastric emptying or capacity. The principal findings on efficacy and mechanisms of action will be described briefly here (extensively reviewed elsewhere[44]).

Devices that divert nutrients

AspireAssist Aspiration Therapy System essentially diverts food out of the stomach after a time elapsed in the postprandial period; this results in diversion of food away from absorption in the small bowel, and mean weight loss of 15 kg is reported at 6 months. Adverse effects arise from electrolyte losses such as reduced serum sodium and potassium; on the other hand, blood glucose and HbA1C are improved.[45] This device clearly impacts those patients whose calorie consumption cannot be reduced in any other way.

DuodenoJejunal Bypass Liner mimics Roux-en-Y gastric bypass, inducing weight loss and improved metabolic control through malabsorption and release of incretin hormones (GLP-1, PYY), with improved glycemic control and delay in gastric emptying.[46] This device delivers food to the jejunum and ileum without proper mixing with pancreaticobiliary juices, delays gastric emptying,[46] and may stimulate the release of GLP-1,[47] with resulting weight loss and improved control of type 2 diabetes.[48]

Devices that occupy space in the stomach

We have shown that the proximal stomach is not the only part of the organ that has capacity to store food; the antrum also accommodates food,[49] and it appears that gastric capacity interventions must include antrum to be effective in the long term. This may explain the disappointing results with surgical vertical banded gastroplasty or gastric banding, or the endoscopic transoral gastroplasty (TOGA).

In 12-month follow-up of the TRIM trial of TOGA conducted at 2 centers, gastric volume reduction procedure using the RESTORe Suturing System device proved to be safe, well tolerated, and technical success was achieved. However, modest decreases in weight, BMI, and waist circumference were observed and, despite some overall positive clinical findings, the applications were not durable, and the effects of the procedure varied widely among the study participants.[50]

Different balloon devices are in development,[51] and they may induce fullness, induce symptoms such as discomfort or nausea that reduce food intake, or accelerate or delay gastric emptying. Examples are the transpyloric shuttle which consists of a large spherical bulb connected to a smaller cylindrical bulb by a flexible tether that passes freely into the duodenum to position the device across the pylorus; this may delay gastric emptying, reducing caloric intake and enabling weight loss. It is associated with nausea, vomiting, pain, and GERD, especially in the first 30 days after deployment.[52]

A second example is the ReShape Intragastric Duo-Balloon, which attempts to occupy space in proximal and distal stomach, and results in weight loss with shorter duration (<7 days) of symptoms such as nausea, vomiting and retching.[53]

A third example is a balloon device which can be left in the stomach for >6 months and results in weight loss with an average reduction of 4.5 kg/m^2. [54] After first removal, this type of balloon has been repeatedly placed into the stomach and resulted in cycling loss of weight that was regained after removal; however, the beneficial effects on type 2 diabetes mellitus, blood pressure, and obstructive sleep apnea are retained over time, despite “cycling” weight regain.[54]

It is currently assumed that the action of these occupying space devices placed in the stomach will limit the size of the stomach available to accommodate food and result in satiation with lower volume intake. There is some evidence that such devices, as balloons, may delay gastric emptying and reduce plasma ghrelin,[55] although this effect on ghrelin is not consistently demonstrated at different times after insertion of the device.[56,57]

Devices that alter gastric emptying or capacity

Delay in gastric emptying results in increased satiation and, potentially, in cessation of food intake. Examples include reversible vagal block (VBLOC), antral injection of botulinum toxin (BOTOX), and endoscopic sleeve gastroplasty.

VBLOC was efficacious in retarding gastric emptying, inducing earlier satiation, and reducing hunger, which resulted in weight loss, especially in patients in whom there was

effective vagal inhibition demonstrated by inhibition of the increase in plasma pancreatic polypeptide in response to sham feeding.[58] VBLOC was associated with significantly greater weight loss compared with sham block;[59] in addition, there are other beneficial effects of vagal block that may be independent of weight loss, such as a 1% mean reduction in HbA1c at 12 months of treatment compared with baseline, mean 28 mg/dL reduction in fasting blood glucose in obese patients with type 2 diabetes mellitus, and reduced blood pressure among those with hypertension.[60] The beneficial effect on glycemia is incompletely understood, although, in rodents, interruption of hepatic afferent vagal pathways prevented steroid-induced insulin resistance shown, for example, by the reduced hepatic glucose production and improved glucose tolerance on challenge with dexamethasone.[61]

