Clinical Management of Obesity

Third Edition

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Louis Aronne, MD
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Foreword by
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THIRD EDITION

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***Clinical Management of Obesity, 3E*.**

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ISBN: 978-1-943236-41-1
Printed in the United States of America

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About The Obesity Society

Founded in 1982, The Obesity Society (TOS) is the leading professional society focused on obesity science, treatment and prevention.

Our Vision: Solving the challenges of obesity through deeper understanding and coordinated action.

Our Mission: The mission of TOS is to advocate and promote the highest quality in research, clinical care, education, and policy development to address the needs of people living with obesity. In addition, we offer our members a community to facilitate professional networking with peers in all fields related to obesity. TOS membership is open to all individuals with a professional interest in obesity, and TOS recognizes the importance of diverse perspectives and experiences in our efforts to better understand, treat, and prevent obesity. TOS is committed to creating a diverse and inclusive organization. We encourage participation of individuals of all backgrounds, regardless of race, nationality, gender, sexual orientation, religion, political affiliation, body size or economic circumstances. We strive to be a leading force in furthering the scientific understanding of obesity and to highlight and promote equitable access to the best evidenced-based practice for its prevention and treatment while working with partner organizations to eliminate the stigma and discrimination associated with this chronic disease.

Our Values: Rigorous science, highest professional standards, and strength through diversity.

TOS, its members, and staff pledge to uphold:

- Compassion for the lives and situations of those living with obesity.
- Responsibility for advocacy, treatment and investigation, all working toward a cure for obesity.
- Respect for each other and all who are touched by obesity.
- Progress for furthering knowledge about obesity using appropriate scientific standards.
- Mentorship for helping, teaching and supporting our colleagues.
- Highest Ethical Standards for all our actions, writings, programs, and services.

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FOREWORD

On behalf of The Obesity Society (TOS), in collaboration with the authors and publisher, and supported by an educational grant from Lilly USA, LLC, we are pleased to offer you the 3rd edition of *Clinical Management of Obesity*. Obesity is among the most widespread chronic conditions, currently affecting around 42% of the US population. Similar to other chronic diseases, obesity requires long-term care and management to prevent significant negative impacts on patients' health and quality of life. Major chronic conditions caused by obesity include, but are not limited to, type 2 diabetes, cardiovascular disease, renal disease, fatty liver disease, sleep apnea, and various cancers. Unfortunately, obesity continues to rise in the United States, consequently increasing the need for clinicians skilled in evidence-based obesity treatment. The primary care setting offers crucial opportunities to identify individuals with obesity, counsel them on its risks, and evaluate their readiness to engage in obesity management interventions. Sadly, many clinicians feel they lack the necessary knowledge to effectively address obesity and its complications in routine healthcare. Therefore, we trust that this guide will equip you with essential knowledge to effectively counsel your patients with evidence-based options for obesity treatment.

Jamy Ard, MD, FTOS
TOS President, 2024

Anthony G. Comuzzie, PhD, FTOS
TOS CEO

Detailed Table of Contents

Prevalence of Obesity and Related Mortality

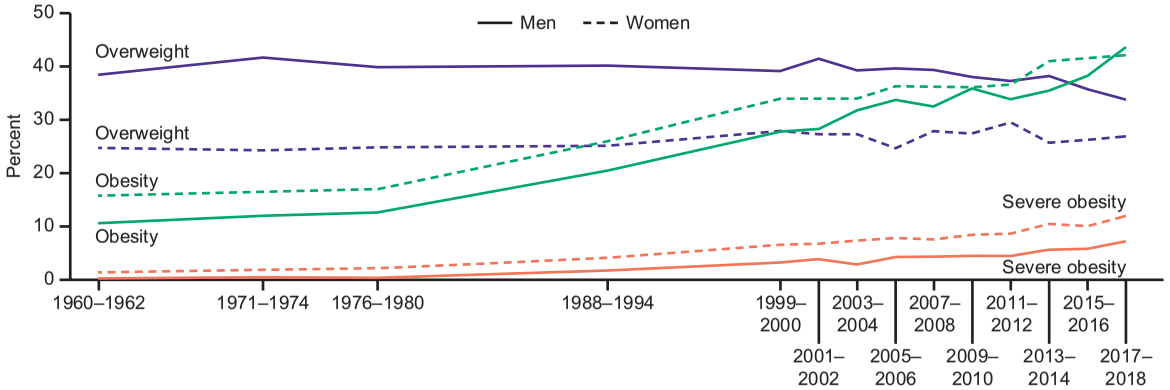
Prevalence

During the past 6 decades, there has been an increasing concern over a significant increase in the prevalence of obesity in the United States. While the overall prevalence of overweight (body mass index [BMI] 25 to <30) adults aged 20 years and over remained constant (30-35%) since the 1960s, the prevalence of obesity (BMI ≥30) increased from 13.4% in 1960-1962 to 30.5% in 1999-2000 and 42.4% in 2017-2018. The prevalence of class three obesity (BMI ≥40) increased from <2% (1960-1962) to 4.7% (1999-2000) to 9.2% (2017-2018).[1,2]

However, the trends among adult men and women differed during this period (**Figure 1.1**). The prevalence of overweight was relatively stable, but the rate was higher among men (~40%) compared with women (~25%) and remained so through 2017-2018, though prevalence rates may now be converging. The prevalence of obesity among men and women rose almost imperceptibly from the early 1960s to the late 1970s, but then increased linearly until it almost tripled in women and more than tripled in men by 2017-2018. The prevalence of obesity exceeded that of overweight by the early 1990s in women and the late 2010s in men.

Although the prevalence of obesity was consistently higher in women than in men in the latter decades of the 20th century, a convergent trend began around the turn of the century until the prevalence of obesity in adult men and women was essentially the same by 2017-2018. At that point, 42.4% of US men and women had obesity.[2] There was no significant difference in prevalence between men and women at any age, nor among age groups - adults aged 60 and over and younger adults were equally likely to have obesity. When grouped by race and gender, the prevalence of obesity in 2017-2018 was significantly

FIGURE 1.1 — Trends in the Prevalence of Overweight, Obesity, and Class III Obesity Among Adults Aged 20 and Over by Sex: 1960-1962 Through 2017-2018



NOTES: Data are age adjusted by the direct method to US Census 2000 estimates using age groups 20-39, 40-59, and 60-74. Overweight is body mass index (BMI) of 25.0-29.0 kg/m^2. Severe obesity is BMI at or above 40.0 kg/m^2. Pregnant women are excluded from the analysis.

Fryar CD, et al. https://www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm. Accessed March 15, 2022.

higher in the non-Hispanic Black population in general (49.6%), and non-Hispanic Black women in particular (56.9%), and significantly lower in non-Hispanic Asian men (17.5%) and women (17.2%). The increasing prevalence trend shows little signs of abating: one projection estimated that by 2030, approximately 1 in 2 adults in the United States will have obesity.[3]

The prevalence of obesity among US children and adolescents also is a growing concern. In the past 50 years, the prevalence of obesity has more than tripled in children and adolescents.[4] In 1971-1974, 5.0% of children aged 2-5 years, 4.0% of children aged 6 to 11 years, and 6.1% of adolescents aged 12 to 19 years had obesity. By 2017-2018, the prevalence rates increased to 13.4% in children 2-5 years of age, 20.3% in children 6-11 years of age, and 21.2% in adolescents 12-19 years of age. Overall, 19.3% of children and adolescents had obesity in 2017-2018, 6.1% had class three obesity, and a further 16.1% were classified as overweight.[4] Like in adults, the increasing trend of obesity prevalence shows no signs of plateauing.

In addition to its direct effects on the lives and livelihoods of millions of people globally, the SARS-CoV-2 pandemic that began in 2019 has had a considerable impact on mental health and undesired weight change. According to the American Psychological Association, 42% of Americans reported undesired weight gain since the start of the pandemic, with 10% reporting gaining more than 50 lb (~27 kg).[5] Significant weight gain has been documented among people under shelter-in-place orders (irrespective of comorbidities or geographic location),[6] and those in self-isolation.[7] Among people who gained more than 5 lb during lockdown, 33% gained even more weight in the post-lockdown period.[8] These and other data reveal that the pandemic has exacerbated the overall trend toward weight gain, although the long-term significance of this development is unknown.

Obesity and Mortality

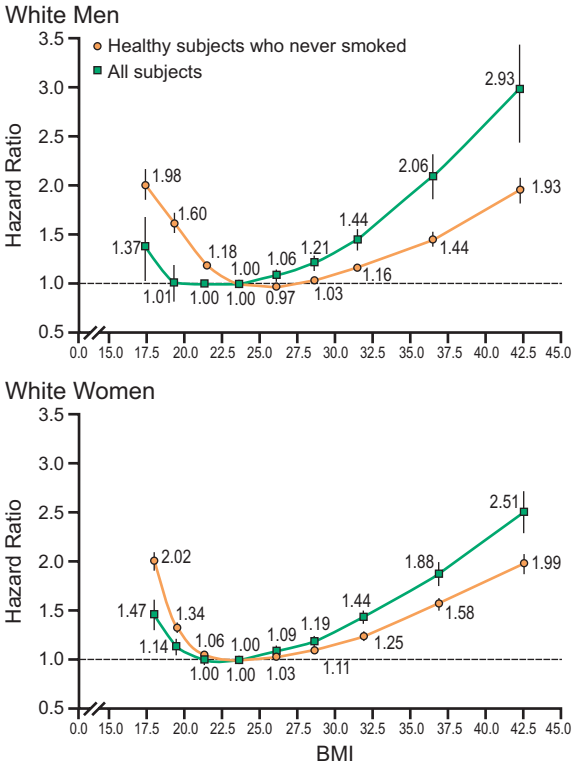
A considerable body of evidence has documented significant associations between obesity and a spectrum of comorbidities (see *Chapter 3*). Similarly, obesity is also associated with increased mortality, both all-cause and cause-specific.[9-12]

All-Cause Mortality

Berrington de Gonzalez and associates analyzed pooled data from 19 prospective studies that included 1.46 million White adults to assess the association between BMI and all-cause mortality.[9] A total of 160,087 deaths were identified during a median follow-up period of 10 years. To minimize the effects of potentially confounding conditions, the results were calculated for all subjects and then sequentially re-analyzed after exclusion of specific subpopulations (eg, healthy subjects who never smoked, those specific medical conditions, etc). The hazard ratios (HR) among healthy participants who never smoked (the population of interest) and all subjects formed a J-shaped relationship between BMI and all-cause mortality with a BMI of 22.5 to 24.9 as the reference category (**Figure 1.2**). In both men and women, the HRs increased in almost a linear fashion according to BMI to reach 2.51 among women and 2.93 among men at BMI 42.5. It is interesting to note that overweight (BMI 25 to <30) was also associated with small increases in HR.

Another review and meta-analysis estimated the all-cause mortality risks associated with normal weight, overweight, and obesity relative to normal weight based on data from 97 prospective studies with a combined sample size of more than 2.88 million individuals and more than 270,000 deaths.[10] The populations of these studies included those from United States, Canada, Europe, Australia, China or Taiwan, Japan, Brazil, Israel, India, and Mexico. Similar to the results of the previously discussed study, the HRs for all-cause mortality relative to normal weight (BMI = 18.5 to <25) increased according to incremental increases in BMI. The all-cause mortality HRs were 0.94 for overweight, 1.18 for obesity (all classes combined), 0.95 for class I obesity (BMI 30-<35), and 1.29 for class II (BMI 35-<40) and class III obesity (BMI ≥40). Thus, relative to normal weight, both obesity (all classes) and class II and III obesity were associated with significantly higher all-cause mortality. Whereas, class I obesity overall was not associated with higher mortality, and overweight was associated with significantly lower all-cause mortality.

FIGURE 1.2 — Hazard Ratios for Death From Any Cause According to BMI for All Study Participants and for Healthy Subjects Who Never Smoked: Pooled Data From 19 Prospective Studies That Included 1.46 Million White Adults, 19 to 84 Years of Age



Subjects were considered healthy if they had no cancer or heart disease at baseline.

Berrington de Gonzalez A, et al. *N Engl J Med*. 2010;363:2211-2219.

Cause-Specific Mortality

Collaborative analyses of 57 prospective studies with 894,576 participants calculated the HRs of all-cause and cause-specific mortality vs baseline BMI.[11] Study participants were mostly (61%) from Western Europe and North America with a mean recruitment age 46,

and a mean BMI of 25. To limit reverse causality, the first 5 years of follow-up were excluded, leaving 66,552 deaths of known cause during a mean of 8 further years of follow-up (mean age at death 67). The numbers of deaths according to specific cause were: 30,416 vascular; 2070 diabetic, renal or hepatic; 22,592 neoplastic; 3770 respiratory; 7704 other. Ischemic heart disease accounted for more than a quarter of all deaths of known cause. Overall, BMIs in the overweight/obese range (25-50) were associated with higher mortality HRs compared with the normal/underweight BMI range (15-25) (**Table 1.1**). The highest HRs were associated with cardiovascular (CV) disease, diabetes, and non-neoplastic kidney and liver diseases. Overall, at a BMI of 30 to 35, median survival was reduced by 2 to 4 years and at a BMI of 40 to 45, it was reduced by 8 to 10 years.

TABLE 1.1 — Cause-Specific Mortality vs BMI in the Ranges of 15-25 kg/m^2 and 25-50 kg/m^2

	Hazard Ratios	
	BMI 15-25 kg/m^2	**BMI 25-50 kg/m^2**
Ischemic heart disease	1.22	1.39
Stroke	0.92	1.39
Other vascular disease	0.84	1.47
Diabetes	0.96	2.16
Kidney disease[a]	1.14	1.59
Liver disease[a]	0.69	1.82
Lung cancer	0.71	0.98
Upper aerodigestive cancer	0.49	0.98
Other specified cancer	0.94	1.12
Respiratory disease	0.31	1.20
Other specified disease	0.62	1.20
External cause	0.82	1.19
Unknown cause	0.72	1.22

[a] Non-neoplastic.

Prospective Studies Collaboration, et al. *Lancet.* 2009;373:1083-1096.

Cancer-Related Mortality

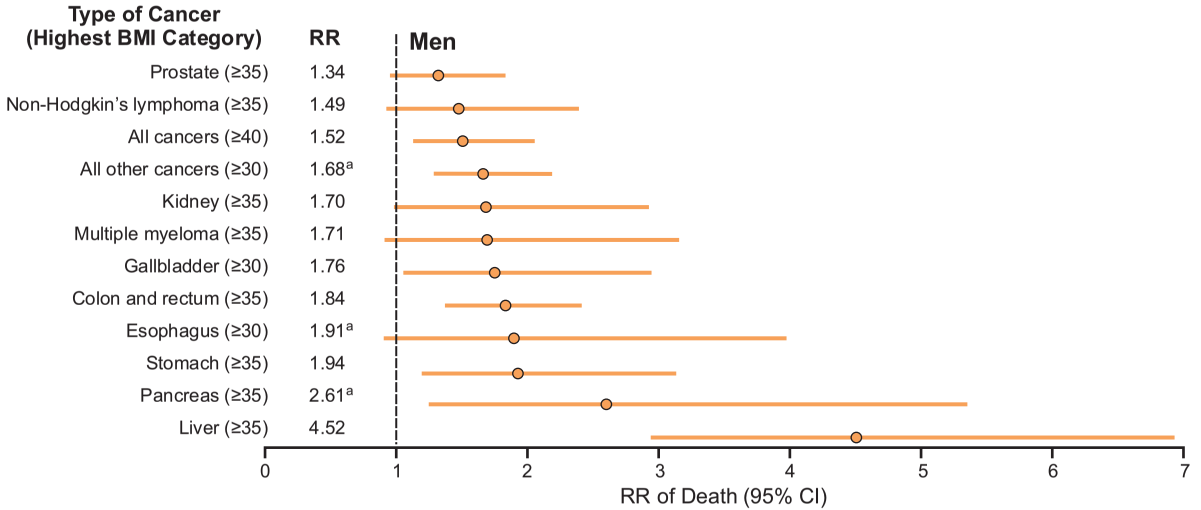
An analysis of a prospectively studied population of more than 900,000 US adults (404,576 men and 495,477 women) who were free of cancer at enrollment in 1982 examined the relation in men and women between the BMI in 1982 and the relative risk (RR) of death from all cancers and from cancers at individual sites during 16 years of follow-up.[12] The cancer-related deaths rates among subjects with a BMI of ≥40 were 52% higher for men and 62% higher for women than the rates in men and women of normal weight. For men, the RR of death was 1.52 while the RR risk was 1.62 for women. On the basis of the associations observed in this study, the authors estimated that current patterns of overweight and obesity in the United States could account for 14% of all cancer-related deaths in men and 20% of all cancer-related deaths in women.[12]

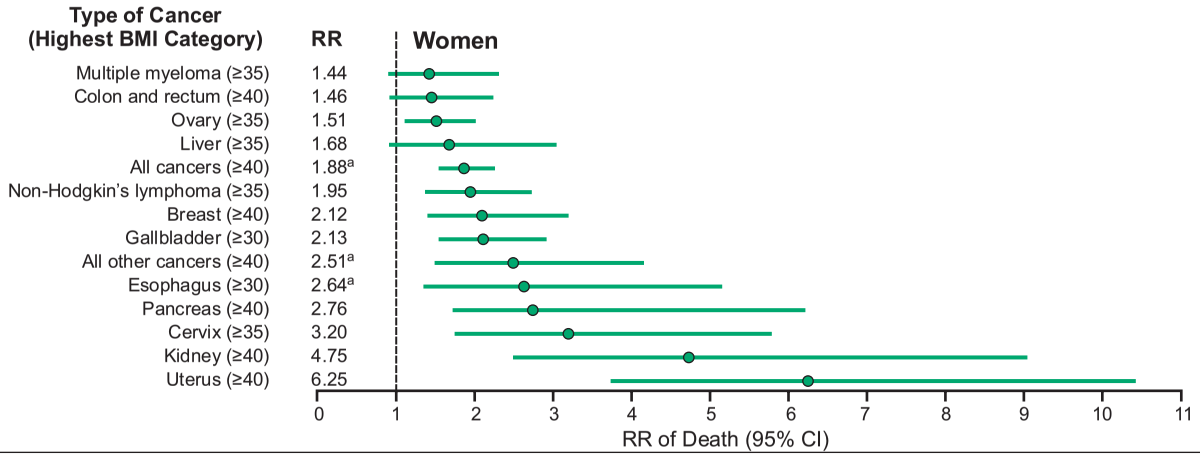
The relationship between obesity and cancer mortality also holds for individual-site cancer mortality. The RRs for mortality from specific cancers among US men with obesity ranged from 1.34 for prostate cancer to 2.61 for pancreatic cancer and 4.52 for liver cancer (**Figure 1.3**, *top*). Among US women, the RRs tended generally to be higher than in men. For example, the most potentially deadly relationships were between obesity and pancreatic (RR 2.76), cervical (RR 3.20), kidney (RR 4.75), and uterine (RR 6.25) cancers (**Figure 1.3**, *bottom*).[12]

COVID-19-Related Mortality

Since the start of the SARS-CoV-2 pandemic, obesity has emerged as an independent risk factor for severe disease and death from COVID-19.[13] In a meta-analysis of 46 studies enrolling more than 600,000 patients, obesity was found to increase the risk of SARS-CoV-2 infection (odds ratio [OR] 2.73), hospitalization for COVID-19 (OR 1.72), severe disease (OR 3.81), ICU admission (OR 2.25), and death (OR 1.61).[14] Another meta-analysis, encompassing 208 studies and more than 3 million patients, uncovered a linearly-increasing risk of COVID-19-related hospitalization in patients with overweight (defined as a BMI of 23–24.9 in Asia-Pacific and 25–29.9 elsewhere; OR 1.19), obesity (BMI ≥25 in Asia-Pacific and ≥30 elsewhere; OR 1.72), and class III

FIGURE 1.3 — Relative Risks for Mortality From Cancer According to BMI Among US Men and Women: 1982 Through 1998





For each RR, the comparison was between subjects in the highest BMI category (indicated in parentheses) and those in the reference category (BMI, 18.5-24.9). Results of the linear test for trend were significant ($P \leq 0.05$) for all cancer sites.

[a] Indicates RR for subjects who never smoked.

Calle EE, et al. *N Engl J Med*. 2003;348(17):1625-1638.

obesity (BMI ≥30 in Asia-Pacific and ≥40 elsewhere; OR 2.53).[15] The risk of death was also significantly higher in patients with obesity (OR 1.25) and extreme obesity (OR 2.06), though not in those with overweight (OR 1.02). Although the mechanistic link between obesity and worse COVID-19 outcomes is not fully understood, possible contributing factors include increased inflammation, impaired immune function, reduced lung capacity, and adipose tissue serving as a viral reservoir.[13,15]

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The Pathophysiology of Obesity

Obesity is a chronic disease manifested as excess adipose tissue. Obesity has multiple etiologies including genetic, environmental, behavioral, and defects in neurohormonal signaling.

Energy Balance/Homeostatic Regulation of Food Intake

Energy homeostasis is the steady state balance between energy intake vs energy expenditure, and humans have evolved multiple mechanisms to maintain energy homeostasis. Homeostatic control of food intake involves complex communication between the central nervous system (CNS) (hypothalamus) and the periphery. Intake involves the process of obtaining and digesting nutrients, as well as the regulation of feeding behavior. Energy expenditure involves basal metabolic rate, non-shivering thermogenesis, diet-induced thermogenesis, and physical activity. Basal metabolic rate accounts for approximately 60% to 70% of total energy expenditure (TEE) and increases with overall body weight as the demand increases with the increased body mass.[1] Thermogenesis contributes to energy expenditure, including the regulation of brown adipose tissue for heat generation. Further, after eating, the body utilizes energy for digestion and absorption in a process called diet-induced thermogenesis. Lastly, physical activity is responsible for approximately 20% to 30% of total energy expenditure and is one of the most modifiable components of energy expenditure.

In order to maintain balance, a neural regulator (the hypothalamus) senses fuel availability and generates appropriate signals to the neural circuits controlling food intake and energy expenditure, referred to as the homeostatic regulation of adiposity and body weight.[2]

Under steady-state conditions, all energy consumed is normally metabolized to maintain basic metabolic rate, thermogenesis, and energy expenditure. Excess fuel is stored to be used later and is required for human survival during times of starvation. However, these pathways are now operating under a condition of sustained positive energy balance and the body's efficient storage of fat can lead to obesity. Ultimately, obesity is a result of a disruption in energy homeostasis.

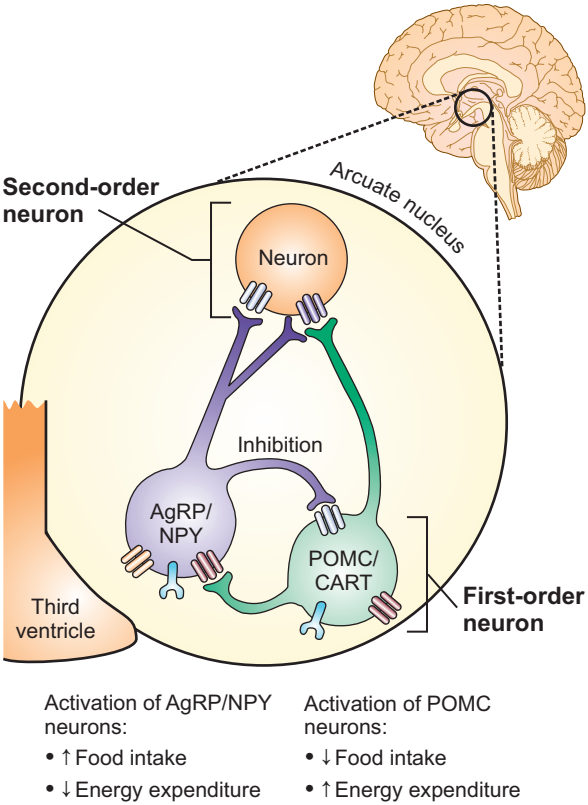
Hypothalamus as Key Regulator

The hypothalamus is the regulation center of appetite and energy expenditure, integrating both CNS and peripheral signals that subsequently modulate feeding behavior and energy balance.[3] The hypothalamus consists of several interconnecting nuclei, including the arcuate nucleus (ARC), which is considered to be the primary region sensing the peripheral metabolic signals leading to feeding behavior and appetite regulation. Within the ARC, there are two distinct neuronal populations: one which expresses orexigenic peptides including neuropeptide Y (NPY) and agouti-related peptide (AgRP) which functions to reduce energy expenditure and increase appetite (**Figure 2.1**).[4]

NPY is a 36 amino acid neural transmitter that is widely distributed throughout the CNS with the highest concentration found in the ARC of the hypothalamus. The appetite-stimulating effects of NPY are mediated by several subtypes of NPY receptors on the orexigenic neuron. The production of NPY from the NPY/AgRP neuron is stimulated by the gut "hunger signal" ghrelin and inhibited by leptin, amylin, insulin, and serotonin (5-HT).

