REVIEW ARTICLE

Gastrointestinal traits: individualizing therapy for obesity with drugs and devices

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Background and Aims: The aims of this article were to review the discrepancy between numbers of people requiring weight loss treatment and results and to assess the potential effects of pharmacologic treatments (recently approved for obesity) and endoscopically deployed devices on quantitative GI 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 about 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 GI and behavioral traits identify subphenotypes 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 GI and behavioral traits measured in obese patients. (Gastrointest Endosc 2016;83:48-56.)

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 (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 nonpregnant, 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 lifestyle therapy, and up to 14.7% could be considered for bariatric surgery.

Abbreviations: BMI, body mass index; GLP-1, glucagon-like peptide 1; PYY, peptide tyrosine tyrosine; RYGB, Roux-en-Y gastric bypass.

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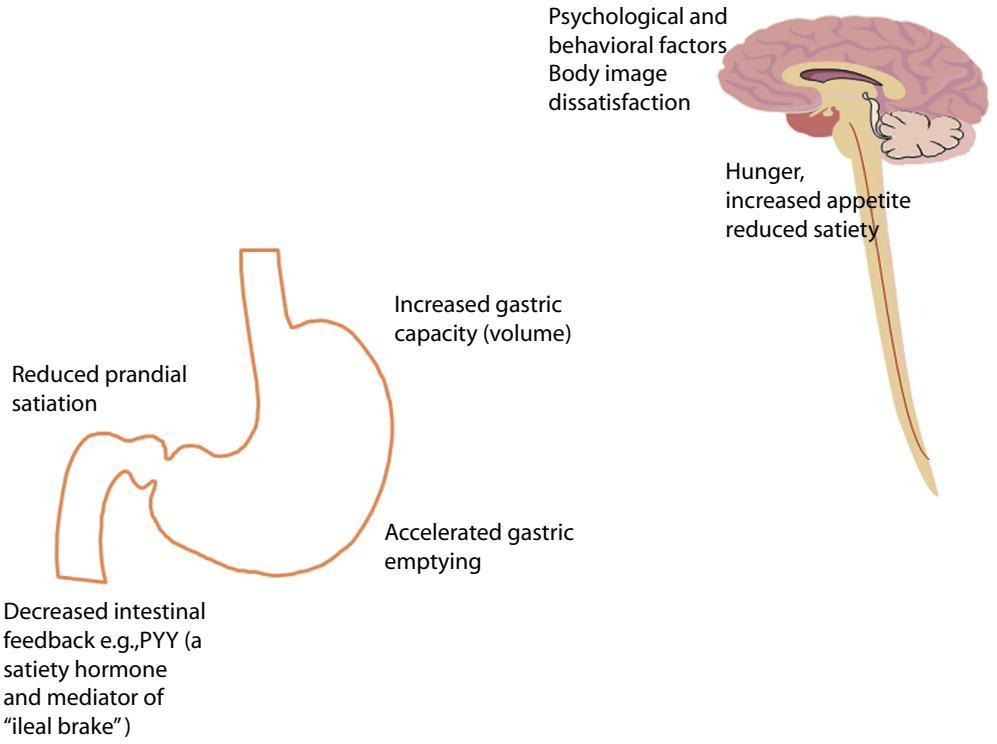

Figure 1. Summary of key factors involved in obesity pathophysiology. *PYY,* peptide tyrosine tyrosine.

A recent review of 45 studies (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 and/or education and counseling: Weight Watchers (New York, NY, USA) by >2.6%, Jenny Craig (Carlsbad, CA, USA) >4.9%, and very-low-calorie programs (eg, Medifast, Owings Mills, MD, USA, and Optifast, Nestlè, S.A., Vevey, Switzerland) >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 pharmacologic 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 copays, and physician propensity to wait a year or longer after approval of each new diet drug before prescribing it, to allow 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 pharmacologic 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 ratios with pharmacologic 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 based on the assumption that one treatment fits all in obesity; this approach may explain the highly variable response to treatment with current pharmacologic 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 small, proof of concept, 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 were to examine actionable quantitative traits in the regulation of food intake in obesity, to identify pharmacologic approaches that may be directed to these actionable traits in obesity, and to examine how the