Gastric antral injection of BOTOX appeared promising, as it also delayed gastric emptying and induced satiation in an open-label trial[62]; however, in a 4-month trial, despite documentation of delay in gastric emptying, there was no significant reduction in body weight.[63] A recently published meta-analysis and meta-regression of 4 randomized, controlled trials evaluating antral BOTOX injection suggested overall benefit (Hedges' g −0.521; 95% CI, −0.845 to −0.040, $P = .031$), but 3 of the 4 trials were individually nonsignificant. In addition, wide-area injection was associated with weight loss (Hedges' g, −0.890; 95% CI, −1.522 to −0.258; $P = .006$), though antrum only injection did not show significant efficacy (Hedges' g, −0.192; 95% CI, −0.788 to 0.404; $P = .528$). In the overall analysis, there was considerable heterogeneity (I^2 55.5%) among studies.[64]

Gastric electrical stimulation may induce antegrade or retrograde stimulation. Overall, results with several devices are associated with variable degrees of weight loss even with the same device.[65] The mechanisms of action include changes in gastric emptying or gastric accommodation and induction of satiety.[66,67]

Endoscopic sleeve gastroplasty results in significant weight loss[68] which is thought to result from reduced gastric capacity, inducing fullness (early satiation) and, possibly, altered gastric emptying. Based on effects of surgical vertical sleeve gastrectomy,[69] it is expected that there will be acceleration of gastric emptying. Results of 1-year follow-up and effects on satiation and gastric emptying were preliminarily reported with >50% reduction in maximum tolerated volume in a satiation drink test and about 80% increase in gastric emptying t1/2.[70]

Adverse effects from devices and future needs

There are adverse effects associated with deployment of the endoscopic devices for obesity which are not addressed in great detail here. The adverse effects include those that are associated with procedures such as the potential for leaks leading to intra-abdominal abscess associated with gastroplasty involving deep suturing; leaks around devices associated with aspiration; mucosal irritation by intragastric balloons; dumping syndrome or gastric retention associated with changes in gastric capacity or motor function; and malabsorption of nutrients as a result of dumping or a duodenal by-pass liner. However, experience with the current devices proves the principle of efficacy and should encourage the development of safer and more readily available devices.

Conclusion

Understanding different obesity phenotypes, which may be relatively easily measured with gastric emptying, satiation and satiety assessments with validated tests, provides opportunity to personalize treatment of obesity using both pharmacotherapies and devices, as summarized in Figure 3. Although further validation is clearly necessary, these insights lead to the conclusion that gastroenterologists have a pivotal role to play in the future treatment of patients with obesity.

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Abbreviations used

GLP1	glucagon-like peptide 1
AgRP	agouti-related peptide
POMC	pro-opiomelanocortin
CART	cocaine- and amphetamine-related transcript
α-MSH	α melanocyte stimulating hormone
PYY	peptide tyrosine tyrosine
RYGB	Roux-en-Y bypass
T2DM	type 2 diabetes mellitus
TOGA	transoral gastroplasty
VBLOC®	vagal block
BOTOX®	botulinum toxin

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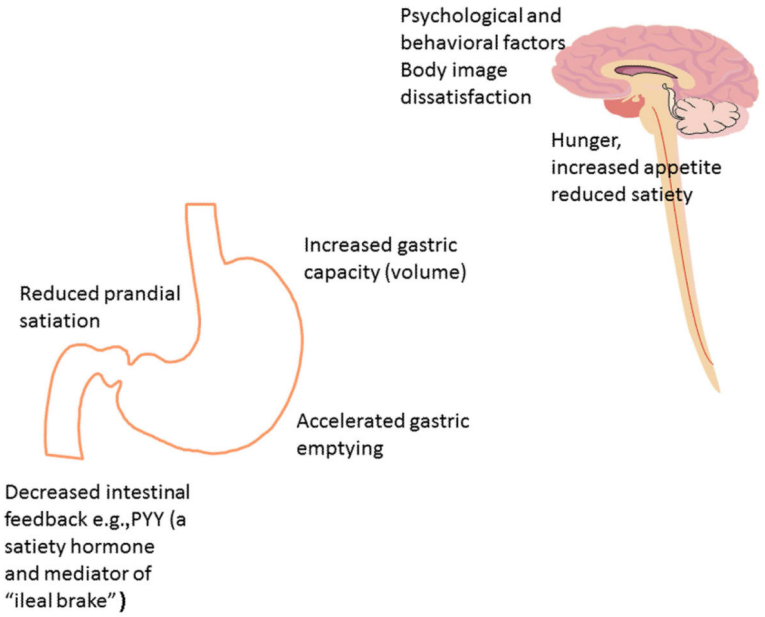