AgRP is a 132 amino acid peptide signaling molecule co-expressed with NPY in the NPY/AgRP neuron. The production of AgRP from the NPY/AgRP neuron is stimulated by ghrelin and inhibited by leptin, amylin, insulin, and 5-HT. AgRP is also highly expressed in the adrenal gland. As an antagonist of α-MSH (melanocyte-stimulating hormone), AgRP competes with α-MSH for binding to the melanocortin receptor 4 (MC4R), leading to lowered satiety and overeating.

FIGURE 2.1 — Two Major Opposing Pathways Affect Food Intake and Energy Expenditure in the Arcuate Nucleus of the Hypothalamus



Key: AgRP, agouti-related protein; CART, cocaine and amphetamine-regulated transcript; NPY, neuropeptide Y; POMC, propiomelanocortin.

Modified from Vetter ML, et al. *Nat Rev Endocrinol*. 2010;6:578-588; and Saper CB, et al. *Nature*. 2005;437(7063):1257-1263.

The other neuronal population is the anorexigenic peptides, including proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). POMC is a prohormone synthesized in the POMC/CART neuron in the ARC of the hypothalamus. Activation of POMC neurons leads to release of α-MSH which binds to MC4R, leading to a reduction in appetite and increased energy expenditure. CART is an approximately 50 amino acid long peptide derived in the POMC/CART neuron. Its main function in the hypothalamus is to stimulate anorexigenic neurons to suppress appetite. First discovered as a respondent to cocaine and amphetamine administration, CART is believed to play roles in reward and addiction regulations. Both NPY/AgRP and POMC neurons project from the arcuate nucleus to the hypothalamus (as well as other brain regions), which contains a dense neuronal population that expresses MC4R. Activation of MC4R by α-MSH relays a satiety signal, resulting in a reduction in food intake. This neuronal regulatory system is regulated by modulators such as leptin and insulin (**Figure 2.2**).[4]

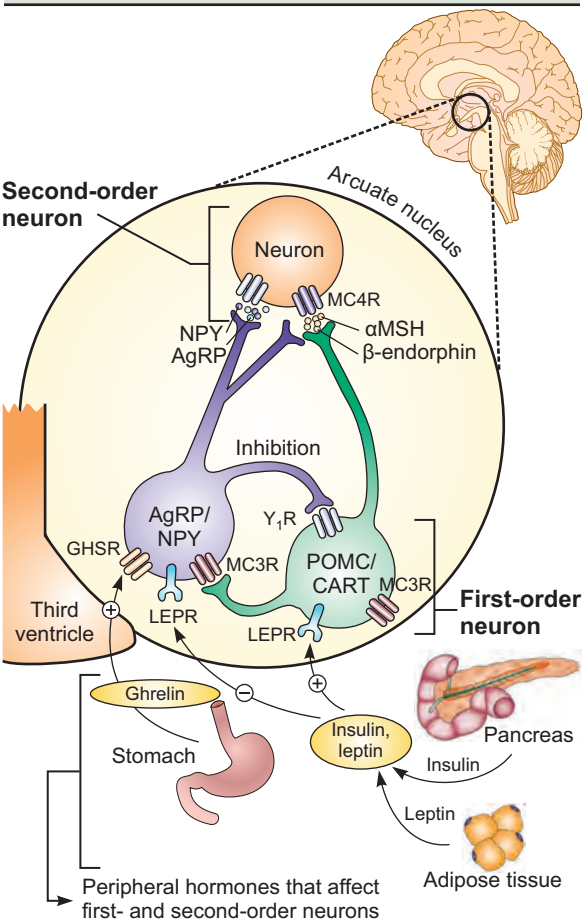
Peripheral Signaling

Peripheral signals send signals to the CNS via three routes:

- Humoral
- Metabolic
- Neural.

Humoral factors include hormones secreted by the gastrointestinal (GI) system, adipose tissue, and pancreas. These signals include peptides, ghrelin, leptin, insulin, cholecystokinin (CCK), and tumor necrosis factor alpha (TNF-α). Metabolic factors include carbohydrates, lipids ketones, and other metabolites. Finally, the autonomic nervous system sends signals from the peripheral organs to the CNS. Subsequently, all of these signals are integrated and regulate both short-term energy intake as well as long-term energy stores to modulate energy intake and energy expenditure.[5] These multiple signaling pathways ensure that food is consumed when needed. However, ongoing

FIGURE 2.2 — Peptide Modulators of Food Intake and Energy Expenditure



Key: AgRP, agouti-related peptide; CART, cocaine and amphetamine-regulated transcript; GHSR, growth hormone secretagogue receptor; LEPR, leptin receptor; MC3R, melanocortin receptor 3; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; Y_1R, neuropeptide Y_1 receptor.

Modified from Vetter ML, et al. *Nat Rev Endocrinol*. 2010;6:578-588; and Saper CB, et al. *Nature*. 2005;437(7063):1257-1263.

access to highly palatable foods may override the inhibitory processes that signal satiety and one may begin to overconsume large amounts of food despite nutrient overload.[6]

Humoral Signaling

Gastrointestinal Signals

The primary role of the GI tract is to digest and absorb nutrients. However, it also plays a role in energy homeostasis via mechanoreceptors and chemosensors which detect the amount and quality of food intake. Gastric distension leads to vagal stimulation due to secretion of serotonin from gastric enterochromaffin cells or from direct stimulation of stretch receptors. The small intestine secretes satiety signals including CCK, peptide YY (PYY), serotonin, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) (**Figure 2.3**).[7]

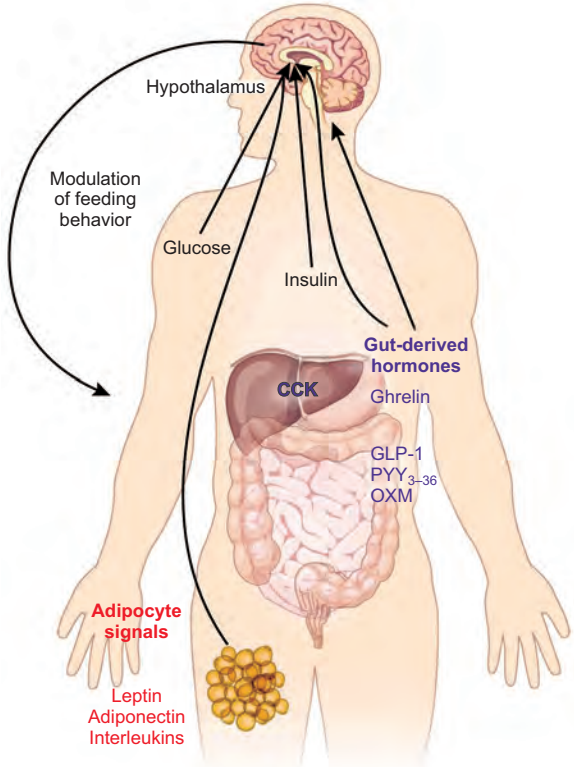
CCK is released from the small intestine (duodenum and jejunum) in response to fat and protein intake and signals satiety. PYY, GLP-1, and GIP are released in the small intestine in response to luminal nutrient stimulation. PYY binds to and inactivates NPY/AgRP leading to anorexia. GLP-1 delays gastric emptying leading to improved satiety, reduces hunger, and enhances glycemic control. GIP acts predominantly on the pancreas to increase glucose-dependent insulin secretion.

Ghrelin, secreted from the stomach, exerts an orexigenic effect. Ghrelin levels are elevated during the fasting state and thus is considered the physiologic "hunger" hormone. Ghrelin levels rise before each meal and rapidly fall after eating. Further, diet-induced weight loss in individuals with obesity show increased plasma ghrelin levels, suggesting that ghrelin may represent a compensatory response to altered energy metabolism.[8]

Adipose Signals

Adipose tissue has been recognized as more than just a depot of excess fat. Adipose tissue is recognized as an active organ that secretes a variety of hormones and adipokines, all of which act on a variety of metabolic processes and influence energy homeostasis.[9] Key signaling molecules include leptin, insulin, TNF-α, IL-6, and resistin (**Figure 2.3**).[7]

FIGURE 2.3 — Brain Sensing of Gut- and Adipocyte-Derived Hormones



Key: GLP-1, glucagon-like peptide 1; $PYY_{3–36}$, peptide YY residues 3–36; OXM, oxyntomodulin; CCK, cholecystokinin.

The brain is responsive to signals from adipose, gut and pancreatic hormones, brain-derived energy balance–associated neurotransmitters and neuropeptides, and dietary nutrients. Gut- and adipocyte-derived hormones, reflecting short- and long-term nutritional status, respectively, circulate in the periphery and signal to specific receptors in the brain.

Yeo GS, Heisler LK. *Nat Neurosci*. 2012;15(10):1343-1349.

Leptin is a hormone discovered in 1994 which is secreted by adipose tissue and in normal individuals, leptin levels correlate with adipose tissue mass. Leptin receptors are highly expressed in the ARC of the hypothalamus. Binding of the leptin receptors induces an increase in anorexigenic POMC/CART signaling and decreased activity of the orexigenic signals NPY/AgRP, resulting in reduced food intake and increased energy expenditure.[10,11] Studies have shown that leptin acts as a satiety factor that signals the CNS that adipose tissue stores are adequate.[12] The absence of leptin acts as a signal of starvation, thus leptin deficient individuals develop severe obesity and hyperphagia. Leptin has successfully treated hyperphagia in leptin deficient individuals; however, most people with obesity have elevated leptin levels, implying leptin resistance and treatment in these patients has been ineffective.

Pancreatic Signals

Insulin is secreted from the pancreatic β cells following a meal and transported to the brain (**Figure 2.2**).[4] Fasting insulin levels positively correlate with body fat mass and insulin has been considered a surrogate marker for adiposity.[3] Insulin receptors are expressed in the hypothalamic nuclei including the ARC. Insulin, similar to leptin, binds to the ARC neurons and results in POMC activation and NPY/AgRP inhibition, leading to reduced food intake.

Reward or "Hedonic" Pathway

Certain forms of obesity may be driven by excessive motivational drive for food and mediated by reward "hedonic" circuitry. Certain foods, particularly those containing sugar and fat, are potently rewarding. In animal models, this can trigger addictive-like behaviors; however, the response to food by humans is more complex. In humans, the rewarding property of food is influenced by many other factors including palatability, availability, economics, and incentives ("supersizing"), and social routines.[13] During periods of energy abundance, the reward system regulation can override the homeostatic pathway (by increasing the desire to consume foods that are highly palatable), leading to obesity.

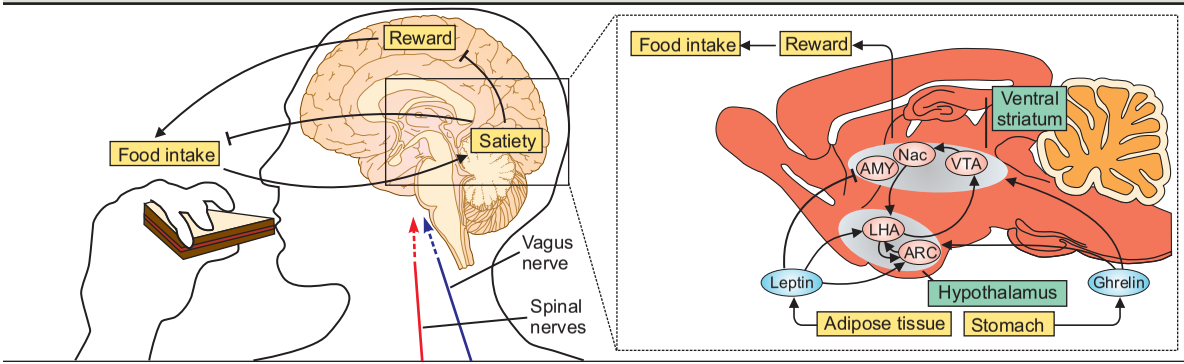
Several neurotransmitters have been implicated in the rewarding effect of food; however, dopamine has been the most thoroughly investigated and is best characterized.[6] Upon exposure to a food reward, dopamine neurons fire, leading to an increase in dopamine release in the nucleus accumbens (NAc). Disruption of the dopamine reward pathway has been implicated in the loss of control seen in obesity (**Figure 2.4**).[14]

In addition, individuals with obesity may respond to food differently than their unaffected counterparts. Data using functional magnetic resonance imaging (MRI) have demonstrated that high glycemic index meals (highly palatable foods) increase activity in the NAc.[15] Furthermore, functional MRI shows significantly greater activation of the NAc in women with obesity compared with women of normal weight. This greater activation was observed in response to pictures of high-calorie (eg, cheesecake, ribs) vs low-calorie foods (eg, steamed vegetables, broiled fish). Exaggerated reactivity to food cues, especially those associated with high-calorie foods, may be a factor underlying obesity. This increased motivational potency of foods in individuals with obesity appears to be mediated in part by a hyperactive reward system.[16]

Role of Obesity Pharmacotherapy

The current approved antiobesity pharmacotherapy targets the above pathways in an effort to manage appetite and reduce weight (see further details in *Chapter 9*). Phentermine increases dopamine and norepinephrine in the hypothalamus enhancing POMC neuron pathways to increase alpha-MSH, which binds to MC4R to partially suppress appetite. Bupropion SR plus naltrexone SR targets the POMC pathway. Bupropion may enhance POMC-mediated appetite suppression; however, it also activates the β-endorphin/opioid-mediated negative feedback loop which mitigates how much bupropion can activate POMC. Thus naltrexone removes this negative feedback and can potentiate bupropion's ability to increase POMC firing, leading to stronger appetite suppression (**Figure 2.5**). Two additional therapeutic agents, liraglutide and semaglutide, are GLP-1 receptor agonists. They affect multiple pathways and organs to

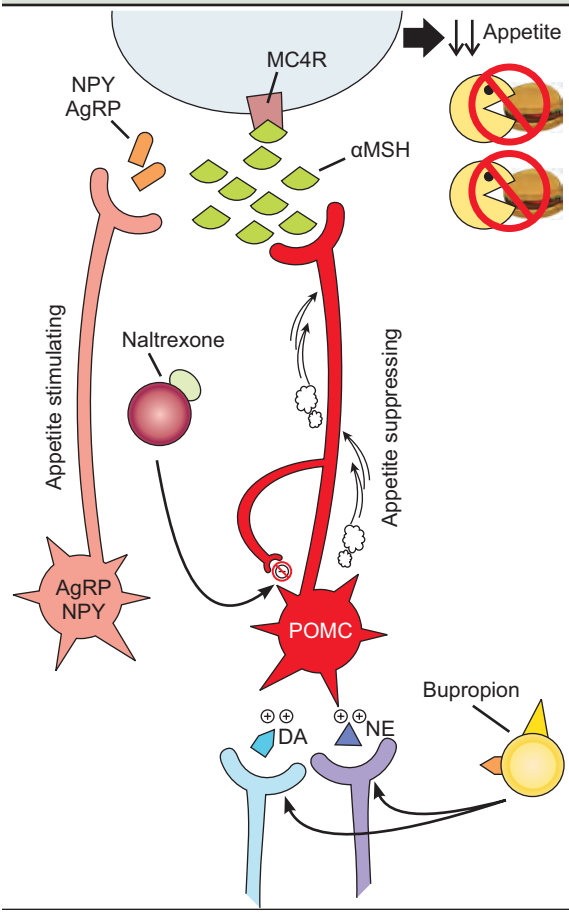
FIGURE 2.4 — CNS Regulates Food Intake, Energy Expenditure, and Reward in Response to Satiety Signals



The CNS integrates input from long-term energy stores and short-term meal-related signals (reward system) to regulate food intake and energy expenditure in a manner that maintains homeostasis over time. In response to energy deprivation, the rewarding properties of food are increased (via projection of dopaminergic neurons in the VTA to the NAc), and the response to satiety signals are reduced, resulting in increased food consumption. Conversely, positive energy balance induced by overfeeding inhibits the reward response and enhances satiety. However, neurocircuits exist that can override the homeostatic control of energy balance. For example, the increased desire to consume foods that are highly palatable can trigger eating at times when food would not otherwise be consumed.

Morton GJ, et al. *Nat Rev Neurosci*. 2014;15(6):367-378; and Saper CB, et al. *Nature*. 2005;437(7063):1257-1263.

FIGURE 2.5 — Naltrexone Potentiates the Actions of Bupropion



Key: AgRP, agouti-related protein; αMSH, α-melanocyte–stimulating hormone; DA, dopamine; MC4R, melanocortin 4 receptor; NE, norepinephrine; NPY, neuropeptide Y; POMC, proopiomelanocortin.

Stahl SM. In: *Stahl's Essential Psychopharmacology*. 4th ed. New York, NY: Cambridge University Press; 2013:537-575.

reduce appetite, energy intake, and hunger, and promote satiety (**Figure 2.6**).

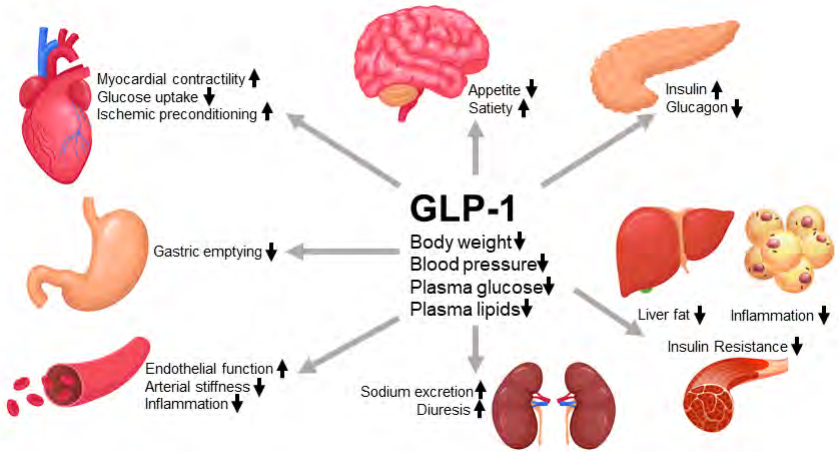
Genetic and Environmental Factors

Genetics

Genetic causes of obesity may derive from monogenic or polygenic hypothalamic defects resulting in impairment in the ability of the hypothalamic circuitry to regulate body weight by controlling energy expenditure, food intake, and some peripheral metabolic actions. The latest version of the human obesity gene map reported 11 human genes that cause monogenic obesity and 52 genomic regions harboring a trait loci associated with obesity.[17] Single gene mutations can result in syndromes in which obesity is a symptom; including Leptin Deficiency, Leptin Receptor Deficiency, Prader-Willi Syndrome, and Bardet-Biedl syndrome and mutations in the *FTO*, *POMC*, and *MC4R* genes.

Leptin deficiency is a mutation of the *LEP* gene which encodes for leptin. It is associated with class III, early-onset obesity and was the first monogenic form of obesity discovered. Carriers of leptin gene mutations are able to normalize their body weight after daily subcutaneous leptin administration. Leptin receptor deficiency is a rare autosomal recessive condition that occurs due to mutations in the leptin receptor (*LEPR*) gene. Along with obesity, leptin receptor deficiency can lead to hypogonadotropic hypogonadism leading to delayed sexual development and infertility. The Prader-Willi syndrome is a neurodegenerative disorder that is caused by genetic abnormalities of the long arm of chromosome 15 (q11-13). Affected infants have poor muscle tone and feed poorly at birth. Later their appetite greatly increases leading to hyperphagia and obesity. They also have behavior problems (irritability, tantrums), delayed development, short stature, and, later, hypogonadotropic hypogonadism. Bardet-Biedl syndrome occurs from mutations to the primary cilium altering cellular signaling and is a disorder characterized by obesity and several other abnormalities, including microorchidism in men, intellectual disability (mental retardation), retinal dystrophy, polydactyly, renal

FIGURE 2.6 — Actions of GLP-1 and GLP-1 Receptor Agonists Promote Weight Loss via Several Mechanisms



Key: GLP-1, glucagon-like peptide 1.

Adapted from Boyle JG, et al. *Clin Sci (Lond)*. 2018;132(15):1699-1709.

malformations (particularly calyceal abnormalities), and polyuria and polydipsia.

Humans with the two copies of the *FTO* gene (fat mass and obesity associated gene) have been found on average to weight 3 to 4 kg more and have a 1.67-fold greater risk of obesity compared with those without the risk allele. In addition, human studies have found that both adults and children with at least one *FTO* risk allele report greater food intake, impaired satiety responsiveness, and more frequent eating loss of control. The increased consumed energy was due to an increased preference for energy dense foods, specifically those with a higher fat content.[18] Furthermore, FTO is strongly expressed in the hypothalamus, particularly the arcuate, paraventricular (PVN), dorsomedial, and ventromedial nuclei, all key regions crucial to energy intake.

POMC deficiency is characterized by severe, early-onset hyperphagic obesity and congenital adrenal insufficiency. In the first months of life, most children with POMC deficiency experience exponential weight gain, hyperphagia, cholestasis, and adrenal insufficiency. Weight gain continues rapidly so that by the end of the first year of life, obesity is severe.

MC4R gene deficiency is the most common form of monogenic obesity with general prevalence of 1-5% in patients with obesity.[19] Pathogenic mutations in *MC4R* cause low MC4R functionality and impact the leptin-melanocortin signaling pathway. The deficiency is characterized by early-onset obesity, hyperphagia, increased linear growth and, interestingly, a lower tendency for developing hypertension.[20] It is typically inherited in an autosomal (co-)dominant pattern, although penetrance is not always complete. Homozygous *MC4R* genotypes are much rarer than heterozygous genotypes, but are associated with more severe obesity.[21]

There are several additional genetic and syndromic causes of obesity; however, they are rare and outside of the scope of this handbook.

Epigenetics

Among the different mechanisms that can lead to interindividual differences in obesity, the epigenetic regulation of gene expression has emerged in the past few

years as a potentially important contributor. Epigenetics are heritable changes in gene activity which are not caused by changes in the DNA sequence itself. Epigenetic mechanisms are intrinsically malleable and can be influenced by factors including diet, pharmacologic agents, and environmental toxins.[22]

As an example, the fetus or neonate is extremely sensitive to perturbation by chemicals with hormone-like activity. Environmental chemicals can disrupt the programming of endocrine signaling pathways that are established during perinatal life and result in adverse consequences into adulthood. These endocrine disruptors include pesticides, bisphenol A, organophosphates, polychlorinated biphenyls, polybrominated biphenyls, phthalates, and heavy metals. As an example, in utero or neonatal exposure to Bisphenol A may interact with other factors that influence fetal and postnatal growth in contributing to the obesity epidemic.

Furthermore, studies have examined the intrauterine environment of women with obesity to understand whether it induces developmental adaptations in the developing fetus that then predispose that fetus to obesity. This has been demonstrated in data from women with obesity who underwent bariatric surgery. The children born after maternal weight loss have a lower risk of developing obesity than do their siblings born before maternal weight loss.[23] Such "metabolic imprinting" of body weight regulation could occur via epigenetic mechanisms.[24]

Environmental Factors

Environmental influences, including the physical, social, and economic environment, have likely all contributed to the obesity epidemic. The physical environment includes easy access/use of automobiles, as well as exposure to pollutants and "obesogens." The social environment includes recreational eating (social eating influences meal duration and consumption norms), ongoing advertisements of unhealthy foods, and availability of larger portion sizes.

Genetics vs Environment

The contribution of genetics and environment to the etiology of obesity has been evaluated by multiple stud-

ies. Twin studies have shown that genetics explain 50% to 90% of the variation in BMI. In a study of same-age, unrelated siblings reared together since infancy, 61% of the variance was genetic, 25% due to the common or shared environment, and 14% due to the unique environment. Thus genetics likely accounts for 60% to 70% of BMI, whereas environmental factors may explain the remaining 30% to 40%.[25]

In a given population, a person may be genetically susceptible to obesity but only unless exposed to certain environmental conditions, such as a readily available, highly-caloric, high-fat diet and sedentary lifestyle, would it be expressed. Environmental conditions in developing countries favor the genetically susceptible towards obesity. Evidence of this comes from immigrants who move to the United States who show marked differences in the incidence of obesity compared with their counterparts who remain in their native countries. In addition, studies of the Native American Pima people have shown that those residing in Arizona have highest prevalence of obesity vs those living in a traditional lifestyle in remote area of Mexico—(BMI was 24.9 vs 33.4). The groups differ in diet and energy expenditure based on location in which they live and affluence. Those living in Mexico have a diet with lower animal fat and reduced caloric intake vs those in Arizona have higher fat and more calorically dense food with more complex carbohydrates.[26]

Gut Microbes

The human gut is populated with both symbiotic and commensal microbes, and there is increasing evidence that the gut microbiota may play a role in the development of obesity. Studies in mice have shown that obesity can be induced in lean mice via fecal transplants from mice with obesity.[27]

The exact mechanism of how gut microbes influence weight is unknown; however, animal models suggest that obesity is associated with alterations in the composition and functional properties of the gut microbiota. Although the data is conflicting, some data suggest a shift in the abundance of two dominating divisions of the bacteria, Bacteroidetes and Firmicutes. Compared

with lean individuals, individuals with obesity have a lower ratio from the phylum Bacteroidetes to that of the phylum Firmicutes.[28] Host bacteria may affect energy balance through several mechanisms, including increased fermentation of undigested polysaccharides and obtaining extra energy from the portion of food, reduced expression of fasting-induced adipocyte factor with inhibitory activity towards lipoprotein lipase and increased release of peptide YY which slows intestinal motility.

The gut microbiome (GM) of patients with obesity also changes in response to medical interventions. Patients with class III obesity who are candidates for bariatric surgery exhibit micronutrient deficiencies and dysbiosis. The two are interdependent as microbes produce micronutrients while micronutrients are required for bacterial survival. Changes in gut microbiota following bariatric surgery have been reported. Multiple factors, including anatomical rearrangement of the gut, weight loss, diet, biliary acids, and hormones all contribute to sustained changes of the GM. Although some studies report favorable changes to the microbiota following bariatric surgery, others point to deleterious consequences. Administration of probiotics could be considered following these procedures to restore the GM, but more studies are needed.[29]

Furthermore, the key importance of antibiotic use and dietary nutrient composition are increasingly recognized. The role of the Western diet in promoting an obesogenic gut microbiota has been evaluated and shown that it may increase the abundance of Firmicutes at the expense of Bacteroidetes, inducing enrichment in genes enabling energy harvest from the diet. Further, the changes in the microbial composition were completely reversed after a shift back to the original diet.[30]

Medical Conditions

Medical conditions linked to obesity including Cushing's syndrome, hypothyroidism, PCOS, and growth hormone deficiency. Psychiatric conditions may also play a role including binge-eating and night-eating disorders. Finally, multiple medications may contribute to obesity (see *Chapter 7* regarding medication-induced weight gain).

Cushing's Syndrome

Cushing's syndrome describes the signs and symptoms associated with prolonged exposure to inappropriately high levels of the hormone cortisol. This can be caused by taking glucocorticoid drugs, or diseases that result in excess cortisol, adrenocorticotropic hormone (ACTH), or corticotropin-releasing hormone (CRH) levels. Progressive weight gain is the most common symptom of Cushing's syndrome. This weight gain usually affects the face, neck, trunk, and abdomen more than the limbs, which may be thin. People with Cushing's syndrome often develop a rounded face and collections of fat on the upper back and at the base of the neck.

Hypothyroidism

The relationship between thyroid dysfunction and obesity is complex and bidirectional. Patients with hypothyroidism often gain weight due to slowing of metabolic activity. The weight gain is usually modest, and marked obesity is uncommon. Increasing serum thyroid-stimulating hormone (TSH) concentrations within the normal range have also been associated with a modest increase in body weight in adults but treatment of subclinical hypothyroidism does not appear to be associated with weight loss.

PCOS

PCOS is clinically characterized by oligomenorrhea and hyperandrogenism, as well as the frequent presence of obesity, glucose intolerance, and dyslipidemia. At least half of all women with PCOS have obesity; however, the relationship between obesity and PCOS is not causal.

Growth Hormone Deficiency

Growth hormone deficiency is associated with weight gain and alterations in body composition, specifically central adiposity and a reduction in lean body mass.[31]

Binge-Eating Disorder

Binge-eating disorder is a psychiatric illness characterized by uncontrolled episodes of eating that usually occur in the evening. During such binges, a person rapidly consumes an excessive amount of food. Most people

who have eating binges try to hide this behavior from others and often feel ashamed about having overweight or depressed about their overeating.

Night-Eating Syndrome

Night-eating syndrome is defined as consumption of at least 25% (and usually more than 50%) of energy between the evening meal and the next morning. It is a well-known pattern of disturbed eating that affects approximately 10% of individuals with obesity.[32]

Sleep

Sleep deprivation has been linked to obesity. Sleep is an important modulator of neuroendocrine function and glucose metabolism. Sleep loss has been shown to result in metabolic and endocrine alterations, including decreased glucose tolerance, decreased insulin sensitivity, increased evening concentrations of cortisol, increased levels of ghrelin, decreased levels of leptin, and increased hunger and appetite.[33] Studies have shown a correlation between chronic short sleep (6 hours or less) and elevated BMI and waist circumference.[34] Short sleepers were as much as 1.7 kg/m^2 heavier and waist 3.4 cm greater than long sleepers (>10 hours).

Hypothalamic Obesity

Hypothalamic obesity (HO) comprises a series of genetic or acquired pathologic processes damaging the hypothalamic centers of body weight and energy expenditure leading to obesity. Specifically, HO is generally associated with damage to the ventromedial hypothalamus leading to hyperphagia, autonomic dysfunction, and decreased energy expenditure. One of the first hypothalamic syndromes described was Babinski-Frohlich syndrome or hypothalamic infantilism obesity whereby a pituitary tumor led to a disorder characterized by headaches, visual changes, obesity, and hypogonadism, which is now known to be due to hypopituitarism. It is now understood that structural damage to the hypothalamus can lead to obesity including neoplasms (eg, craniopharyngiomas), vascular malformations, and inflammatory or infiltrative diseases.

Adaptive Responses and Hormonal Changes to Weight Loss

Weight loss itself is difficult for most patients; however, maintaining the weight loss can be even more challenging. There are compensatory changes that occur with weight loss which may promote weight regain due to decreased daily resting energy expenditure (REE) and changes in peripheral signals that affect appetite stimulation and suppression.

Weight loss is associated with a reduction in TEE that is out of proportion to changes in lean body mass, the primary determinant of resting energy expenditure. Liebel and colleagues evaluated 18 subjects with obesity vs 23 subjects who had never had obesity. They were studied at their usual body weight and after losing 10% to 20% of their weight by underfeeding.[35] The 24-hour energy expenditure, resting and nonresting, were evaluated. Results demonstrated that maintenance of a body weight at a level 10% or more below the initial weight was associated with a mean reduction in TEE of 6 ± 3 kcal per kilogram of fat-free mass per day in subjects who never had obesity (P <0.001) and 8 ± 5 kcal per kilogram per day in subjects with obesity (P <0.001). REE and non-REE each decreased 3 to 4 kcal per kilogram of fat-free mass per day in both groups of subjects. The thermic effect of feeding and non-REE increased by approximately 1 to 2 and 8 to 9 kcal per kilogram of fat-free mass per day, respectively, after weight gain. When adjusted for body composition, a 10% decrease in body weight resulted in 15% lower energy expenditure, which the authors note is substantial considering that an intake of 2500 kcal (an average daily intake) would result in a positive energy balance of 375 kcal. Thus, maintenance of a reduced weight was associated with compensatory changes in energy expenditure which oppose the maintenance of a body weight that is different from the usual weight.

These compensatory changes may account for the challenges in achieving long-term weight loss success. This reduction in TEE appears to persist indefinitely as long as the reduced weight is maintained. The lower TEE is important in that it means that the individual will need

to restrict energy intake indefinitely or regain the lost weight.[36]

Furthermore, weight loss is also associated with an increase in the drive to eat and a reduction in satiety. Increased hunger and decreased satiety following weight loss are associated with increases in the 24-hour profile of circulating levels of the orexigenic hormone ghrelin, and reductions in the levels of the anorexigenic hormones PYY, CCK, leptin, and insulin.[37] These changes in appetite-related hormones appear to persist for at least 1 year following weight reduction and may remain altered indefinitely in a manner that promotes weight regain.[38]

Summary

Obesity is a disease with a complex etiology. Food intake is regulated by two complementary drives, the homeostatic and hedonic pathways. The homeostatic pathway controls energy balance by increasing the motivation to eat following depletion of energy stores. In contrast, hedonic or reward-based regulation can override the homeostatic pathway during periods of relative energy abundance by increasing the desire to consume foods that are highly palatable, subsequently leading to obesity. In addition, there are multiple factors which may contribute to a person's specific risk for developing obesity, including genetic and environmental factors. Adaptive metabolic responses drive weight regain and it is important for patients to understand that the difficulties surrounding weight loss and weight maintenance are not simply a matter of will-power.

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Obesity-Related Comorbidities

Introduction

A vast body of data unequivocally documents the direct and indirect links between excessive body weight and a wide spectrum of comorbidities (**Figure 3.1**). Although the underlying pathophysiologic mechanisms are not yet fully elucidated, many of these mechanisms involve an array of factors secreted by metabolically dysfunctional adipose tissue (**Figure 3.2**) (see *Chapter 2*). Obesity is also associated with an increased risk of all-cause mortality, with the hazard ratio (HR) increasing from 1.45 for class I obesity to 1.94 for class II and 2.76 for class III obesity.[1]

Obesity and Inflammation

Obesity has been linked to a chronic state of inflammation which may be involved in the development of comorbidities such as metabolic syndrome, cardiovascular disease, non-alcoholic steatohepatitis, and cancer.[2] The association of obesity and levels of inflammatory biomarkers has been demonstrated in an analysis of data from the 1999-2004 National Health and Nutrition Examination Study (NHANES). Serum concentrations of C-reactive protein (CRP) and fibrinogen were compared across different weight classes. With CRP levels for normal weight individuals as a reference, CRP levels nearly doubled with each increase in weight class from +0.11 mg/dL for overweight to +0.73 mg/dL for class III obesity (BMI ≥40; **Table 3.1**). Similarly, with normal weight individuals as a reference, fibrinogen levels also increased with increasing weight class and were highest for individuals with class III obesity (+93.5 mg/dL). Furthermore, individuals with hypertension or diabetes have higher levels of CRP and fibrinogen levels compared

FIGURE 3.1 — Comorbidities Associated With Obesity

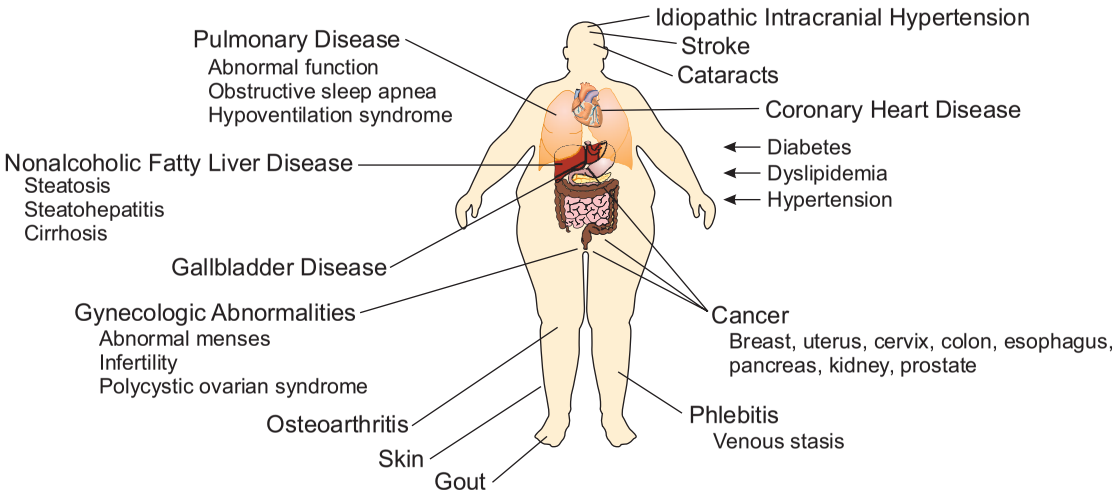


FIGURE 3.2 — Factors Secreted by Adipose Tissue

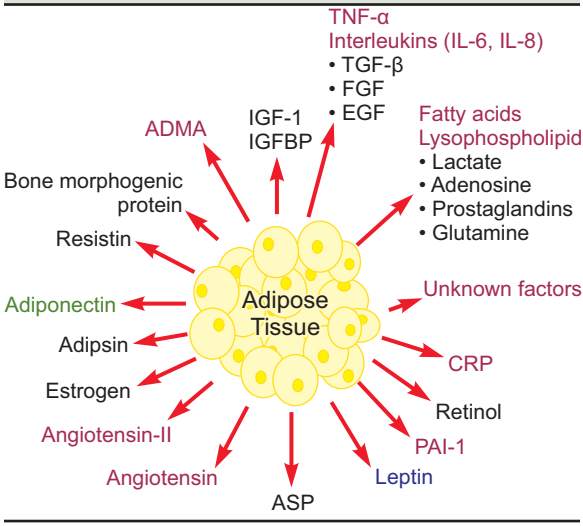


TABLE 3.1 — Associations Between Biomarker Levels and Obesity Class: NHANES 1999-2004

		Change From Reference Value (mg/dL)	
Obesity Class	**BMI**	**CRP**	**Fibrinogen**
Normal weight	<25.0	0.05[a]	287[a]
Overweight	25-29.9	0.11 ± 0.03	11.5 ± 0.39
Class			
I	30-34.9	0.21 ± 0.03	25.6 ± 5.0
II	35-39.9	0.43 ± 0.09	40.0 ± 7.6
III	≥40	0.73 ± 0.09	9.35 ± 10.1

All *P* values <0.01 compared with reference value.

[a] Reference values.

Nguyen XM, et al. *J Gastrointest Surg*. 2009;13(7):1205-1212.

with individuals without hypertension or diabetes, even when stratified according to BMI (**Table 3.2**).

Prevalence of Major Comorbidities

The associations between obesity and its common comorbidities, such as diabetes, hypertension, dyslipidemia, and obstructive sleep apnea, have been reported by a considerable number of epidemiologic studies. The results from a selected sample of such studies are summarized below. Overall, the results from these studies indicate that the prevalence of the major comorbidities of obesity tend to increase with increases in body weight.

Diabetes

Obesity, and particularly central adiposity, is the dominant risk factor for the development of type 2 diabetes (T2D). It is also one of the most important modifiable risk factors for the prevention of T2D.[3]

In an analysis of data from adults with diabetes who participated in NHANES 1999-2006, the prevalence of diabetes increased with increasing weight classes, from 8% for normal weight individuals to 43% for individuals with class III obesity.[4] Moreover, a separate study using the data from NHANES surveys determined that from 1999/2000 to 2013/2014 the prevalence of obesity and T2D has increased by 9.8% and 2.9%, respectively. The increase in the prevalence of T2D was limited to individuals with abdominal obesity, with no significant change in prevalence in the group without obesity. These findings highlight that obesity is a critical risk factor for developing diabetes, and imply that targeting obesity may slow the rise in T2D cases.[5]

A considerable body of evidence demonstrates that the long-term risk of T2D increases significantly with increasing body weight.[6] For example, according to data from the Behavioral Risk Factor Surveillance System, the prevalence of diabetes and mean body weight both increased by 49% from 1990 to 2000 (**Figure 3.3-A**). The effect of long-term weight change on the risk for clinical diabetes was evaluated in 114,281 women enrolled in the Nurses' Health Study. As shown in **Figure 3.3-B**, after adjusting for age, body weight was the major risk factor for diabetes during 14-year follow-up. Among

TABLE 3.2 — CRP and Fibrinogen Levels According to Diabetes and Hypertension Status

		Mean CRP Levels (mm/dL)				Mean Fibrinogen Levels (mm/dL)			
Obesity Class	**BMI**	**No T2D**	**T2D**	**No HTN**	**HTN**	**No T2D**	**T2D**	**No HTN**	**HTN**
Normal weight	<25	0.30	0.63	0.26	0.48	376	413	344	381
Overweight	25-29.9	0.36	0.46	0.35	0.45	364	381	353	376
Class									
I	30-34.9	0.49	0.55	0.48	0.54	375	402	373	381
II	35-39.9	0.70	0.95	0.68	0.75	401	411	381	392
III	≥40	1.01	1.05	0.99	1.20	442	444	439	436

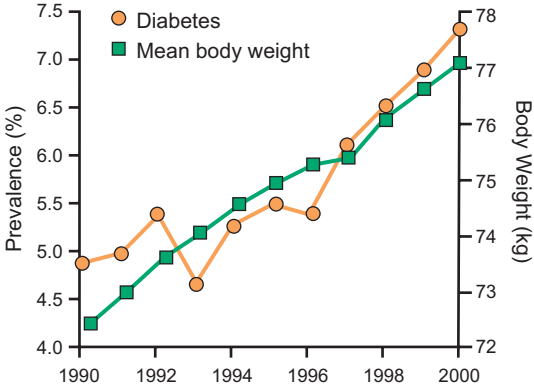
HTN, hypertension; T2D, type 2 diabetes.

$P = 0.02$.

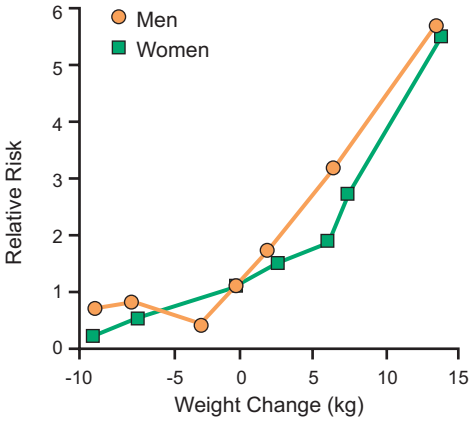
Nguyen XM, et al. *J Gastrointest Surg*. 2009;13(7):1205-1212.

FIGURE 3.3 — Relationships Between Body Weight and Diabetes

A. Relationship Between Increasing Body Weight and Diabetes Prevalence: 1990-2000



B. Relationship Between Weight Gain in Adulthood and the Risk of T2D in Men and Women



Haffner SM. *Obesity (Silver Spring)*. 2006;14(suppl 3):121S-127S.

women with a 5 to 7.9 kg weight gain, the relative risk for diabetes was 1.9 and for those with an 8.2 to 10.9 kg weight gain, the relative risk was 2.7.

Consistent with these observations, several studies have shown that weight loss is associated with a significant reduction in the risk of diabetes. In a prospective, 20-year study of 7176 British men, the rate of new diabetes was 11.4 per 1000 person-years among subjects with obesity vs 1.6 among normal-weight subjects (P <0.0001), but the effect of weight change during a 5-year follow-up on the development of diabetes found a relative risk of 0.62 among those losing weight compared with 1.0 for stable weight and 1.76 among those gaining >10% body weight (P <0.0001).[7]

Not only is weight reduction associated with lower risk of developing diabetes, but weight loss may help achieve remission of existing T2D. A study in the UK (DiRECT) demonstrated that following an intensive weight-management program, 46% of participants in the intervention group and 4% participants in the control group (P <0.0001) achieved diabetes remission after 12 months. Remission varied with weight loss in the whole study population, with achievement in none of the 76 participants who gained weight, six (7%) of the 89 participants who maintained 0–5 kg of weight loss, 19 (34%) of the 56 participants with 5–10 kg loss, 16 (57%) of 28 participants with 10–15 kg loss, and 31 (86%) of 36 participants who lost 15 kg or more.[8] After 24 months, 53 (36%) intervention participants and five (3%) control participants had sustained remission of diabetes.[9] Thus, a diabetes remission can be achieved with weight management programs delivered by primary care practices, for patients with T2D diagnosed within past 6 years.

Dyslipidemia

Obesity and elevated BMI are associated with higher prevalence of dyslipidemia. Data analysis from 1999-2006 NHANES shows the prevalence of abnormal total cholesterol level (>200 mg/dL) increased from 40% for BMI <25 to 48% for a BMI ≥35.[10] Dyslipidemia is common in patients with hypertension, T2D, and metabolic syndrome, and elevated serum levels of total choles-

terol, LDL cholesterol, and non-HDL cholesterol are all associated with an increased risk of hypertension.[11] One study verified the additive interaction between dyslipidemia and overweight or obesity in relation to developing hypertension. Compared with normal-weight individuals without dyslipidemia, those with dyslipidemia and obesity had the highest risk of hypertension (adjusted OR: 5.82, 95% CI: 3.08–10.99), and those with dyslipidemia and overweight had a 4.77 times higher risk of hypertension compared to the reference group. Therefore, people who have overweight or obesity and suffer from dyslipidemia are at higher risk of hypertension.[11] Treatment of a comorbidity such as dyslipidemia is an integral part of care for patients with obesity in order to reduce their risk of developing cardiovascular disease.[12]

Hypertension

Excess body weight is one of the major risk factors for hypertension. According to an American Heart Association (AHA) estimate, at least 75% of the incidence of hypertension is related directly to obesity.[13] The results of many studies indicate that the prevalence of hypertension increases with increasing body weight.[14] Although reported prevalence rates have varied somewhat between studies likely due to differences in study populations, the relationship of hypertension prevalence and increasing body weight remains. In one study, the prevalence of hypertension increased from 18.1% in normal weight individuals to 52.3% in those with class III obesity.[15] Thus, individuals with class III obesity had a nearly five times higher risk (adjusted odds ratio [OR] 4.8) for hypertension.

Other Coronary Heart Disease Risk Factors

Obesity is a well-documented risk factor for the development of coronary heart disease (CHD) and stroke, especially when coincident with hyperglycemia, hypertension, and/or dyslipidemia.[14] Changes in 10-year CHD risk associated with levels of obesity and the prevalence of hypertension and abnormal total cholesterol level (>200 mg/dL) were assessed using data from 12,500 participants in the 1999-2006 NHANES.[10] The prevalence of hypertension increased according to increases in BMI, from 24% for BMI <25 to 54% for BMI ≥35. Among

men, these changes resulted in an increase in 10-year CHD risk of 3.1% with a BMI <25 to a peak of 5.6% for a BMI of 30 to 34.9. The 10-year CHD risk for women increased from 0.8% with BMI <25 to a peak of 1.5% for BMI ≥35.