Figure 1.
Summary of key factors involved in obesity pathophysiology.

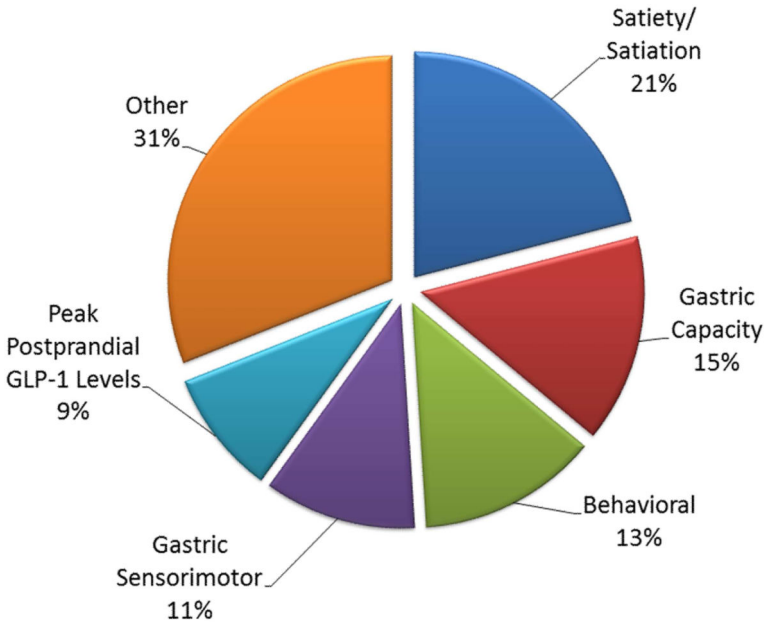

Figure 2.

Principal components analysis demonstrating the quantitative traits that contribute to obesity. Data derived from reference 12 (Acosta A, Camilleri M, et al. Gastroenterology 2015).

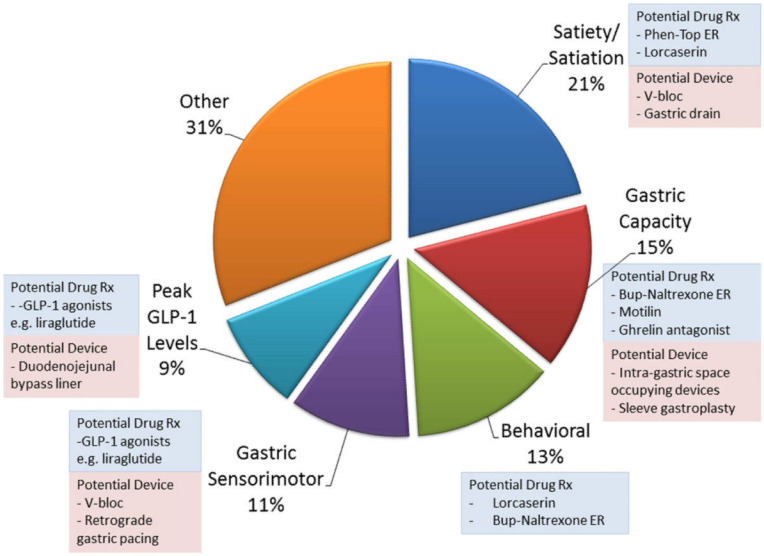

Figure 3.

Potential application of medications and devices directed at quantitative traits associated with obesity.