One study quantified how much of the effects of BMI on CHD and stroke are mediated through blood pressure (BP), cholesterol, and glucose, and how much is independent of these factors.[16] Using data from 97 prospective cohort studies that collectively enrolled 1.8 million participants between 1948 and 2005, and included 57,161 CHD and 31,093 stroke events, the hazard ratios (HRs) of BMI on CHD and stroke with and without adjustment for all possible combinations of BP, cholesterol, and glucose were estimated. For each cohort, the authors excluded participants who were younger than 18 years, had a BMI lower than 20, or who had a history of CHD or stroke. The HR of BMI on CHD and stroke with and without adjustment for all possible combinations of BP, cholesterol, and glucose was estimated. The HR for each 5 kg/m^2 higher BMI was 1.27 for CHD and 1.18 for stroke after adjustment for confounders. These findings suggest that 46% of the excess risk of BMI for CHD and 76% the excess risk for stroke is mediated by these factors. BP was the most important mediator, accounting for 31% of the excess risk for CHD and 65% for stroke. Both overweight (BMI ≥25 to <30) and obesity (BMI ≥30) were associated with a significantly increased risk of CHD and stroke compared with a BMI of ≥20 to <25.

Since obesity, hypertension, diabetes, and dyslipidemia are clinical markers of the metabolic syndrome, an analysis of data from 13,745 adults who participated in NHANES 1999-2004 assessed the relationship of body weight and changes in the prevalences of these comorbidities and the metabolic syndrome itself.[15] With increasing overweight and obesity class, there were increases in the prevalences of hypertension, diabetes, dyslipidemia, and the metabolic syndrome (**Table 3.3**). The adjusted ORs of these comorbidities in individuals with class III obesity were also significantly greater compared with normal weight individuals (**Table 3.3**).

TABLE 3.3 — Prevalence and Adjusted Odds Ratios of Comorbidities According to Body Weight

	Prevalence		
	BMI <25 (%)	BMI ≥40 (%)	Adjusted Odds Ratio for BMI ≥40[a]
Hypertension	18.1	52.3	4.8
Diabetes	2.4	14.2	5.1
Dyslipidemia	8.9	19.0	2.2
Metabolic syndrome	13.6	39.2	2.0

[a] Normal-weight individuals as the reference.

Nguyen NT, et al. *J Am Coll Surg*. 2008;207(6):928-934.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a syndrome characterized by repetitive episodes of upper airway obstruction that occur during sleep.[17-19] Associated features include loud snoring, fragmented sleep, repetitive hypoxemia/hypercapnia, and daytime sleepiness. Obesity, particularly central adiposity, are potent risk factors for sleep apnea since they can increase pharyngeal collapsibility through mechanical effects on pharyngeal soft tissues and lung volume, and also through the central nervous system (CNS) via different interactions of adipokines and adipocyte-binding proteins on binding receptors that may affect airway neuromuscular control.[19]

An OSA "event" can be either an apnea, characterized by complete cessation of airflow for at least 10 seconds, or a hypopnea in which airflow decreases by 50% for 10 seconds or decreases by 30% if there is an associated decrease in the oxygen saturation or an arousal from sleep. To assess the severity of OSA, the number of events per hour is reported as the apnea-hypopnea index (AHI). An AHI of <5 is considered normal. An AHI of 5-15 is mild; 15-30 is moderate, and >30 events per hour is severe sleep apnea.

In the general adult population, the prevalence of OSA is 2% to 3% among middle-aged women and 4% to 5% among middle-aged men. In contrast, the prevalence

among individuals with obesity has been reported to be ≥30% and from 50% to 98% among those with class III obesity.[18,20] Among individuals referred for diagnostic sleep studies for OSA, 60% to 90% have overweight; the relative risk for the development of OSA among patients with obesity has been reported to be ≥10.[18,20,21]

The impact of changes in body weight on OSA has been demonstrated by the Wisconsin Sleep Cohort Study[22] and the Sleep Heart Health Study.[23] The overall incidence of moderate to severe OSA over a 5-year period was 11.1% in men and 4.9% in women, respectively. Men with >10 kg weight gain during the follow-up period had a 5-fold risk of increasing their severity of OSA. In contrast, for the same degree of weight gain in women, there was a 2.5-fold risk associated with a similar degree of weight gain. Complementing the available body of observational data are studies on the effects of weight loss which show that reducing OSA severity is possible with a decrease in body weight. Although often limited by few small study samples and the lack of appropriate control groups, the unvarying observation is that weight loss can improve severity of disease in many patients and may be completely curative in some.[20]

Additional Comorbidities

Since many individuals with obesity may have multiple concurrent comorbidities, one study analyzed the primary care electronic health records of 223,089 adults aged ≥30 years to assess the prevalence and impact of BMI category on the probabilities of concurrent comorbidities.[24]

The presence of concurrent comorbidities was found to be strongly associated with levels of obesity. In normal weight men, the prevalence of multiple comorbidities was 23%, with increases to 27% in overweight, 33% in class I obesity, 38% in class II, and 44% in class III obesity. In women, the pattern was similar except the increases with each stage were higher than those in men (28%, 34%, 41%, 45%, and 51%, respectively). The odds of multiple comorbidities increased successively with each BMI category (**Table 3.4**). For participants with overweight, the odds of one disease, compared with none, were 25%

TABLE 3.4 — Impact of BMI Category on Increasing Number of Concurrent Comorbidities

BMI Category	Relative Odds of		
	One or More	Two or More	Three or More
Gender			
Male	[Reference]	[Reference]	[Reference]
Female	1.28	1.33	1.36
Underweight	0.82	0.82	0.82
Normal weight	[Reference]	[Reference]	[Reference]
Overweight	1.25	1.29	1.36
Class I obesity	1.54	1.65	1.83
Class II obesity	1.81	2.04	2.34
Class III obesity	2.24	2.63	3.09

Booth HP, et al. *Fam Pract*. 2014;31(1):38-43.

higher than for normal weight patients. In patients with class I obesity, the relative odds were 54% higher, and higher by 81% with class II obesity, and 124% with class III obesity. The effect of increasing BMI category on concurrent comorbidities was similar to that of ageing, with patients with obesity having a prevalence of concurrent comorbidities similar to that of normal weight patients several decades older.

Osteoarthritis

An increasing body of evidence supports the role of obesity as an independent modifiable risk factor for the development of osteoarthritis (OA), particularly in weight-bearing joints such as the hips and knees.[25-27] In one study, 2764 Italian general practitioners provided data from 10 consecutive patients with OA pain.[28] In these 12,827 patients, the most painful joints were the knee (53.6%), the hip (23.6%), and the hand (22.8%). An association with a BMI of ≥25 was found in 74.8% of men and in 68.3% of women. The BMIs associated with knee and hip OA were consistently higher than those associated with hand OA.[28] A case control study also found that relative to a BMI of 24, the risk of knee OA increased progressively from 0.1 in individuals with a BMI <20 to 13.6 in those with a BMI of ≥36.[29]

Although the link between obesity and OA is well established, the etiological relationship has yet to be fully defined since OA has a multifactorial etiology. The biomechanical relationship is well known: increased loads on articular cartilage result in subsequent wear and cartilage breakdown.[27] Conversely, clinical studies have shown that weight loss can have a favorable effect on OA. For instance, one study reported that for every one pound of weight lost, there was a four-pound reduction in the load exerted on the knee for each step taken during daily activities.[30] However, since obesity-related OA can affect not only the weight-bearing joints (hips and knees) but also the hands, this suggests a role for circulating cytokines associated with adipose tissue, including leptin, adiponectin, and resistin, which may influence OA through direct joint degradation or control of local inflammatory processes.[27,31]

Cancer

Many prospective cohort studies and systematic reviews have confirmed a significant association between obesity and cancer. The strongest association is between an elevated BMI and cancer risk and mortality. Historical data from the past 25 years indicate that obesity is a cause of approximately 14% of cancer deaths in men and up to 20% of cancer deaths in women.[32] The American Cancer Prevention Study II followed >900,000 subjects who were free from cancer in 1982 and had a mean follow-up of 16 years.[33] Among those with a BMI ≥40, mortality from all causes of cancer was 52% higher in men and 62% higher in women compared with those with a normal BMI.

The Million Women Study from the United Kingdom recruited over 1.2 million women, aged 50 to 64 years during 1996 to 2001 and followed for a mean of 5.4 years for cancer incidence and 7 years for cancer mortality.[34] Increasing BMI was associated with a significant increase in risk for 10 out of 17 of the most common types of cancer. A prospective study among 287,700 men in the NIH-AARP Diet and Health Study found that during a mean follow-up of 5 to 6 years, the relative risk for mortality from prostate cancer was 1.46 and 2.12 for a BMI ≥30 and ≥35, respectively.[35]

A systematic review and meta-analysis of 221 datasets from 141 publications that included 282,137 incident cancer cases determined the RRs for 20 cancer types associated with each five-point increment in BMI.[36] For example, in a man with a BMI of 28, the RR for colon cancer would be 1.24 compared with a man with a BMI of 23. Similarly, in a man with a BMI of 32, the RR for colon cancer would be 2.48 compared with a man with a BMI of 23. In a woman with a BMI of 28, the RR for colon cancer would be 1.09 compared with a woman with a BMI of 23. If that women had a BMI of 32, her RR for colon cancer would be 2.18 compared with a woman with a BMI of 23.

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study that followed more than 368,000 men and women who were cancer-free at for a mean of 6.1 years, a BMI ≥29.4 was significantly associated with the risk of colon cancer in men but not women.[37] Conversely, the RR for renal cell carcinoma associated with increased BMI in women was 2.25, but no significant increase was observed for men (RR, 1.22).[38] Therefore, these results indicate a progressive increment in RR by BMI that can differ by cancer type and gender.

Depression

A reciprocal association between obesity and major depressive disorder (MDD) has long been recognized, specifically that obesity increases the risk of MDD (and other psychiatric disorders) and conversely, the presence of MDD increases the risk of weight gain. For example, the National Epidemiologic Survey on Alcohol and Related Conditions evaluated the relationship between BMI and psychiatric disorders in 41,654 individuals.[39] Compared with normal weight subjects, BMI was significantly associated with mood, anxiety, and personality disorders. The odds ratio for a psychiatric disorder was 1.21- to 2.08-fold greater among individuals with class I/II obesity and individuals with class III obesity, respectively, and the OR for a lifetime prevalence of MDD was 1.53 and 2.02 among those with class I/II obesity and class III obesity, compared with normal weight subjects.

Another major survey of 217,379 US community-dwelling adults found that individuals with current

depression or a lifetime diagnosis of depression or anxiety were significantly more likely to have unhealthy behaviors including obesity, smoking, physical inactivity, binge drinking, and heavy drinking.[40] The adjusted OR for coincident depression and obesity (BMI ≥30) was 1.6 vs 1 for individuals without obesity, and the OR increased with increasing severity of MDD. In a study among 4641 middle-aged women, the prevalence of moderate or severe MDD increased from 6.5% with a BMI <25 to 25.9% with a BMI >35.[41] The OR for having MDD was 4.4 for a BMI of 30 to 35 and 4.95 for a BMI of ≥35.

A systematic review and meta-analysis of 15 studies (n = 58,745) found that obesity at baseline increased the risk of onset of depression at follow-up (OR 1.55; P <0.001).[42] This association was more pronounced for MDD than for depressive symptoms (P = 0.05). Overweight also increased the risk of onset of depression at follow-up (OR 1.27; P <0.01). Conversely, depression at baseline increased the odds for developing obesity (OR 1.58; P <0.001).

Anxiety

Anxiety is an important part of the association between obesity and mental health. A series of interviews, conducted internationally as part of the World Mental Health Surveys initiative, examined the association of mental disorders and obesity and the effect of demographics on this association. The study noted a significant relationship between BMI ≥30 or >35 and anxiety, with a pooled odds ratio of 1.2 for BMI ≥30 and 1.4 for BMI >35. This relationship was even stronger than that of obesity and depressive disorder, which showed a pooled odds ratio of 1.1 for BMI ≥30 and 1.3 for BMI >35. The relationship between obesity and anxiety disorder was significant for women and for respondents who have not completed secondary education, with pooled odds ratios of 1.3 and 1.2, respectively. Overall, the association between obesity and anxiety observed in the study was modest but significant.[43]

Gallbladder Disease

The prevalence of cholesterol gallstones is increased in persons with obesity, more commonly in women than in men.[44-46] The risk is especially high in those with the

highest BMI. The increased prevalence of stones is mostly due to supersaturation of bile with cholesterol because of an increased synthesis by the liver and secretion into bile.

The effects of overweight and obesity (BMI >30) on symptomatic gallstones were assessed in the 58,400 participants in a Swedish Twin Study. Overweight and obesity were both associated with a significant increase in the risk of symptomatic gallstones (OR = 1.86 and 3.38, respectively).[45] A separate analysis of the Health Professionals Follow-Up Study, a prospective cohort study in 29,847 US men, sought to determine whether abdominal obesity, as measured by abdominal circumference and/or waist-to-hip ratio, is a separate risk factor for symptomatic gallstones.[47] Men with waist circumference ≥102.6 cm (40.4 in) had a significantly greater risk (RR 2.29; P <0.001 for trend) for symptomatic gallstones compared with men with waist circumference <86.4 cm (34 in). Men with a waist-to-hip ratio ≥0.99 also had a significantly greater risk for symptomatic gall stones (RR 1.78; P <0.001 for trend) compared with men with a waist-to-hip ratio <0.89.

Gallbladder disease is a common cause of hospitalization, especially among women, and has a considerable impact on health care costs. A large epidemiologic study from England and Scotland found a significant association between obesity and symptomatic gall-bladder disease among 1.3 million women (mean age, 56 years).[46] Women with a higher BMI at study entry were more likely to be admitted and to spend more days in the hospital for symptomatic gallbladder disease. For each 1000 person-years of follow-up, women with BMI 18.5 to 24.9 spent a mean of 16.5 days hospitalized vs 44 days for women with BMI 30 to 39.9.

Weight loss also increases the risk of gallstones. The prevalence of new gallstones reaches 10% to 12% after 8 to 16 weeks of a low-calorie diet and more than 30% within 12 to 18 months after gastric by-pass surgery.[44,46,48] About one third of the stones are symptomatic. Risk factors for gallstones during weight loss are; a relative weight loss >24% of initial body weight, weight loss rate of >1.5 kg per week, a very low calorie diet with no fat, a long overnight fast period, and a high serum triglyceride level.

Non-alcoholic Fatty Liver Disease (NAFLD)

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of disorders that range from simple steatosis to nonalcoholic steatohepatitis (NASH) and, ultimately, cirrhosis and hepatocellular carcinoma.[49] Studies of NAFLD prevalence and incidence indicate that the diagnosis is heterogeneous and relies on a variety of assessment tools, including liver biopsy, radiological tests such as ultrasonography, and blood testing such as liver enzymes.[50] NAFLD affects ~15% to 30% of the general population, and has a prevalence of ~70% in people with T2D.[51]

Many studies have identified obesity as a risk factor for NAFLD. In an analysis of data from 832 Hispanic adults in which the diagnosis of NAFLD was based on ultrasound and no history of alcohol abuse or hepatitis C infection, a BMI >26.9 was significantly and independently associated with NAFLD with an odds ratio of 6.2.[52] In a cross-sectional study of 326 Israelis who participated in a National Health Survey, the prevalence of NAFLD was 30%; NAFLD was more common in men (38%) than in women (21%), and obesity (BMI ≥30) was independently associated with NAFLD (odds ratio 2.9).[53] A meta-analysis found that NAFLD has an increased overall mortality (OR 1.57) deriving from liver-related and CV disease, and a 2-fold risk of diabetes.[54]

Polycystic Ovarian Syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism and chronic oligo-anovulation. However, many features of metabolic syndrome are inconsistently present in the majority of women with PCOS.[55] Approximately 50% of women with PCOS have overweight or obesity and most of them have the abdominal obesity phenotype.[55] However, obesity is not a part of the PCOS phenotype in many parts of the world. Given the high prevalence of PCOS among relatively normal weight populations, obesity per se is likely not a direct cause of PCOS. However, obesity does exacerbate many aspects of the phenotype, especially CV risk factors such as glucose intolerance, insulin resistance, and dyslipidemia.[56] It is also associated with a poor response to infertility treatment and an increased risk for pregnancy complications in those women who do conceive.[57]

While many women with PCOS have overweight, obesity, or central obesity, the effect of excess weight on the outcomes of PCOS is inconsistent. A systematic review and meta-analysis of studies that enrolled a total of 15,129 women described the prevalence of overweight, obesity, and central obesity in women with and without PCOS.[58] Women who have overweight or obesity and concomitant PCOS had decreased sex hormone-binding globulin (SHBG), increased total testosterone, free androgen index, hirsutism, fasting glucose, fasting insulin, homeostatic model assessment-insulin resistance index, and worsened lipid profile. Obesity significantly worsened all metabolic and reproductive outcomes measured except for hirsutism compared with normal weight women with PCOS. In women with overweight there were no differences in total testosterone, hirsutism, total cholesterol, and low-density lipoprotein cholesterol compared with normal weight women and no differences in SHBG and total testosterone compared with women with obesity. Central obesity was associated with higher fasting insulin levels. The Australian Longitudinal Study on Women's Health was a community-based observational study that enrolled 9145 women aged 28-33 years.[59] Self-reported PCOS prevalence was 5.8%. Women reporting PCOS had higher weight, mean BMI (32.5), and greater 10-year weight gain (2.6 kg). BMI was the strongest correlate of PCOS status with every BMI increment increasing the risk of reporting PCOS by 9.2%.

The relationship between PCOS and obesity is a complicated one. Not all women who have PCOS also have obesity, and not all women with obesity have PCOS. Thus, it is not clear whether PCOS leads to weight gain, or if the excess weight contributes to developing PCOS.[58] Certainly, obesity is a common finding in PCOS and aggravates its metabolic features such as insulin resistance.

Chronic Renal Failure (CRF)

Although obesity has been implicated as a possible risk factor for microalbuminuria in individuals with hypertension and diabetes, general population studies suggest that obesity also may be harmful to the kidneys in individuals without hypertension, diabetes, or preexisting renal disease.[60] A nationwide, population-based,

case-control study in Sweden assessed the effect of body weight and the risk of moderately severe CRF. Eligible cases were men (n =597) and women (*n* = 329) whose serum creatinine levels, for the first time and permanently were ≥3.4 mg/dL (300 µmol/L) and 2.8 mg/dL (250 µmol/L), respectively.[60] Using the World Health Organization (WHO) cut points for BMI levels, there were significant 3-fold increases in both men and women with a BMI ≥35. Men and women who reported a BMI ≥25 at age 20 had a significant 3-fold elevated risk for CRF compared with patients with BMI <25. BMI at age 40 and at age 60 showed similar relationships with CRF risk as did highest lifetime BMI.

GERD

Gastroesophageal reflux disease (GERD) is a common condition that has been steadily increasing in prevalence, disproportionately so in the younger population.[61] According to several studies, obesity increases the risk of developing GERD and related erosive esophagitis by 1.5-2.0.[62] In a meta-analysis of 9 studies that examined association between GERD symptoms and obesity, data from 8 studies yielded a pooled adjusted odds ratios for GERD symptoms of 1.43 (95% CI, 1.158 to 1.774) for BMI of 25-30 and 1.94 (CI, 1.468 to 2.566) for BMI >35.[63] These findings suggests that the risk progressively increases with an increase in BMI.

Stress Urinary Incontinence (SUI)

Urinary incontinence is a condition that affects almost half of middle-aged women and has profound negative impacts on the quality of life.[64] Studies on the association of urinary incontinence and obesity suggest that for every 5 units of BMI increase, there is a 20% to 70% increase in the risk of daily urinary incontinence.[64] In women with obesity (BMI ≥ 40), the prevalence of incontinence was 60% to 70%, with pure stress incontinence accounting for 28%, pure urge incontinence for 4%, and mixed incontinence for 32%, suggesting a stronger association with stress-induced incontinence compared to urge incontinence or overactive bladder syndrome.[64] Another study identified maximal cough pressure as a possible mechanism for the relationship between obesity and stress urinary incontinence (SUI).

Maximal cough pressure was significantly associated with SUI for women with obesity (OR 3.191 [95% CI: 1.326-7.683], $P<0.01$), but not for women with normal weight or overweight. Further path model analyses demonstrated a significant relationship between BMI and SUI through maximal cough pressure (indirect effect, $P=0.038$), compared to other possible mechanisms.[65]

Infertility

Infertility affects one in seven couples, and there is a well-documented link between obesity and infertility in both men and women.[66] The risk of female infertility is three times higher in women with obesity than in women of normal weight, with fertility being impaired in both natural and assisted conception. Although there are several mechanisms by which obesity impacts fertility, studies have uncovered a strong association between obesity and anovulatory infertility.[67] Male fertility is also affected by high BMI. One meta-analysis revealed an inverse association between excess weight and sperm count. Men with overweight had significantly increased odds of having oligozoospermia (OR 1.11 [95% CI: 1.01-1.20]) or azoospermia (OR 1.39 [95% CI: 0.98-1.97) compared with normal-weight men. Men with obesity also had a higher risk of oligozoospermia (OR 1.42 [95% CI: 1.12-1.79]) or azoospermia (OR 1.81 [95% CI: 1.23-2.66]) compared with normal-weight men.[68]

Pregnancy Complications

As in every other demographic bracket (see *Chapter 1*), obesity is becoming increasingly prevalent in women of childbearing age. Maternal obesity, regardless of weight before the pregnancy, is an independent risk factor for complications in pregnancy.[69] In a systematic review of 22 reviews and meta-analyses, maternal obesity was found to be associated with gestational diabetes, pre-eclampsia, gestational hypertension, depression, and instrumental and caesarean birth.[70] Maternal obesity was also linked with adverse outcomes for the fetus, including preterm birth, large-for-gestational-age babies, fetal defects, congenital anomalies, and perinatal death.

Lower Limb Venous Disease (LLVD)

Lower limb venous disease affects up to 50% of the population worldwide,[71] and is thus commonly comorbid

with obesity. A number of epidemiologic studies have established obesity as a risk factor for LLVD, including varicose veins, chronic venous insufficiency, chronic venous ulceration, deep vein thrombosis, and venous thromboembolism.[71-74] Obesity is thought to contribute to LLVD via several mechanisms, including increased coagulation, venous stasis, and the transmission of intraabdominal pressure to the legs by femoral veins.[75]

Metabolic syndrome

Metabolic syndrome is a collection of metabolic conditions that increase the risk of cardiovascular disease, stroke, and T2D (see *Chapter 4* and *Chapter 6* for more information). The metabolic risk factors are all closely related to weight gain. Metabolic syndrome now affects 30–40% of people by age 65, and is largely driven by weight gain, specifically the increase in intra-abdominal fat accumulation.[76] A study analyzing the NHANES data from 2003-2004 to 2013-2014 revealed that cardiovascular risk factors, diabetes, and obesity were all increasing among US adults during the period.[77] While metabolic syndrome doubles the risk of CVD, the individual constituents of metabolic syndrome are reversible, and therefore can be treated by weight management.[76]

Metabolically Healthy Obesity?

Although obesity is typically accompanied by unfavorable metabolic profiles, it has been reported that this may not always be the case. The term "metabolically healthy obesity" (MHO) has been used to describe obesity that does not have the burden of any metabolic abnormalities. Although the definitions of and criteria for MHO vary considerably,[78] one study examined the MHO phenotype using NHANES, a nationally representative sample of adults living in the United States, and found a prevalence of 32% among adults with obesity over the age of 20.[79]

Several epidemiologic studies have shown that participants with MHO are not at increased risk of developing CV disease over 3 to 13 years of follow-up compared with healthy individuals without obesity[80-86] and are at lower risk compared with participants with non-MHO obesity.[87] However, there are inconsistencies in the data,

and other studies with an extended follow up period (>15 years) showed that participants with obesity but without metabolic syndrome at baseline were still at increased risk of major CV disease events compared with healthy participants without obesity.[88-90]

A systematic review and meta-analysis of eight studies (n = 61,386; 3988 events) that evaluated participants for all-cause mortality and/or CV events found that individuals with MHO had an increased risk (RR; 1.24) for events only when compared with metabolically healthy normal-weight individuals in studies with 10 or more years of follow-up were considered.[91] All metabolically unhealthy groups had a similarly elevated risk: normal weight (RR: 3.14), overweight (RR: 2.70), and obesity (RR: 2.65). The authors conclude that individuals with obesity have an increased risk for death and CV events over the long-term regardless of metabolic status, and that metabolically unhealthy overweight is also associated with these adverse outcomes.

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Benefits of Weight Loss

Introduction

There is a large and expanding body of evidence for the many benefits of intentional weight loss in individuals with overweight/obesity. While it is well known that there are significant improvements in patients both at risk for and who suffer from T2D, the benefits of weight loss extend beyond to include improvements in hypertension, dyslipidemia, metabolic syndrome, and OSA, as well as improvements in both mood and functional status.

To date, the largest body of data on the benefits of intentional weight loss has come from two long-term prospective, multicenter, randomized studies that compared the effects of intensive lifestyle intervention (ILI) to usual clinical care in two different populations. The Diabetes Prevention Program (DPP) was performed in individuals with overweight/obesity who were at high risk for T2D, while the participants in the Look AHEAD (Action for Health in Diabetes) study had previously been diagnosed with T2D.

DPP AND DPPOS

Objectives and Design

The DPP study was a multicenter, prospective, randomized clinical trial in 3234 adults in the United States who were at high risk for the development of T2D.[1] The primary objective was to assess whether an ILI or treatment with metformin could prevent or delay the onset of diabetes compared with standard lifestyle recommendations (eg, diabetes support and education [DSE]) in US adults at high risk for diabetes.

The primary outcome was development of T2D diagnosed on the basis of an annual oral glucose-tolerance test or a semiannual fasting plasma glucose test. Metformin treatment was initiated at a dose of 850 mg

once daily in one of the treatment groups, with placebo tablets also given once a day in the control group. At 1 month in the metformin group, the dose of metformin was increased to 850 mg twice daily.

The goals for the participants randomized to the ILI were to achieve and maintain a weight reduction of at least 7% of initial body weight through a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 minutes per week. A 16-lesson curriculum covering diet, exercise, and behavior modification was taught by case managers on a one-to-one basis during the first 24 weeks and continued on a flexible schedule thereafter. Masked treatment was discontinued when the DPP study demonstrated that ILI reduced the incidence of diabetes by 58% and metformin by 31% compared with the DSE control group during an average duration for all participants of 2.8 years in the DPP.

The long-term persistence of the results of the DPP study is being assessed in the ongoing Diabetes Prevention Program Outcomes Study (DPPOS).[2] All active DPP participants were eligible for continued follow-up, of whom 2766 (88%) enrolled for a median additional follow-up of 5.7 years. After this, there was a 13-month "bridge period" before implementation of the DPPOS protocol. During this bridge period, those in the metformin and DSE groups entered into a 1- to 2-week drug washout. After treatments were unmasked, the DSE intervention was stopped. All participants, including those in the original ILI group and those who had developed diabetes, were offered a group-administered version of the 16-session lifestyle curriculum followed by lifestyle sessions every 3 months, with provision of educational materials to reinforce the original weight loss and physical activity goals. All participants are followed in their original groups with their clinical care provided by practitioners outside of the study.

Prevention/Delay of Diabetes

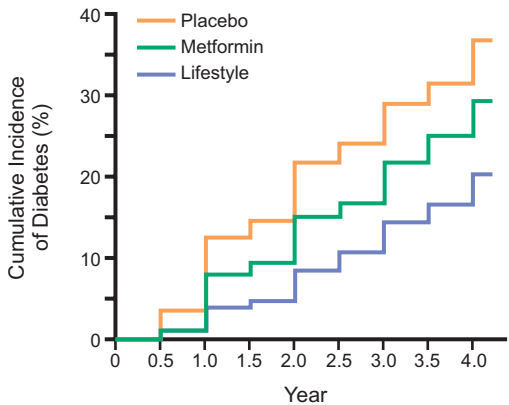
The primary objective of the DPP and DPPOS trials was to assess whether an ILI or treatment with metformin could prevent or delay the onset of diabetes compared with standard lifestyle recommendations. After

mean follow-up of 2.8 years, the cumulative incidence of diabetes was lower in the metformin and ILI groups than in the DSE group. The crude incidences of diabetes were 11.0, 7.8, and 4.8 cases per 100 person-years in the DSE, metformin, and ILI groups, respectively (**Figure 4.1**), and the estimated cumulative incidences of diabetes in the DSE, metformin, and ILI were 28.9%, 21.7 %, and 14.4%, respectively.[3]

These results translate into a risk reduction of 58% with ILI and by 31% with metformin compared with DSE. Given these results, the estimated numbers of persons who would need to be treated for 3 years to prevent one case of diabetes during this period were 6.9 with ILI and 13.9 with metformin. Of particular interest is that these reductions in the cumulative incidences of diabetes were accomplished with only moderate degrees of weight loss namely 0.1 kg, 2.1 kg, and 5.6 kg in the DSE, metformin, and ILI groups, respectively.

During a 10-year mean follow-up in the DPPOS study, the ILI group initially lost the most weight (mean of 7 kg by 1 year) but gradually regained it, although they still weighed about 2 kg less than they did at DPP

FIGURE 4.1 — DPP Study: Cumulative Incidence of Diabetes at 3 Years in Individuals with Overweight/ Obesity at High Risk for Diabetes



Modified from Knowler WC, et al; Diabetes Prevention Program Research Group. *N Engl J Med*. 2002;346(6):393-403.

randomization.[2] The metformin group lost a mean of 2.5 kg during DPP and maintained most of that weight loss. The mean weight loss in the DSE group was <1 kg from DPP randomization. The ILI group subsequently regained about 1 kg, whereas the metformin and DSE groups initially lost and then regained weight back to their respective levels at DPPOS baseline. Beyond 10 years following randomization, a slight weight loss trend emerged in all three groups. Fifteen years after randomization, patients from the placebo group had a mean weight loss of 2.32 kg, compared to 3.48 kg in the metformin group and 3.23 kg in the ILI group.[4]

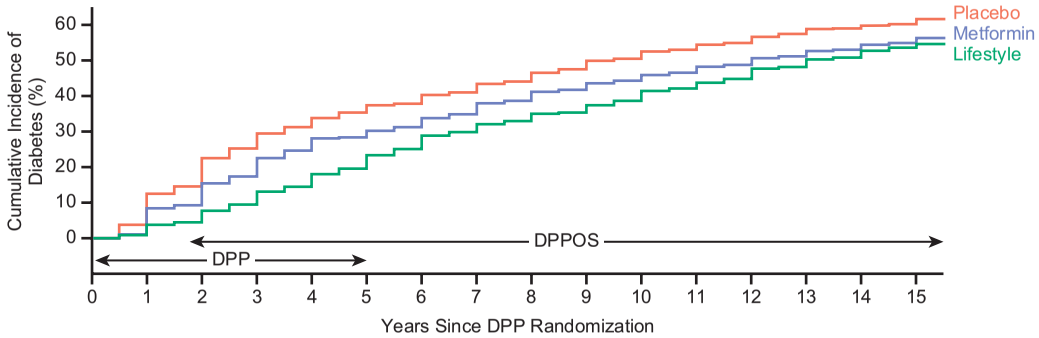
Diabetes incidence during DPPOS did not differ significantly between the three initial randomized groups. However, this finding was not attributable to a rebound effect in the ILI group but rather to a decrease in diabetes incidence in the placebo and metformin groups that resulted in similar rates as achieved by lifestyle intervention, which changed little throughout 10 years of follow-up (**Table 4.1**). Therefore, 10 years after DPP randomization, the cumulative incidence of diabetes remained lower in the ILI and metformin groups than in the DSE group, despite changes in treatments after a mean of 3.2 years. Fifteen years after randomization, the cumulative incidence of diabetes was 28% lower in the ILI group and 18% lower in the metformin group, compared to the placebo ($P<0.0001$ and $P = 0.001$, respectively).[4] The cumulative incidence of diabetes during DPP and DPPOS is shown in **Figure 4.2**.

TABLE 4.1 — Incidence (Cases per 100 Person-Years) of Diabetes During DPP, Bridge Period, and DPPOS

Period	ILI Group	Metformin Group	DSE Group
DPP	4.8	7.8	11.0
End of masked treatment	5.0	7.7	10.8
Bridge period	5.5	10.6	7.8
DPPOS	5.9	4.9	5.6
Combined incidence	5.3	6.4	7.8

Diabetes Prevention Program Research Group, et al. *Lancet*. 2009; 374(9702):1677-1686.

FIGURE 4.2 — DPPOS Study: Cumulative Incidence of Diabetes at Over 15 Years Since Randomization in the DPP Study of Individuals with Overweight/Obesity at High Risk for Diabetes



N at risk																
Placebo	935	900	799	699	640	595	562	522	485	445	416	387	364	339	317	255
Metformin	926	918	841	766	692	647	611	575	529	499	465	441	420	393	370	289
Lifestyle	915	908	876	829	782	730	671	617	582	550	509	475	443	400	372	285

Diabetes Prevention Program Research Group, et al. *Lancet Diabetes Endocrinol.* 2015;3(11):866-875.

Reduction in Cardiovascular Risk Factors

In the original DPP cohort, 30% had hypertension, 29% had hypertriglyceridemia, and 44% had hypercholesterolemia at baseline. Annual assessments showed progressive increases in the prevalence of hypertension and dyslipidemia in the DSE and metformin groups compared with a decrease in the ILI group by year 3.[5] Triglyceride levels fell in all treatment groups but fell significantly more with ILI. Total cholesterol and LDL cholesterol levels were similar among treatment groups. ILI significantly increased the HDL cholesterol level compared with the other interventions. After 3 years of follow-up, the use of medications to achieve preestablished treatment goals in the ILI group was reduced (by 27% to 28% for antihypertensive agents and 25% for lipid-lowering medications) compared with DSE and metformin groups.

The DPPOS study is providing additional follow-up of the randomized DPP study population, thereby allowing an assessment of the durability of the beneficial effect of ILI and DSE interventions and metformin treatment on CV risk factors. After unmasking of treatment and a brief bridge period, all groups received a lifestyle intervention. Also, metformin was continued (unless terminated by the care provider) in participants who were in the original metformin arm.[6] After 10 years of follow-up from the DPP baseline, there were reductions in SBP (-2 to -3 mm Hg) and DBP (-6 to -6.5 mm Hg), as well as in LDL cholesterol (-0.51 to -0.6 mmol/L) and triglycerides (-0.23 to -0.25 mmol/L) in all groups, with no between-group differences (**Figure 4.3**). In addition, HDL cholesterol levels rose significantly (0.14 to 0.15 mmol/L) in all groups. Analysis of medication use found reductions in the overall use of lipid-lowering ($P = 0.01$) and antihypertensive ($P = 0.09$) medications throughout the follow-up period, however, their use was lower in the original ILI group during DPPOS. At 15-years of follow-up, there was no difference between the three treatment groups as a whole in the prevalence of the aggregate microvascular outcome (nephropathy, neuropathy, and retinopathy; 11-13%). Interestingly, among women, ILI did result in a lower prevalence of the aggregate microvas-

cular outcome (8.7%) than either metformin treatment (11.2%; $P = 0.02$) or placebo (11%; $P = 0.03$), but the mechanistic basis of this difference is not understood.[4]

Incidence and Resolution of Metabolic Syndrome

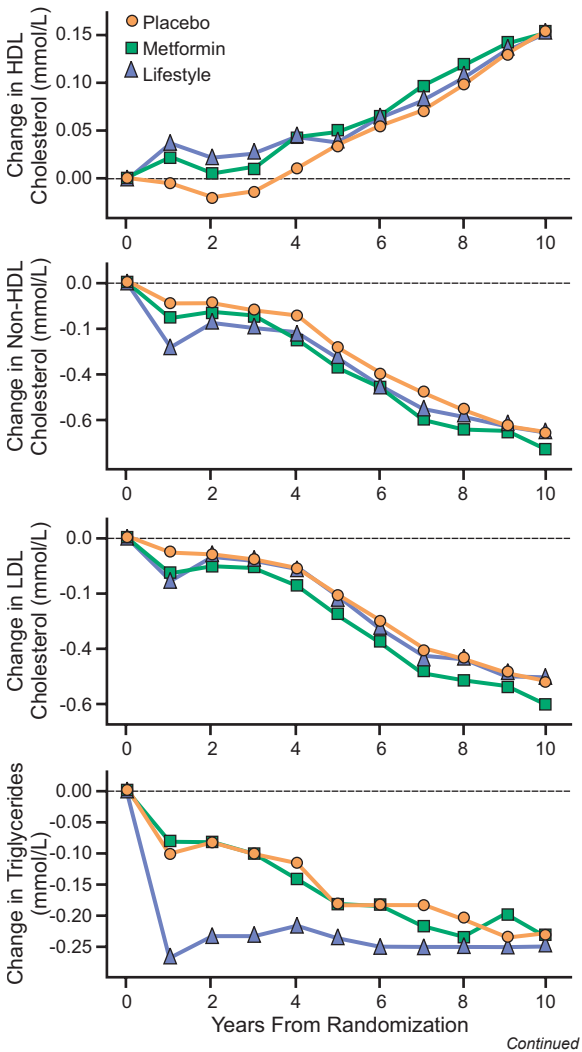
The metabolic syndrome is "a complex cluster of interrelated risk factors for CV disease and diabetes which occur together more often than by chance alone."[8] Three abnormal findings out of the five listed in **Table 4.2** would support a diagnosis of metabolic syndrome. The presence of the metabolic syndrome is a clinically useful indicator of high morbidity and mortality risk. Patients with the metabolic syndrome are at twice the risk of developing CVD over the subsequent 5 to 10 years as those without the syndrome. In addition, the metabolic syndrome confers a 5-fold increase in the risk of developing T2D.[8]

At baseline in the DPP study, 53% of randomized patents had the metabolic syndrome defined as having three or more characteristics (increased waist circumference; elevated BP; low HDL, elevated triglycerides, and elevated fasting plasma glucose) that met criteria from the National Cholesterol Education Program Adult Treatment Panel III.[9]

By year 3, the prevalence of metabolic syndrome among all study participants increased from 55% at baseline to 61% after 3 years in the DES group ($P = 0.003$) and from 54% to 55% in the metformin group ($P > 0.2$). In the ILI group, overall prevalence decreased from 51% to 43% ($P < 0.001$). Among individuals without metabolic syndrome at baseline, 53% of those in the DSE group had acquired the metabolic syndrome by year 3 compared with 47% in the metformin group and 38% in the ILI group. Thus, the ILI results in reduction of 41% in incidence of the metabolic syndrome compared with DSE and a significant 29% reduction compared with metformin ($P < 0.001$), which itself yielded a 17% lower incidence than DSE ($P = 0.03$).

Among the individuals with the metabolic syndrome at baseline, the differences by treatment group were less striking; however, the prevalence at 3 years did vary significantly by treatment group ($P < 0.001$): 18% of the DSE group, 23% of the metformin group, and 38% of the ILI group no longer had the syndrome.

FIGURE 4.3 — DPPOS Study: Changes From DPP Baseline in CVD Risk Factors During10 Years of Follow-Up



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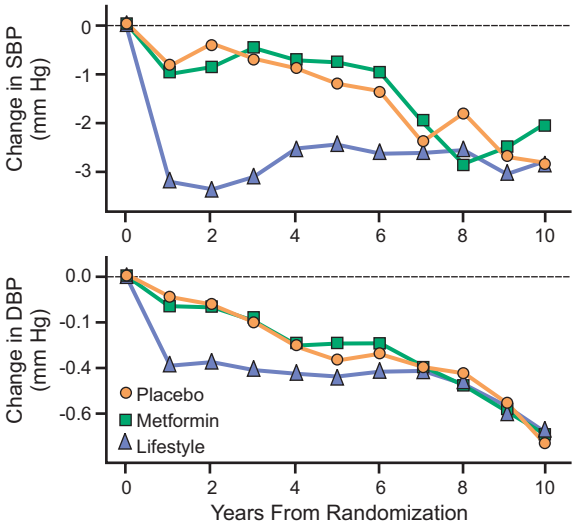


Diabetes Prevention Program Outcomes Study Research Group, et al. *Diabet Med*. 2013;30(1):46-55.

TABLE 4.2 — Risk Factors of Metabolic Syndrome

Trait	Categorical Cut Point
Elevated waist circumference	≥35 inch (female); ≥45 inch (male) (Note: population-/country-specific definitions)
Elevated triglycerides (or drug treatment ↑ triglycerides)	≥150 mg/dL
Reduced HDL-C (or drug treatment ↓ HDL-C)	<40 mg/dL (male); <50 mg/dL (female)
Elevated BP (or hypertension history or drug therapy)	SBP ≥130 mm Hg and/or DBP ≥85 mm Hg
Elevated fasting glucose (or drug therapy for hyperglycemia)	≥100 mg/dL

Three abnormal findings out of the five listed above would support a diagnosis of metabolic syndrome.

Modified from Alberti KG, et al. *Circulation*. 2009;120(16):1640-1645.

Look AHEAD

Objectives and Design

The Look AHEAD study was a prospective, multicenter, randomized, controlled trial designed to determine whether intentional weight loss reduces CV morbidity and mortality in individuals with overweight and T2D.[10] The primary objective was to assess the long-term effects (up to 11.5 years) of an intensive weight loss program delivered over 4 years in individuals with overweight or obesity and T2D. The primary study outcome was time to incidence of a major CV event. Other outcomes included components of CVD risk, cost and cost-effectiveness, diabetes control and complications, hospitalizations, intervention processes, and quality of life.

Participants were randomly assigned to one of two intervention groups: an ILI designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity, or to enhanced usual care (ie, DSE).[11] The two principal goals of the ILIs were to induce a mean loss ≥7% of initial weight and to increase participants' moderately-intense physical activity to ≥175 minutes a week. A total of 5145 US individuals with overweight/obesity and with T2D were randomized to ILIs (n = 2570) or DSE (n = 2575). Overall, 59% of the participants were women; 37% were from racial or ethnic minorities; 14% reported a history of CVD at baseline, their average age was 58.7, and their average BMI was 36.

Reduction in Cardiovascular Events and Risk Factors

Although Look AHEAD did not achieve its primary efficacy outcome, ie, improvement in the time to incidence of a major CV event, it did demonstrate benefits in components of CVD risk.

After 1 year, patients in the ILI group lost an average 8.6% of their initial weight compared with 0.7% in the DSE group (P <0.001).[12] Fitness, assessed by submaximal exercise test to determine ≥80% of age-predicted maximal heart rate, increased by 20.9% in the ILI group compared with 5.8% in the DSE group (P <0.001). A greater proportion of ILI patients experienced reductions in the incidence of diabetes, hypertension, and the use of lipid-lowering drugs. Mean A1C decreased from 7.3% to 6.6% with ILI (P <0.001) vs from 7.3% to 7.2% with DES. In

addition, there were significantly greater improvements in SBP and DBP, triglycerides, and HDL cholesterol among ILI-treated patients than among DSE-treated patients (all $P < 0.01$).

Averaged over 4 years, patients in the ILI group had significantly greater improvements in weight, fitness, glycemic control, SBP, and levels of HDL cholesterol and triglycerides than those in the DSE group (**Table 4.3**). There was no significant difference in DBP. Although the DSE group experienced greater overall reductions in LDL cholesterol levels, changes in LDL cholesterol levels did not differ between the groups after adjusting for use of lipid-lowering medications.[13]

Changes in weight and risk factors at each of the 4 years are shown in **Figure 4.4**. The ILI group experienced significantly greater weight losses than the DSE group at each year. The maximal weight loss (8.6%) in the ILI group occurred at year 1 and the mean weight loss by year 4 was 4.7% compared with 1.1% in the DSE group ($P < 0.001$). For several risk factors, the between group differences were most apparent at year 1. At each of the 4 years, the ILI group continued to have greater improvements in SBP and in A1C and HDL cholesterol levels. Among patients who were using antihypertensive to antihyperglycemic medications at baseline, a greater proportion of patients in the ILI group than the DSE group discontinued use of these medications.

Conversely, among those not using these medications at baseline, fewer patients in the ILI group initiated the use of these agents. However, the percentage of patients using lipid-lowering medications almost doubled during the 4 years, with greater initiation in the DSE than in the ILI group. The ADA goals for A1C and BP were met by a significantly greater proportion of patients in the ILI group compared with the DSE group at years 1, 2, and 3. The percentage of patients achieving the ADA goals for LDL cholesterol level did not differ until year 4, when 64.5% of DSE patients compared with 61.0% of ILI patients ($P = 0.01$) met this goal.

Remission of Diabetes

An ancillary analysis of the 4-year Look AHEAD study results examined the association of long-term ILI

TABLE 4.3 — Look AHEAD Study: Mean Changes in Weight, Fitness, and CVD Risk Factors in ILI and DSE Groups and the Difference Between Groups Averaged Across 4 Years

	Mean Changes Over 4 Years			
Measure	**DSE Group**	**ILI Group**	**Difference (ILI-DSE)**	***P* Value**
Weight (% initial)	-0.88	-6.15	-5.27	<0.0001
Fitness (% METS)	+1.96	+12.74	+10.78	<0.0001
A1C	-0.09	-0.36	-0.27	<0.0001
SBP (mm Hg)	-2.97	-5.33	-2.36	<0.0001
DBP (mm Hg)	-2.48	-2.92	-0.43	0.012
HDL cholesterol (mg/dL)	+1.97	+3.67	+1.70	<0.0001
Triglycerides (mg/dL)	-19.75	-25.56	-5.81	0.0006
LDL cholesterol (mg/dL)	-12.84	-11.27	+1.57	0.009
LDL cholesterol (mg/dL)[a]	-9.22	-8.74	+0.47	0.42

[a] Adjusted for medication use.

Look AHEAD Research Group, Wing RR. *Arch Intern Med*. 2010;170(17):1566-1575.

with the frequency of remissions from T2D defined as transition from meeting diabetes criteria to a prediabetes or nondiabetic level of glycemia (fasting plasma glucose <126 mg/dL and A1C <6.5% with no antihyperglycemic medication).[14]

The results showed that the ILI group was significantly more likely to experience a partial or complete remission with prevalences of 11.5% during the first year and 7.3% at year 4 compared with 2.0% for the DSE group at both time points (P <0.001 for each) (**Figure 4.5**). In the ILI group, 9.2%, 6.4%, and 3.5% of participants experienced continuous, sustained remission for at least 2, at least 3, and 4 years, respectively, compared with <2% of patients in the DSE group at the same time points.

Although the prevalence of complete remission was more common in the ILI group than in the DSE group across all years of the study (prevalence ratio, 6.6; P <0.001), the absolute prevalence of complete remission was low, ranging from 1.3% with or ILI vs 0.1% with DSE (P <0.001) in year 1 to 0.7% with ILI vs 0.2% with DSE at year 4.

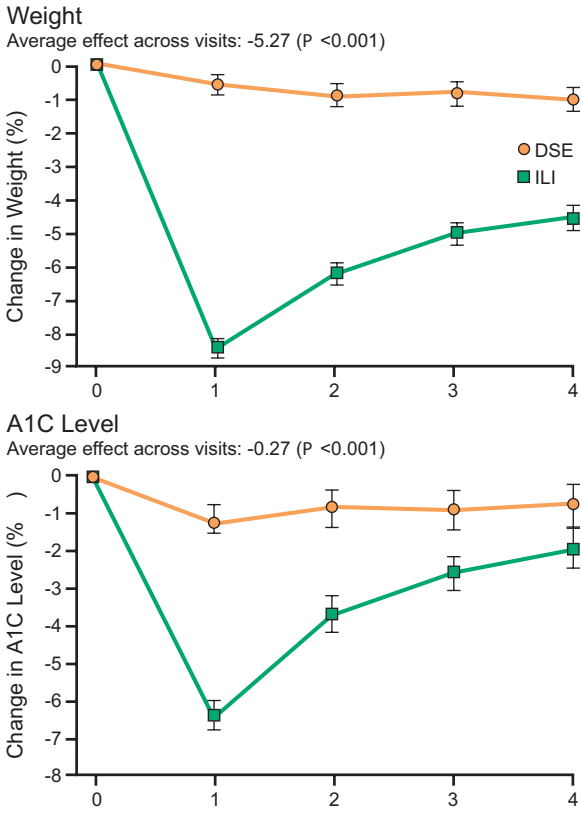
Magnitude of Weight Loss and Clinical Benefits

Individuals with overweight and obesity are frequently encouraged to lose 5% to 10% of their weight and are told that weight losses of that magnitude will help improve their CVD risk factors. The Look AHEAD study provided the opportunity to assess the effects of various magnitudes of weight loss on improvements in CVD risk factors.

An observational analysis of data from the Look AHEAD study examined the association between the magnitude of weight loss and changes in CVD risk factors at 1 year and the odds of meeting predefined criteria for clinically significant improvements in risk factors in individuals with T2D.[15]

After 1 year, patients were divided into the following categories based on their weight changes from baseline to 1 year: gained >2%; remained weight stable (±2%); lost ≥2% to 5%; lost ≥5% to 10%; lost ≥10% to 15%; or lost ≥15%. There was a strong graded association for changes in glucose, A1C, SBP, DBP, triglycerides, and HDL cholesterol (all P values <0.0001) (**Figure 4.6**). Each higher increment of weight loss was associated with greater

FIGURE 4.4 — Look AHEAD Study: Changes in Weight and CVD Risk Factors During 4 Years in Patients in the ILI and DSE Groups



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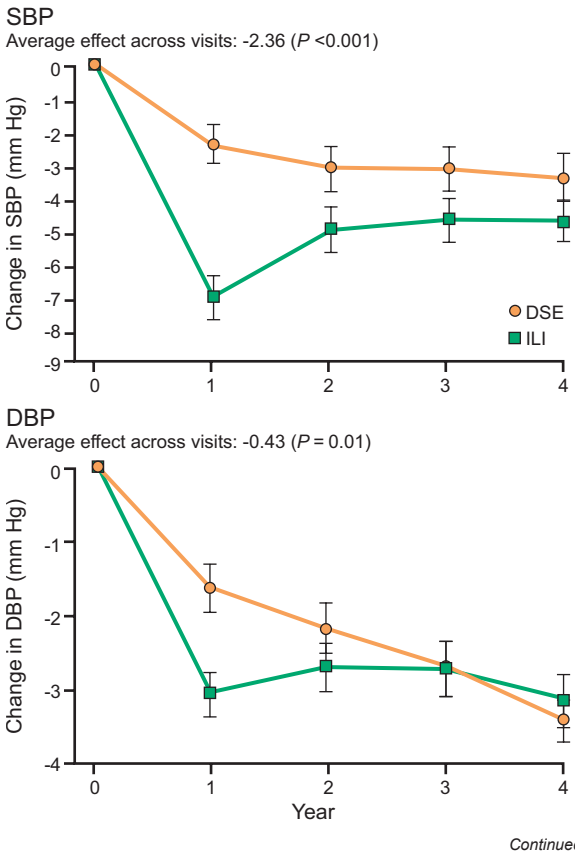

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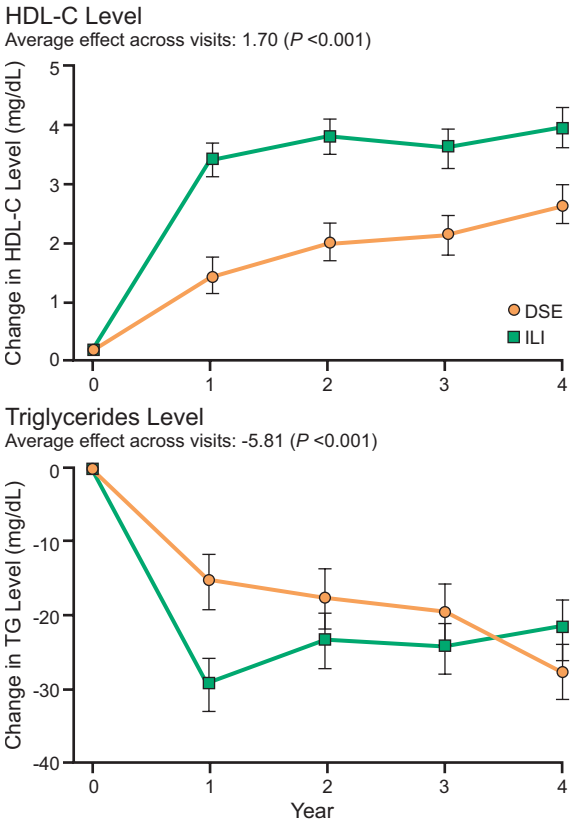

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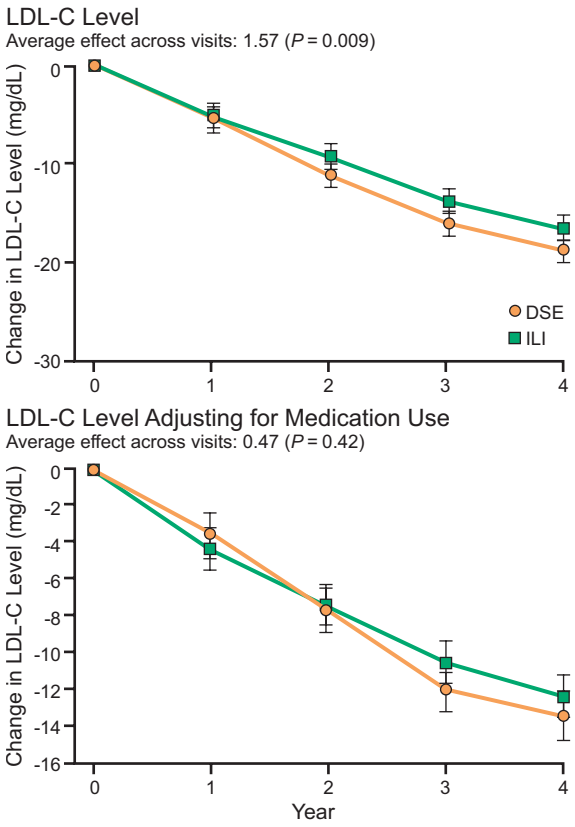
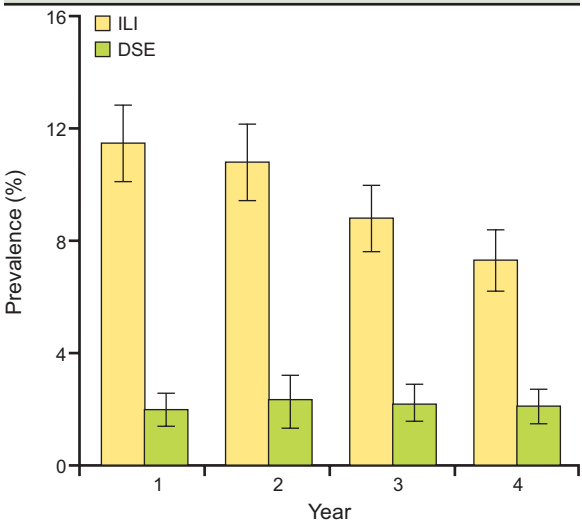


Look AHEAD Research Group, Wing RR. *Arch Intern Med*. 2010; 170(17):1566-1575.

FIGURE 4.5 — Look AHEAD Study: Prevalence of Any Remission (Partial or Complete) by Intervention Condition and Year in Patients with Overweight/Obesity and T2D



Gregg EW, et al. *JAMA*. 2012;308(23):2489-2496.

improvements in the risk factor. In contrast, the magnitude of improvement in LDL cholesterol did not differ across the weight categories. Furthermore, the odds of having a clinically meaningful improvement in risk were strongly related to the magnitude of weight loss achieved such that the odds of a clinically meaningful improvement also increased with each weight loss increment.

Individuals who lost 2% to 5% of their body weight had increased odds of having significant improvements in SBP (OR 1.24), glucose (OR 1.75), A1C (OR 1.80), and triglycerides (OR 1.46), while those who lost 5% to <10% of their body weight had increased odds of significant improvement in all risk factors. These results support for the assertion that modest weight losses of 5% to 10% (and even 2% to 5%) of initial weight are sufficient to produce significant, clinically relevant improvements in CVD risk factors in patients with overweight or obesity and T2D.[15]

Weight Loss in Patients with Class III Obesity

There has been a long-held belief that dietary and lifestyle interventions are less effective in individuals with class III obesity than in those with less excessive body weight. A substudy from the Look AHEAD trial compared the effect of ILI on weight loss and CVD risk in patients with T2D who had class III obesity (BMI ≥40) to those who had overweight (BMI 25 to <30), class I obesity (BMI 30 to <35), and class II obesity (BMI 35 to <40).[16] At 1 year, the weight loss in patients with class III obesity in the ILI group was -9.04% of initial body weight, which was significantly greater (P <0.05) than patients with overweight (-7.43%) and comparable to those with class I (-8.72%) or class II obesity (-8.64%).

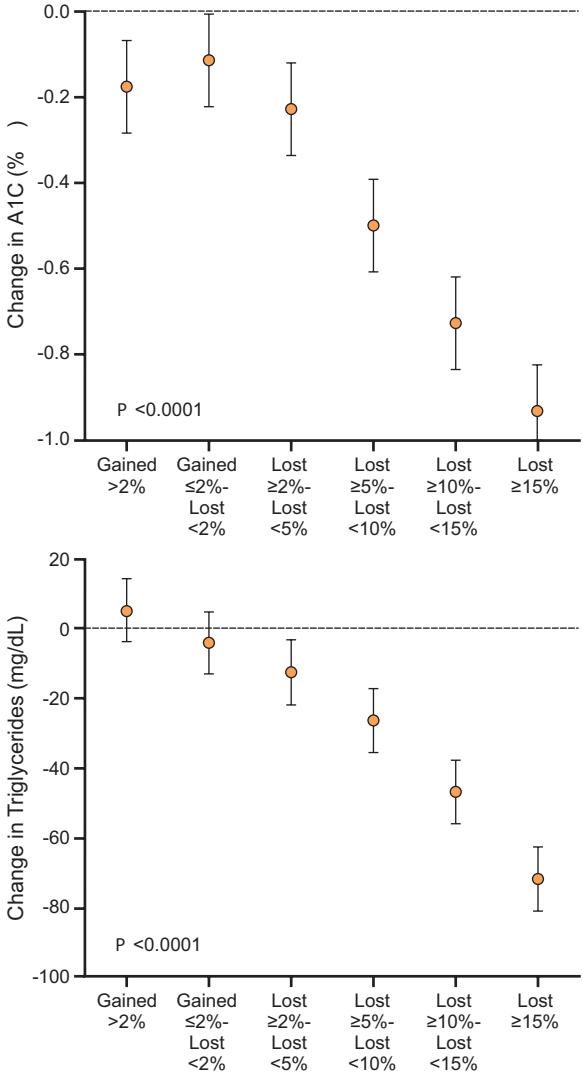
There also were comparable improvements in fitness, physical activity, LDL cholesterol, triglycerides, BP, fasting glucose, and A1C at 1 year across all BMI groups. Finally, treatment adherence (eg, treatment session attendance) among individuals with class III obesity was excellent and did not differ among weight categories (patients with class III obesity 80% vs others 83%; P = 0.43). These results demonstrate that dietary and lifestyle interventions can be considered in individuals with class III obesity.

Depression

Some evidence suggests there are bidirectional associations among depression, obesity, and diabetes.[17-19] Since the Look AHEAD study population consisted of individuals with overweight/obesity and T2D, a separate analysis of the Look AHEAD cohort was performed to determine whether moderate weight loss would be associated with incident symptoms of depression and suicidal ideation, and whether symptoms of depression at baseline would limit weight loss at 1 year.[20] Virtually all (n = 5129) trial participants completed the Beck Depression Inventory (BDI) and had their weight measured at baseline and 1 year. A BDI score of ≥10 indicated potentially significant symptoms of depression.

During this 1-year study, there was a significantly lower number of incident cases of symptoms of depression in the ILI group at 1 year than in the DSE group (6.3% vs 9.6%; P <0.001), which remained significant

FIGURE 4.6 — Effect of Modest Weight Loss on Glycemic and CVD Risk Factors in Patients with Overweight/Obesity and T2D



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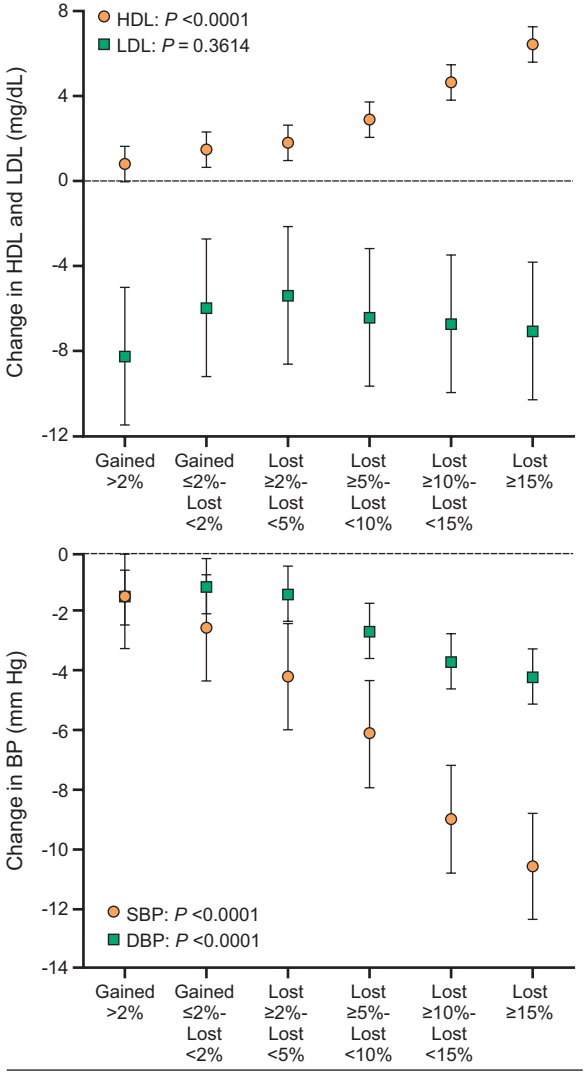


Wing RR, et al; Look AHEAD Research Group. *Diabetes Care*. 2011;34(7):1481-1486.

after controlling for use of antidepressant medications. The overall change from baseline weight at 1 year (regardless of a depression status) was -8.6% in the ILI group and -0.7% in the DSE group (P <0.001) (**Figure 4.7**). ILI group participants who reported mild or symptoms of depression at baseline showed a decrease of 5.3 points on the BDI at 1 year compared with a decrease of 0.6 points in those individuals reporting no symptoms of depression. In the DSE group, there was a decrease of 3.7 points among individuals with symptoms of depression at baseline compared with an increase of 0.2 points in participants without depressive symptoms at baseline.[20]

Although participants in both intervention groups with mild or greater symptoms of depression at baseline lost significantly less weight than individuals with no symptoms of depression (4.3% vs 4.8%), this difference cannot be considered as clinically meaningful. Similarly, the difference in weight loss between participants with and without symptoms of depression in the ILI group (7.8% vs 8.7%) is not clinically meaningful. According to the authors, these findings indicate that individuals with overweight/obesity and T2D individuals with mild or greater symptoms of depression are able to achieve similar degrees of weight loss as people with overweight/obesity without T2D.

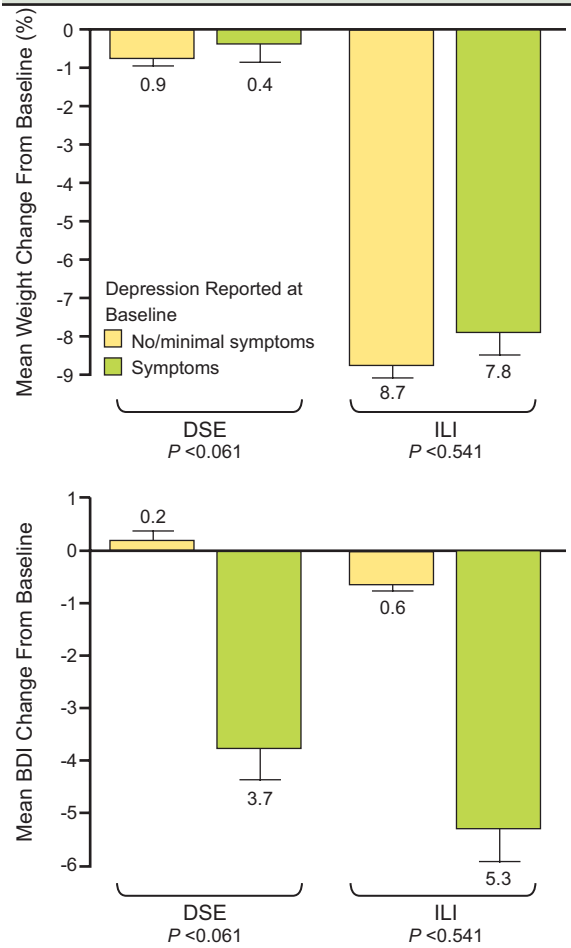
Obstructive Sleep Apnea

OSA is strongly associated with obesity and untreated OSA is associated with significant CVD morbidity and mortality, debilitating daytime symptoms, and increased risk of work and motor vehicle accidents.[21]

The Sleep AHEAD ancillary study of Look AHEAD assessed the prevalence of OSA among 305 individuals with overweight/obesity and T2D.[22] Almost all (86.6%) of these individuals had OSA of various levels of severity. The mean AHI was 20.5; 33.4% had mild OSA, 30.5% moderate OSA, and 22.6% severe OSA. Independent of other variables, a 1-cm increase in waist circumference was associated with a 10% increase in the predicted odds of the presence of OSA (AHI ≥5). In participants with AHI ≥5, BMI was the only significant predictor of severe OSA.

A total of 264 of the above individuals were assigned to either ILI or DSE intervention. Their mean baseline

FIGURE 4.7 — Look AHEAD Study: Changes in BDI Scores and Percent Weight Loss During 1 Year by Intervention and Baseline Depression Status



Faulconbridge LF, et al; Look AHEAD Research Group. *Obesity (Silver Spring)*. 2012;20(4):783-793.

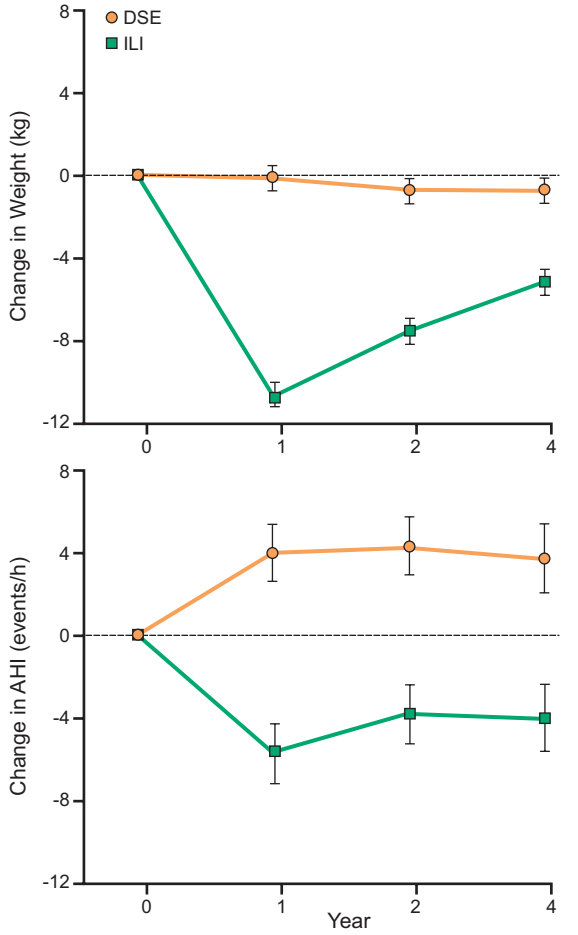
weight was 102.4 kg, their mean BMI was of 36.7, and their mean AHI was 23.2 (16.5 events/hour). At 1 year, more than three times as many patients in the ILI group than in the DSE group had total remission of their OSA, and the prevalence of severe OSA among ILI participants was half that of the DSE group.

Subsequently, these patients were followed to assess whether the initial benefit of weight loss on OSA severity at 1 year is maintained at 4 years.[23] Mean weight loss in the ILI group was 10.7, 7.4, and 5.2 kg at 1, 2, and 4 years, respectively, compared with a <1-kg weight loss in the DSE group at each time (P <0.001). The between-group differences in AHI were 9.7, 8.0, and 7.7 events/hour at 1, 2, and 4 years respectively (P <0.001) (**Figure 4.8**). Remission of OSA at 4 years was five times more common with the ILI (20.7%) than DSE (3.6%). Furthermore, these beneficial effects on the AHI group at 1 year persisted at 4 years, despite an almost 50% weight regain. However, it is important to note that while weight loss of 5% to 10% can result in significant benefits in many comorbidities, an ~10 kg average weight loss may be required to achieve a significant decrease in the AHI index.

There is considerable evidence that bariatric surgery has a beneficial effect on the risk of diabetes, blood pressure, dyslipidemia, and mortality in individuals with class III obesity (see *Chapter 10*). Bariatric surgery also has been shown to result in significant weight loss and risk factor reduction in individuals with class III obesity. A few studies have compared the effect of surgical and conservative weight loss strategies on OSA.

One 1-year study treated 133 subjects (mean BMI of 45.1, mean AHI 17.1), 63% of whom had OSA, with either a 1-year ILI-program (n = 59) or Roux-en-Y gastric bypass (RYGB) (n = 74) and repeated polysomnography.[24] The average weight loss was 8% in the ILI-group and 30% in the RYGB-group (P <0.001). Mean AHI scores decreased in both treatment groups, although significantly more in the RYGB-group than in the ILI group (-13.1 vs -6.0, respectively). Twenty-nine RYGB-patients (66%) had remission of OSA compared with 16 ILI-patients (40%). However, after further adjustment for BMI change, the treatment group difference was no

FIGURE 4.8 — Long-Term Effect of Weight Loss on Obstructive Sleep Apnea Severity in Patients With Obesity and T2D



Kuna ST, et al; Sleep AHEAD Research Group of the Look AHEAD Research Group. *Sleep*. 2013;36(5):641-649.

longer statistically significant ($P = 0.709$). As a result, the authors concluded that while the study demonstrated that RYGB was more effective than ILI at reducing the prevalence and severity of OSA, further analysis also suggests that weight loss, rather than the surgical procedure per se, explains the beneficial effects.[24]

Look AHEAD-E

The Look AHEAD study received a 5-year extension in 2016 called Look AHEAD-Extension or Look AHEAD-E, with the aim of assessing the effects of lifestyle changes on healthy aging in older adults with T2D (including, among others, increased lifespan and lower healthcare costs).[25] No data from Look AHEAD-E have been published to date.

ADAPT

Osteoarthritis

Obesity has been identified as an independent modifiable risk factor for the development of OA, particularly in knees.[26,27] Several studies have demonstrated the benefits of weight loss in individuals with overweight/obesity and OA of the knee.

The 18-month, randomized, single-blind Arthritis, Diet, and Activity Promotion Trial (ADAPT) in 316 community-dwelling adults (ages 60 years and older) with overweight and obesity (BMI >28), and with knee pain, radiographic evidence of knee OA, and self-reported physical disability assessed whether long-term exercise and dietary weight loss are more effective, either separately or in combination, than usual care in improving physical function, pain, and mobility.[28] The primary outcome measure was self-reported physical function as measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Secondary outcomes included weight loss, 6-minute walk distance, stair-climb time, WOMAC pain and stiffness scores, and joint space width.

Both weight loss intervention groups (diet only, diet plus exercise) lost significantly ($P < 0.05$) more weight compared with the healthy lifestyle group. Individuals in the diet-only group lost an average of 4.9% of their body

weight and those in the diet plus exercise group lost 5.7% of their body weight. Mean weight losses in the exercise-only and healthy lifestyle groups were 3.7% and 1.2%, respectively. After 18 months, WOMAC physical function revealed that individuals in the diet plus exercise group significantly improved their physical function (P <0.05) relative to the healthy lifestyle control group. There were no significant differences between the exercise-only or diet-only groups and the healthy lifestyle group.

Summary

Data from both the DPP and LOOK AHEAD trials clearly demonstrate that modest weight loss can have significant improvements on obesity-related comorbidities. Modest weight loss can reduce the incidence of diabetes by up to 58% and provide remission rates of up to 11% for those undergoing intensive lifestyle treatment. In addition, patients can achieve improvements in LDL, HDL, SBP as well as reduce the incidence of metabolic syndrome by 41%. Other obesity-related complications, including OSA, depression, and declining functional status may also be improved. Furthermore, this benefit is not limited to patients who have mild/moderate obesity but is actually achieved in those with class III obesity (BMI >40) and therefore all patients should be considered for treatment.

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Approach to Patients With Obesity

Introduction

The clinical management of obesity can be challenging in primary care. Clinicians are often busy and feel ill-equipped to address the disease and may therefore be unable to treat it. However, given that more than 70% of the adult US population has either overweight or obesity (see *Chapter* 1) and the majority suffer from at least one or more weight-related comorbidity, it is a disease that primary care physicians (PCPs) and other practitioners must address.

The treatment of obesity is based on both the clinical and laboratory assessment of each patient. Combining this information can provide an assessment of the severity of the obesity, determine the associated risks, and guide an appropriate and individualized treatment approach.

Weight-Specific History

A medical evaluation must include specific questions about the person's weight and lifestyle in order to develop an individualized treatment plan.

- Review of the patients' current weight as well as his/her highest adult weight and lowest weight.
- Review of any specific periods of weight gain. Patients will often be able to pinpoint life events (marriage, child birth, new job, relocation, a death in the family) which may have been associated with significant lifestyle changes and or psychosocial stressors which triggered weight gain. In addition, determining whether the weight gain began in childhood can help determine whether the patient needs an evaluation for secondary causes of obesity.
- What type of diets has the patient tried in the past? How many times has the patient attempted weight

loss and did it work? It is important to understand what works well for the patient and to determine if the patient's weight cycles. By examining a weight-cycling history, the clinician can try to understand the previous challenges faced both in losing the weight but more importantly, with maintaining weight loss. Once this is discussed, the clinician can help determine what approach might work best for each patient.

- Review the patient's current dietary habits including general habits (do they skip breakfast or eat one large meal per day?), review frequency of eating out vs home meal preparation and determine who does the usual grocery shopping (to help determine whether patients have a perceived lack of control over their own intake).
- Review related psychiatric history, including anxiety or depression, which may translate into disordered eating habits. Determine whether the patient may suffer from binge eating or other maladaptive eating patterns (binge-purge, night-eating) as these may require further referral to a mental health specialist. Often patients may be ashamed of some of their behaviors but it is imperative to assess these in order to tailor the treatment plan and identify barriers to success.
- Evaluate the patient's physical lifestyle. It is important to determine whether the patient has a sedentary lifestyle, whether he/she exercises, and how you may be able to improve his/her physical activity and incorporate it into his/her daily life (eg, you may be able to encourage the patient to walk where the patient would have otherwise driven, encourage the patient to use the stairs vs elevator, etc). It is important to uncover whether there are barriers in the patient's ability to perform activities (eg, osteoarthritis [OA] of the knees) and help address these issues as part of the treatment plan.
- Diet recall—it is important to fully understand the patient's daily food choices and portions. There are a number of tools including a 24-hour diet recall, food frequency questionnaire and/or food journal which

can help make a basic assessment. It is also important to note frequency and quantity of both liquid/caloric drinks as well as alcohol intake.

Review of Weight-Promoting Medications

Certain medications can cause weight gain and increase body fat, thereby making weight loss more difficult. **Table 5.1** provides a partial list of drugs and drug classes that contain medications associated with weight gain; see *Chapter 7* for more information. These drugs differ in their propensity to increase body weight. The mechanism responsible for medication-induced weight gain has not been carefully studied for most of these agents, but must be related to an increase in energy intake (eg, antipsychotics and steroid hormones), a decrease in energy expenditure (eg, β-adrenergic receptor blockers), a decrease in energy loss (eg, decreased glycosuria from diabetes therapy), or a combination of these factors.[1] Weight-loss therapy can be facilitated by decreasing the dose or substituting the medication with another drug that has less weight gain potential, if possible.

Diagnosing Overweight and Obesity

The first step in creating a comprehensive treatment plan is to evaluate the patient. In addition to a typical history (which includes the patient's medical and surgical history, family history, social history, allergies, and medications) the clinical evaluation of a patient with overweight or obesity should include specific questions about the person's weight and lifestyle, weight-promoting medication history (see *Chapter 4*) as well as the evaluation of BMI, waist circumference, and a complete physical examination.

BMI

Measuring the BMI is the first step to determine the degree of adiposity. BMI can be calculated quickly and without expensive equipment. More importantly, it can identify patients with increased risk of morbidity and mortality.

However, BMI is an imperfect measure of health as the categories do not take into account many factors such as muscularity and frame size. BMI is particularly

TABLE 5.1 — Classes of Medications Promoting Weight Gain

Tricyclic Antidepressants
■ Amitriptyline
■ Nortriptyline
■ Imipramine
Monoamine Oxidase Inhibitors
■ Phenelzine
SSRIs
■ Paroxetine
■ Citalopram
Tetracyclic Antidepressant
■ Mirtazapine
Atypical Antipsychotics
■ Clozapine
■ Olanzapine
■ Risperidone
■ Quetiapine
Antimanic Agent
■ Lithium
Anticonvulsants
■ Valproic acid
■ Carbamazepine
Steroids
■ Glucocorticoids
■ Progestins
Antidiabetics
■ Insulin
■ Sulfonylureas-glyburide
■ Thiazolidinediones
■ Rosiglitazone
■ Pioglitazone
α-Adrenergic Blockers
■ Prazosin
■ Doxazosin
■ Terazosin

Continued

TABLE 5.1 — *Continued*

Nonselective β-Blockers
■ Propranolol ■ Atenolol ■ Metoprolol
Antihistamines
■ Diphenhydramine ■ Meclizine ■ Cyproheptadine
Antineoplastics
■ Megestrol

inaccurate for people who are fit or athletic, as the higher muscle mass tends to put them in the overweight category by BMI, even though their body fat percentages frequently fall in a normal range. BMI also does not account for body frame size; a person may have a small frame and be carrying more adipose than optimal, but their BMI may fall in the normal range. Conversely, a large-framed individual may be quite healthy with a fairly low body fat percentage but be classified as overweight by BMI. Similarly, BMI cutoffs for identifying excess adiposity and risk of cardiometabolic disease are lower for some ethnicities. Specifically, a lower BMI threshold for screening of obesity is recommended in South Asian, Southeast Asian, and East Asian adult populations based on the evidence that lower BMI values are correlated with risk of T2D in these ethnicities.[2]

Despite this, BMI categories are regarded as a satisfactory tool for measuring whether individuals have underweight, overweight, or obesity. To estimate BMI, multiply the individual's weight (in pounds) by 703, then divide by the height (in inches) squared. This approximates BMI in kilograms per meter squared (kg/m^2) (**Table 5.2**).

Waist Circumference and Waist-Hip Ratio

Although BMI has traditionally been the chosen indicator by which to measure body size, alternative measures that reflect abdominal adiposity, such as waist circumference, waist-hip ratio, and waist-height ratio,

TABLE 5.2 — BMI

Category	BMI Range (kg/m^2)
Low	≤18.5
Normal	18.5-25.0 (standard weight: 22)
Overweight	25.0-30.0
Obese:	
Class I	30.0-35.0
Class II	35.0-40.0
Class III	≥40.0

have been suggested as being superior to BMI in predicting CVD risk.

Visceral fat, also known as intra-abdominal fat, is located inside the peritoneal cavity, in between internal organs and the torso, as opposed to subcutaneous fat, which is found underneath the skin, and intramuscular fat, which is found interspersed in skeletal muscle. An excess of visceral fat is known as central obesity. Increased visceral adipose tissue is associated with a range of metabolic abnormalities, including decreased glucose tolerance, reduced insulin sensitivity and adverse lipid profiles, which are risk factors for T2D and CVD.

The absolute waist circumference (>102 cm [40 in] in men and >88 cm [35 in] in women) and the waist-hip ratio (>0.9 for men and >0.85 for women) are both used as measures of central obesity. Waist circumference measurement is particularly useful in patients who are categorized as normal or overweight. Men who have waist circumferences >40 inches, and women who have waist circumferences >35 inches, are at higher risk. Individuals with waist circumferences greater than these values should be considered one risk category above that defined by their BMI. Measuring the waist circumference is not necessary in patients with BMI ≥35 because patients in this BMI category are already at increased risk.

According to the NIH guide to obesity (NHLBI Obesity Education Initiative, 2000), the waist circumference measurement should be made at the top of the iliac crest with the measuring tape held snuggling at a level parallel to the floor. The patient should stand

with their feet close together, arms at the side, and body weight evenly distributed. Waist circumference should be measured at the end of a normal expiration, when the lungs are at their functional residual capacity. Each measurement should be repeated twice; if the measurements are within 1 cm of one another, the average should be calculated. If the difference between the two measurements exceeds 1 cm, the two measurements should be repeated.

Percent Body Fat

Since the pathology of obesity is increased when both the number and size of adipose cells are increased, estimation of body fat percentage is a useful step during risk assessment. Body fat percentage is the total mass of fat divided by total weight. Total body fat includes essential body fat and storage body fat. Essential body fat is necessary to maintain life and reproductive functions. The percentage of essential body fat for women is greater than that for men, due to the demands of childbearing and other hormonal functions. The percentage of essential fat is 2% to 5% in men, and 10% to 13% in women. Storage body fat consists of fat accumulation in adipose tissue, part of which protects internal organs in the chest and abdomen. The minimum recommended total body fat percentage exceeds the essential fat percentage value reported above. A number of methods are available for determining body fat percentage, such as measurement with calipers, bioelectrical impedance analysis, and dual energy x-ray absorptiometry (DXA, formerly DEXA).

Suggested body fat percentages have been proposed (**Table 5.3**) and the numbers vary based on sex, age, and ethnicity.[3]

The skin-fold estimation methods are based upon a test whereby a pinch of skin is precisely measured by calipers at several standardized points on the body to determine the subcutaneous fat layer thickness.[4] These measurements are converted to an estimated body fat percentage by an equation. Some formulas require as few as three measurements, others as many as seven. The accuracy of these estimates is more dependent on a person's unique body fat distribution than on the number of sites measured. Although it may not give an accurate

TABLE 5.3 — Variations in Percentage of Body Fat for Black, Asian, and White Peoples

	Females (Fat %)			Males (Fat %)		
BMI	**Black**	**Asian**	**White**	**Black**	**Asian**	**White**
Age 20-39						
18.5	20	25	21	8	13	8
25	32	35	33	20	23	21
30	38	40	39	26	28	26
Age 40-59						
18.5	21	25	23	9	13	11
25	34	36	35	22	24	23
30	39	41	41	27	29	29

Gallagher D, et al. *Am J Clin Nutr*. 2000;72(3):694-701.

reading of real body fat percentage, it is a reliable measure of body composition change over a period of time, provided the test is carried out by the same person with the same technique.

DXA is a method for estimating body fat percentage, and determining body composition and bone mineral density. X-rays of two different energies are used to scan the body, one of which is absorbed more strongly by fat than the other. A computer can subtract one image from the other, and the difference indicates the amount of fat relative to other tissues at each point. A sum over the entire image enables calculation of the overall body composition.

The bioelectrical impedance analysis (BIA) method is a low-cost way to estimate body fat percentage. The general principle behind BIA: two or more conductors are attached to a person's body and a small electric current is sent through the body. The resistance between the conductors will provide a measure of body fat between a pair of electrodes, since the resistance to electricity varies between adipose, muscular, and skeletal tissue. Fat-free mass (muscle) is a good conductor as it contains a large amount of water (approximately 73%) and electrolytes, while fat is anhydrous and a poor conductor of electric current. Factors that affect the accuracy and precision of this method include instrumentation, subject factors,

technician skill, and the prediction equation formulated to estimate the fat-free mass. There is little scope for technician error, but factors such as eating, drinking and exercising must be controlled since hydration level is an important source of error in determining the flow of the electric current to estimate body fat.[5]

Office Equipment and Atmosphere

The care of patients with obesity requires an appropriately equipped office free of bias. The patient should feel welcomed and comfortable as soon as they enter the office. It is very important to treat the patient with respect and make them feel physically and emotionally comfortable. The office should have appropriately sized chairs in both the waiting room and in the exam rooms, wider scales with hand bars to hold onto that can be used for patients up to at least 500 lb, appropriate exam tables, long tape measures, highly adjustable BP cuffs, and gowns of appropriate sizing. All staff members should receive training on weight bias and stigma to help ensure each patient is treated appropriately and with respect.

Physical Examination

The physical exam should be focused on both characterizing obesity, as well as looking for causes and associated complications. As mentioned above, the patients' height and weight should be carefully measured and recorded in addition to their waist circumference. The patients' vital signs should be taken with special care to the fact that they may need specialized equipment to determine accurate readings. In assessing the BP, it is important to use an accurate size cuff because if it is too narrow, the BP may be falsely elevated. The cuff should be approximately 40% to 50% of the upper arm circumference. The clinician may need either a large adult cuff or thigh cuff, depending on the patient.

A routine physical exam should be performed in a supportive and nonthreatening manner. Attention should be paid towards looking for associated medical conditions including thin, atrophic skin (a feature of Cushing's disease), hyperpigmented skin around the neck or axilla (acanthosis nigricans, associated with insulin resistance), large neck circumference (increased risk of OSA), and hirsutism (may indicate polycystic ovarian syndrome).

Laboratory Evaluation

Basic laboratory evaluation should include examination for obesity-related conditions. This should include a fasting plasma glucose, fasting lipid panel, thyroid stimulating hormone (TSH; thyroid function modulates weight), liver transaminases to look for non-alcoholic steatohepatitis (NASH), as well as basic metabolic panel (to assess kidney function). Laboratory testing for specific disease and medication should be done depending on the patient history. For example, hemoglobin A1C (A1C) is important to monitor in patients with diabetes and their response to treatment.

Baseline Laboratory Evaluation

- Fasting plasma glucose
- Fasting lipid panel (total cholesterol, LDL, HDL, triglycerides)
- TSH and free thyroxine
- Complete metabolic panel (for ALT, AST, creatinine, BUN and electrolytes)
- A1C and fasting insulin
- Complete blood counts

Further evaluation for endocrine or genetic causes and related comorbidities may be warranted depending on the patient's medical history and physical exam. For example, depending on the physical exam, a work-up for Cushing's disease may be warranted (central obesity, abdominal striae, moon facies, buffalo hump) and this can be done with either a 24-hour urinary free cortisol or an overnight dexamethasone suppression test.

Evaluation for Weight-Related Comorbidities

Upon completion of the basic medical assessment, additional medical problems may be unmasked. In patients with obesity, many of these conditions should be further evaluated as they may complicate or alter the treatment plan:

- Respiratory—hypoventilation syndromes are common in patients with obesity and include both OSA and obesity hypoventilation syndrome. These

conditions can lead to pulmonary hypertension, arrhythmias, and depression. The risk for OSA can quickly be assessed by using the STOP-BANG questionnaire (**Figure 5.1**) or the Epworth Sleepiness Scale (**Figure 5.2**). It is important to promptly evaluate for these conditions with the appropriate referrals for either a sleep study or to a sleep medicine specialist for further evaluation and treatment.

- Cardiovascular—the American Heart Association classifies obesity as a major modifiable risk factor for coronary heart disease, independent of its comor-

FIGURE 5.1 — STOP BANG Questionnaire for Sleep Apnea

	Yes	No
STOP		
***S*noring**		
Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?		
***T*ired**		
Do you often feel tired, fatigued, or sleepy during daytime?		
***O*bserved**		
Has anyone observed you stop breathing during your sleep?		
Blood *P*ressure		
Do you have or are you being treated for high blood pressure?		
BANG		
***B*MI >35?**		
***A*ge >50 years old?**		
***N*eck circumference >15.75 inches (40 cm)?**		
***G*ender male?**		
Calculate OSA Risk		
≥3 yes answers: high risk for OSA		
<3 yes answers: low risk for OSA		

FIGURE 5.2 — Epworth Sleepiness Scale

Situation	Chance of dozing or sleeping[a]
Sitting and reading	
Watching TV	
Sitting inactive in a public place	
Being a passenger in a motor vehicle for an hour or more	
Lying down in the afternoon	
Sitting and talking to someone	
Sitting quietly after lunch (no alcohol)	
Stopped for a few minutes in traffic	
Total score	

[a] Each situation receives a score of 0-3: 0 = would never dose; 1 = slight chance of dozing; 2 = moderate chance of dozing; 3 = high chance of dozing.

The scores for each situation are added up, giving the total score, whose normal range is between 0 and 10. A total score above 10 requires medical assessment

Adapted from Doneh B. *Occup Med (Lond)*. 2015;65(6):508.

bidities. Specific comorbid conditions may include coronary artery disease, hypertension, left ventricular hypertrophy, cor pulmonale, and obesity-associated cardiomyopathy.

- Gastrointestinal—common complications include nonalcoholic fatty liver disease (fatty liver infiltration, NASH) and reflux esophagitis.
- Orthopedic—many patients suffer from OA which may limit their physical functioning and ability to perform an exercise program.
- Metabolic—numerous metabolic disturbances may be found including T2D, prediabetes, metabolic syndrome, and dyslipidemia. These conditions should be aggressively managed during the course of any weight loss intervention.

- Reproductive—women often have weight-related reproductive challenges including anovulation, early puberty, infertility, hyperandrogenism, polycystic ovaries and pelvic stress incontinence. Screening and appropriate referrals should be made as needed.
- Cutaneous—intertrigo (bacterial and/or fungal) is a common challenge faced by patients with obesity. It is important to assess and subsequently counsel patients on good hygiene to prevent further complications.
- Psychiatric—major psychiatric illness may present an obstacle or even contraindication to treatment. A common finding is mild-moderate depression, and patients should be screened and may require behavioral therapy and/or medication with referral to psychiatry depending on the severity.

Disease Staging and Risk Assessment

The patient's risk status should be assessed by determining the degree of overweight or obesity based on BMI, the presence of abdominal obesity based on waist circumference, and the presence of concomitant CVD risk factors or comorbidities. Some obesity-associated diseases and risk factors place patients in a very high-risk category for subsequent mortality. These diseases will require aggressive modification of risk factors in addition to their own clinical management.

Much, if not most, of the relevant information for clinical risk assessment and disease staging of patients with overweight/obesity is readily available to the clinician in routine clinical practice. Additional information can be obtained from several validated assessment and disease staging tools such as the EOSS (discussed in *Chapter 6*).

Assessment of Motivation

Before initiating a treatment plan, it is important to determine whether a patient is ready to make the necessary changes, as not all patients are ready to lose weight. When counseling the patient, the plan should be individualized to their specific needs and allow for flexibility in order to prevent the patient from feeling like a failure.

Realistic Goal Setting

Patients often have unrealistic expectations about how much weight they would like to lose. It is not necessary to achieve an "ideal" body weight or normal BMI because health benefits are often achieved when a patient loses as little as 5% to 10% of their total body weight. The rate of weight loss is not necessarily important, however, usual goals target approximately 1-2 lb/week over the course of 6 months. Goal setting should occur in conjunction with the patient and may be modified over time. Weight loss alone should not be the only aim of treatment, rather improvement in obesity-related comorbidities should be a primary goal and monitored throughout treatment (see *Chapter 6*). Long-term treatment plans should be in place to assist with weight maintenance and avoidance of weight regain.

Creating a Treatment Plan

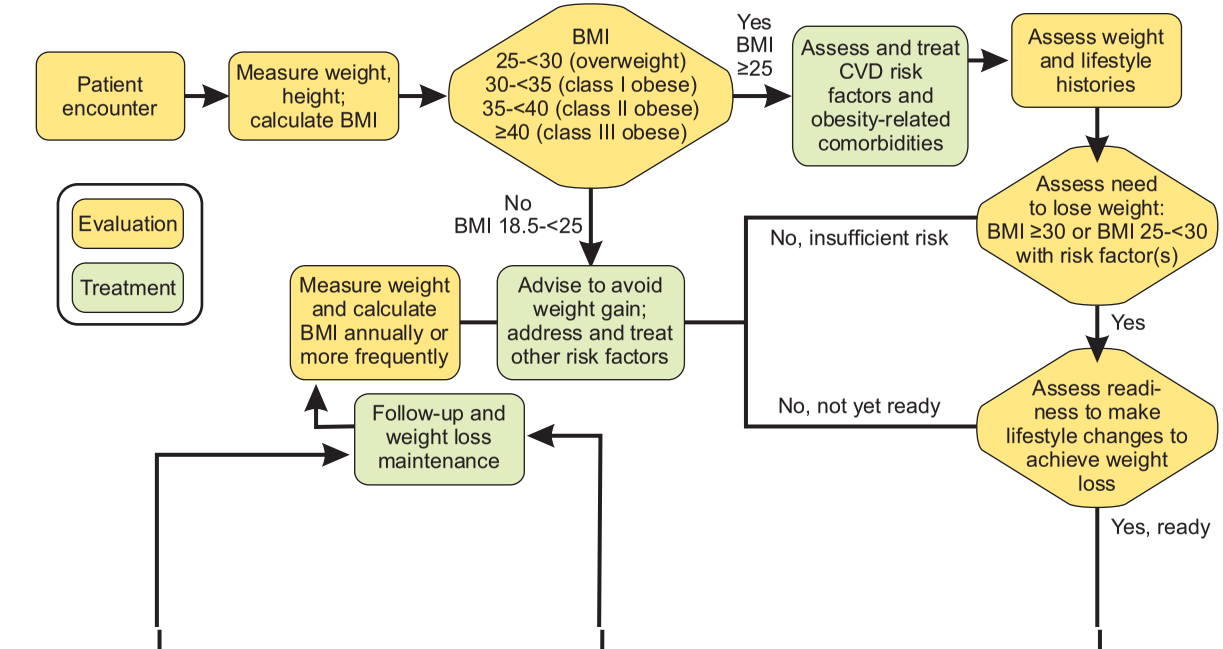
The treatment of obesity should be based upon the degree of adiposity and the prevalence and risks of weight-related comorbidities. A higher risk patient may require a more aggressive intervention such as pharmacotherapy and surgery. All plans should be flexible to accommodate an individual's needs and preferences. The Algorithm for the Medical Care of Patients with Obesity published by the AACE and ACE in 2016 provides an obesity-specific treatment algorithm for the management of patients with overweight or obesity (see *Chapter 6*).

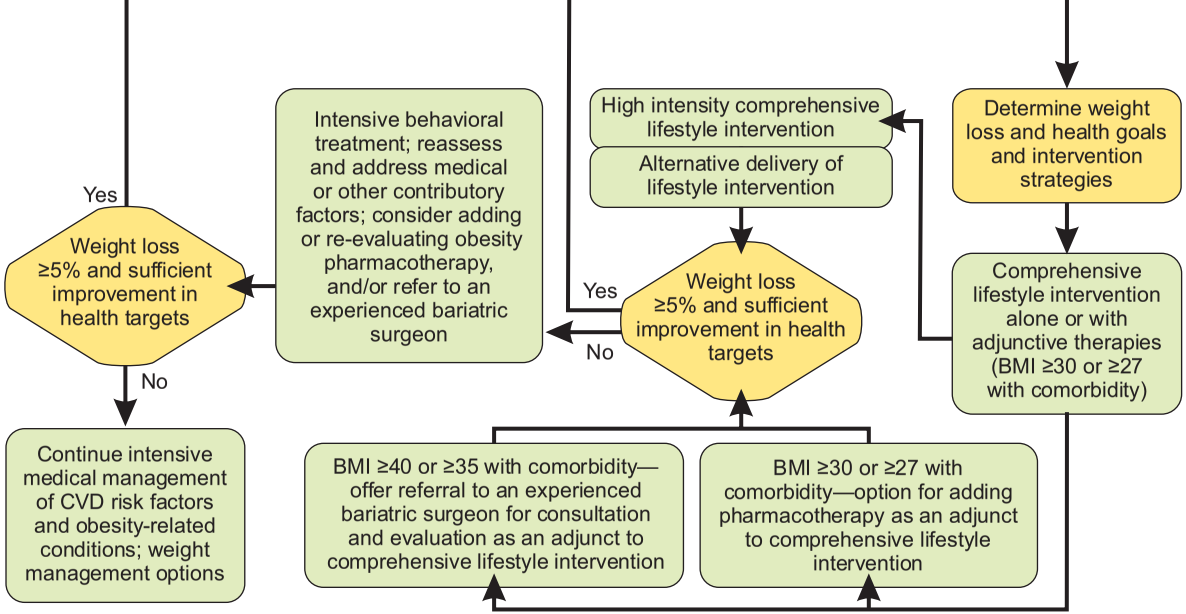
In addition, **Figure 5.3** is the treatment algorithm from the 2013 AHA/ACC/TOS Guideline For The Management Of Overweight And Obesity In Adults.[6] It is based on the Chronic Disease Management Model for Primary Care of Patients with Overweight and Obesity to guide PCPs in the evaluation, prevention, and management of patients regarding excess body weight. The algorithm is not intended to supplant initial assessment for CV risk factors or diseases but rather focuses on the identification of patients with excess body weight and those at risk for obesity-related health problems. Its purpose is to guide weight management decision making. This intervention should be a foundation for additional

weight management efforts, such as addition of medications or bariatric surgery.

All treatment programs should include a comprehensive team approach and may include a physician, registered dietician, social worker, psychiatrist, nurse, and surgeon. Effective management requires sufficient time and frequent monitoring in order to keep the patient motivated and provide accountability. Once a patient achieves a reasonable goal weight, it may take as much, if not more, time to maintain the weight loss. Given that obesity is a chronic disease, it is paramount that patients have long-term monitoring in order to help prevent weight regain.

FIGURE 5.3 — 2013 AHA/ACC/TOS Treatment Algorithm for Patients With Overweight and Obesity





Jensen MD, et al. *Circulation*. 2014;129(25 suppl 2):S102-138.

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A Complications-Centric Approach to the Treatment of Obesity

A Holistic Perspective

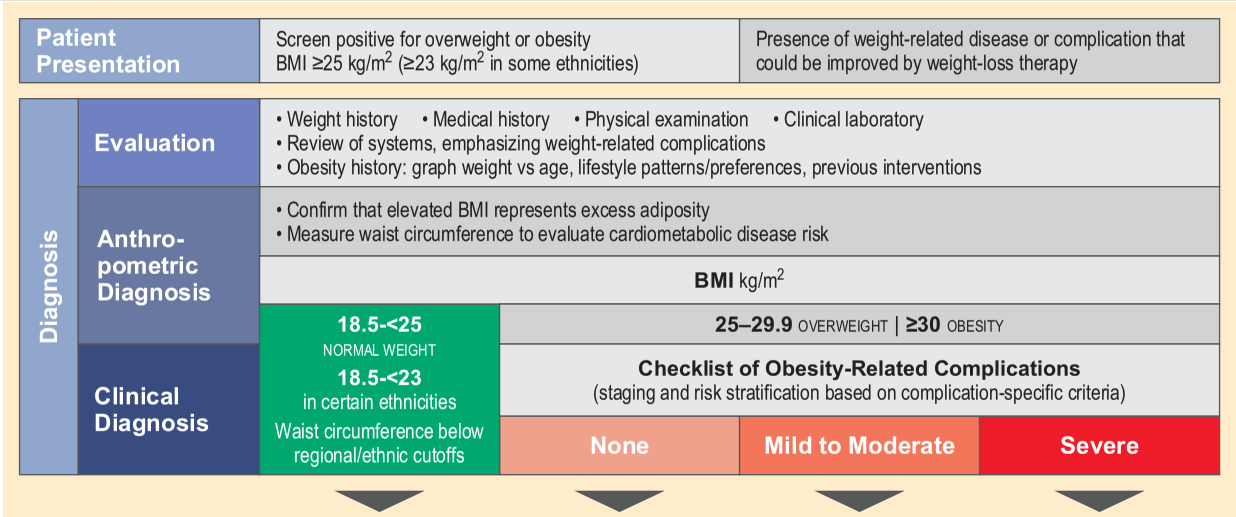
The Algorithm for the Medical Care of Patients with Obesity, published by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology in 2016 focuses on the whole patient and includes specific treatment algorithms for the management of patients with overweight and obesity. It proposes a "complications-centric model" for the treatment of obesity (**Figure 6.1**). This evidence-based approach to the treatment of obesity incorporates lifestyle, medical, and surgical options, balances risks and benefits, and emphasizes medical outcomes that address the complications of obesity rather than cosmetic treatment goals.[1]

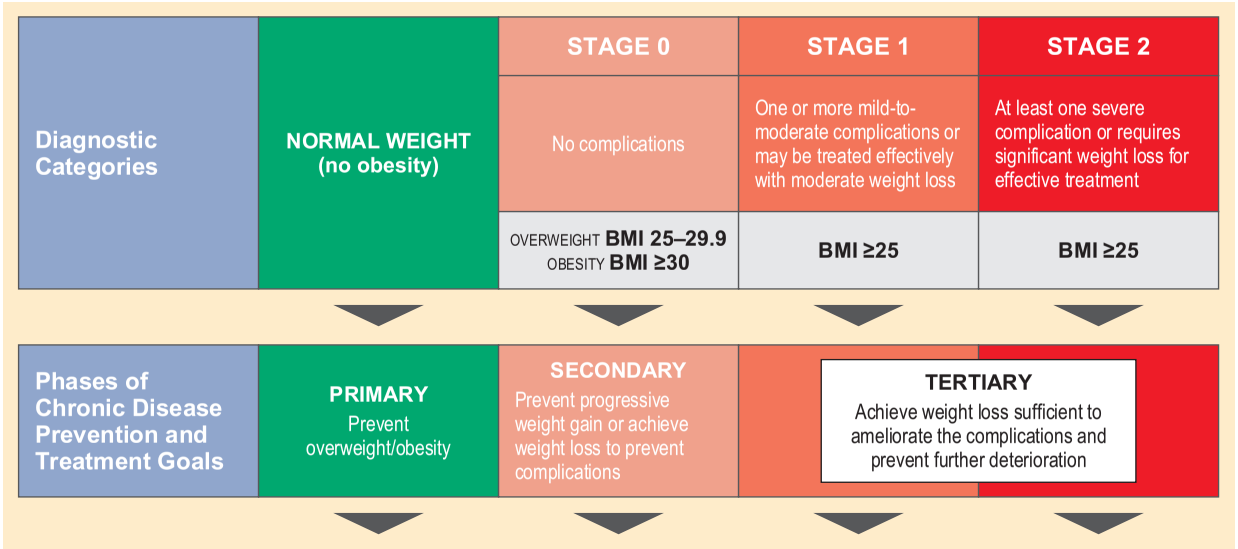
Obesity as a Disease

Of particular interest regarding this algorithm is its stated fundamental premise namely: "Obesity is a disease with genetic, environmental, and behavioral determinants that confers increased morbidity and mortality."[1,2] This premise is not new. The 1998 National Heart, Lung, and Blood Institute (NHLBI) Clinical Guidelines for Clinical Treatment of Overweight and Obesity also stated that "obesity is a complex multifactorial chronic disease that develops from an interaction of genotype and the environment."[3] There is considerable evidence that obesity is associated with cardiometabolic and other comorbidities (see *Chapter 3*) and consequently, with increased risk for morbidity, mortality, decreased quality of life, and increased health care cost.

A resolution stating that obesity should be reclassified as a multi-metabolic and hormonal disease state

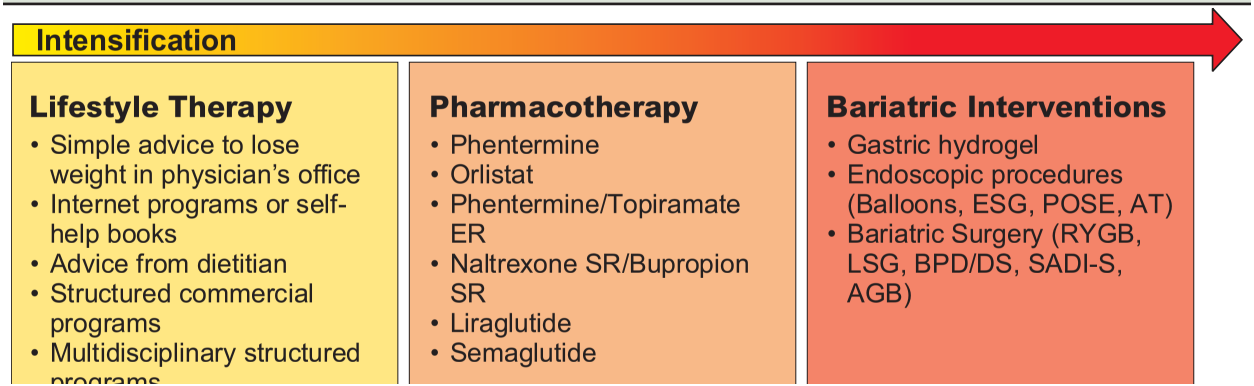
FIGURE 6.1 — Complications-Centric Model for Care of Patients with Overweight/Obesity




Diagnostic Categories
NORMAL WEIGHT (no obesity)
STAGE 0
No complications
OVERWEIGHT BMI 25–29.9
OBESITY BMI ≥30
STAGE 1
One or more mild-to-moderate complications or may be treated effectively with moderate weight loss
BMI ≥25
STAGE 2
At least one severe complication or requires significant weight loss for effective treatment
BMI ≥25
Phases of Chronic Disease Prevention and Treatment Goals
PRIMARY
Prevent overweight/obesity
SECONDARY
Prevent progressive weight gain or achieve weight loss to prevent complications
TERTIARY
Achieve weight loss sufficient to ameliorate the complications and prevent further deterioration

Continued

FIGURE 6.1 — *Continued*



Garvey WT, et al. *Endocr Pract*. 2016;22(suppl 3):1-203.

was presented to the American Medical Association (AMA) House of Delegates at its June 2013 meeting by the AACE, and supported by the American College of Cardiology, the Endocrine Society, and the American Society for Reproductive Medicine, as well as the American Academy of Pediatrics, the American Academy of Family Physicians, and the American Society of Bariatric Physicians. This resolution was ultimately accepted by the AMA House of Delegates.

From Weight Loss to Risk Reduction

Obesity is typically defined in terms of anthropometric measures, primarily BMI, which originally was designed as an epidemiologic research tool, ie, a rough population-level indicator of body weight. Many observational studies have consistently reported strong associations between elevated BMI values and morbidity and mortality risk. In one large study, for example, each five-point increase in BMI >25 was associated with increases of 29% for overall mortality, 41% for vascular mortality, and 210% for diabetes-related mortality.[4] However, BMI is not an optimal method for measuring actual "body fatness" in an individual.[5,6] For example, as the 1998 NHLBI Guidelines pointed out, some people with a BMI in the "normal" range can have excessive body fat, as well as metabolic dysfunctions. Others with BMIs in the same obesity range have no excess fat or cardiometabolic dysfunction. Conversely, some individuals with high BMIs are normal metabolically and may have normal blood pressure and cholesterol levels.[3]

The difference between the long-established (1998) NHLBI Clinical Guidelines for Overweight and Obesity and the AACE guidelines does not reside in their specific clinical assessment and treatment recommendations. Rather, the AACE Obesity Treatment Algorithm adopts a complications-centric model that focuses on risk assessment, staging, and stage-specific interventions, one of which is weight loss treatment itself. Thus, one difference between a BMI-centric model and a complications-centric model is that the primary treatment goal of the former is weight loss itself, while with the complications-centric model, the primary treatment goal is reduction

of the risk for (or at least slowing the progression of) the many comorbidities associated with obesity. In other words, in the AACE algorithm, *weight loss itself is a key therapeutic intervention* for risk reduction in an individual patient.

The Premise: Weight Loss Reduces Comorbidity and Mortality Risk

A fundamental premise of the complications-centric approach is that weight loss resulting from diet and lifestyle changes alone or in combination with pharmacologic or surgical treatment can reduce the risk of many of the obesity-associated comorbidities in a progressively "dose-related" manner. The large body of evidence demonstrating the clinical benefits of weight loss itself is reviewed in *Chapter 4.*

For example, 1-year results from the ongoing Look AHEAD (Action for Health in Diabetes) trial provide empirical support for the assertion that modest weight losses of 5% to 10% of initial weight are sufficient to produce significant, clinically relevant improvements in CVD risk factors in patients with overweight or obesity and T2D.[7] Look AHEAD is a multicenter, randomized clinical trial assessing the long-term effects of lifestyle interventions on CV morbidity and mortality in 5145 patients with overweight or obesity with T2D who were randomized to intensive lifestyle intervention (ILI) or to usual care.

After 1 year, patients were divided into the following categories based on their weight changes from baseline to 1 year: gained >2%; remained weight stable (±2%); lost ≥2% to 5%; lost ≥5% to 10%; lost ≥10% to 15%; or lost ≥15%. There was a strong graded association for changes in glucose, A1C, SBP, DBP, triglycerides, and HDL cholesterol (all *P* values <0.0001). Each higher increment of weight loss was associated with greater improvements in the risk factor. Furthermore, the odds of having a clinically meaningful improvement in risk were strongly related to the magnitude of weight loss achieved such that the odds of a clinically meaningful improvement also increased with each weight loss increment.

Evaluation, Risk Assessment, and Disease Staging

According to the 2016 AACE/ACE Obesity Treatment Algorithm, patients who will benefit the most from medical and surgical intervention have obesity-related comorbidities.[1] Therefore, the guidelines recommend that the primary factor guiding treatment planning and evaluation should be the presence and severity of complications, not BMI per se. Much, if not most, of the relevant information for clinical risk assessment and disease staging of overweight/obesity is readily available to the clinician in routine clinical practice. Additional information can be obtained from several validated assessment and disease staging tools.

Edmonton Obesity Staging System (EOSS)

As mentioned previously, BMI is not a perfect measure of health. In 2009, Sharma and colleagues proposed a new clinical staging system for obesity—the Edmonton Obesity Staging System (EOSS)—intended to complement (but not replace) current anthropometric classifications of obesity.[5] This measure ranks individuals with overweight/obesity according to a 5-point ordinal scale, which incorporates obesity-related comorbidities and functional status (**Table 6.1**). The EOSS is based on simple clinical assessments that include medical history and clinical and functional assessments, as well as simple routine diagnostic investigations.

Subsequently, Padwal and colleagues assessed the ability of the EOSS to predict all-cause mortality using a nationally representative US population sample (NHANES III [1988–1994] and NHANES [1999–2004] with mortality follow-up through to the end of 2006).[6] Final unweighted sample sizes were 4367 individuals with overweight/obesity from the NHANES III 1988–1994 population and 3600 from the NHANES 1999–2004 population. EOSS scores were a strong predictor of increasing all-cause mortality in the overall population (**Figure 6.2**). This predictive ability was independent of BMI and the presence of other risk factors such as metabolic syndrome. The results also were similar among individuals who never smoked.[6]

TABLE 6.1 — Edmonton Obesity Staging System (EOSS)

Stage	Cardiometabolic	Mechanical/Functional
0	No risk factors	No functional impairments or impairments in well-being
1	Subclinical risk factors	Mild limitations and impairment of well-being
	Prediabetes	
	Metabolic syndrome	
	NAFLD	
2	End-stage metabolic disease	Moderate limitations and impairment of well-being
	Type 2 diabetes	
	Hypertension	
	Sleep apnea	
3	End-stage CVD disease	Significant limitations and impairment of well-being
	MI	
	Heart failure	
	Stroke	
4	Significant limitations and impairment of well-being	Severe limitations and impairment of well-being

Sharma AM, Kushner RF. *Int J Obes (Lond)*. 2009;33(3):289-295.

There are several limitations of this staging system. For example, the comorbidities within EOSS, such as diabetes and OA, were initially and arbitrarily assigned to be equivalent in terms of their burden of illness. Therefore, it is not yet clear whether certain comorbidities should receive a higher weighting. Another limitation is that the EOSS was based on analysis of total mortality data only. A final limitation is that even though the EOSS system is based on a simple clinical rationale, its sensitivity, specificity, reliability, and utility in clinical practice has not yet been assessed. Such studies are currently underway.[6]

Metabolic Syndrome

The metabolic syndrome is "a complex cluster of interrelated risk factors for CV disease and diabetes which occur together more often than by chance alone."[8]

These risk factors include dyslipidemia, central obesity, hypertension, and/or insulin resistance.

Different diagnostic criteria for the metabolic syndrome have been proposed by various organizations, including the:

- National Cholesterol Education Program's Adult Treatment Panel III report (ATP III)
- WHO
- International Diabetes Foundation (IDF)
- AACE
- AHA/NHLBI.

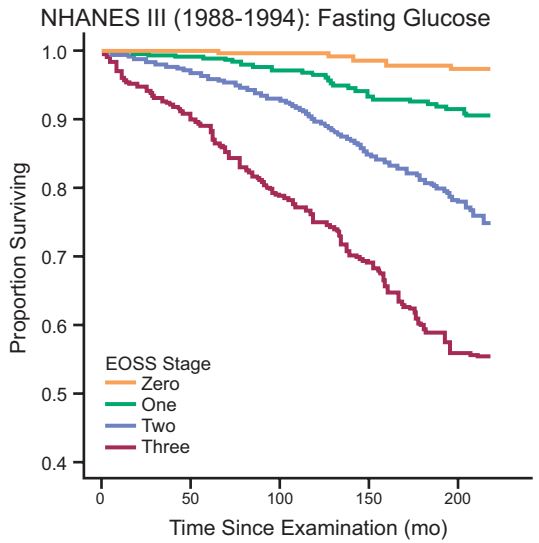
However, in 2009, a joint meeting of IDF Task Force on Epidemiology and Prevention, NHLBI, AMA, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity resulted in a unified set of diagnostic criteria.[8] Three abnormal findings out of the five listed in **Table 6.2** would support a diagnosis of metabolic syndrome. The main difference among previous criteria was whether a measure of central adiposity, such as waist circumference, should be an obligatory component, and if so, what measurement cut points should be used. It was agreed that measurement of waist circumference should not be an obligatory component, but that waist measurement should continue to be a useful preliminary screening tool.[8]

The presence of the metabolic syndrome is a clinically useful indicator of high morbidity and mortality risk. However, it is not an absolute risk since it does not consider many of the patient-specific factors that determine absolute risk such as age, sex, ethnicity, cigarette smoking, and LDL-cholesterol levels. Nonetheless, patients with the metabolic syndrome are at twice the risk of developing CVD over the subsequent 5 to 10 years as those without the syndrome. In addition, the metabolic syndrome confers a 5-fold increase in the risk developing T2D.[8]

Cardiometabolic Disease Staging System

Given the strong relationship between a diagnosis of cardiometabolic syndrome and increased risk of mor-

FIGURE 6.2 — Prediction of All-Cause Mortality Using EOSS or BMI Criteria



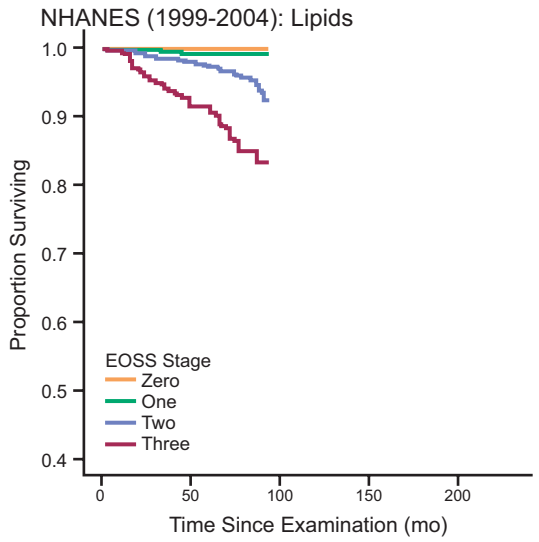


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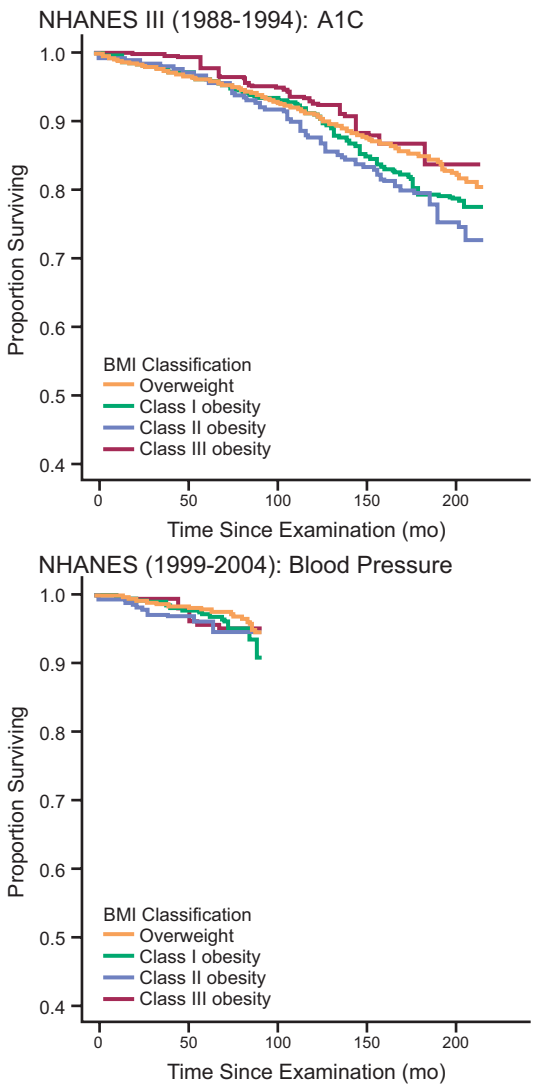
FIGURE 6.2 — *Continued*



Padwal RS, et al. *CMAJ*. 2011;183(14):E1059-E1066.

TABLE 6.2 — Risk Factors of Metabolic Syndrome

Trait	Categorical Cut Point
Elevated waist circumference	≥35 inch (female)
	≥40 inch (male)
	Note: Population/country specific definitions
Elevated triglycerides (or drug treatment to reduce triglycerides)	≥150 mg/dL
Reduced HDL-C (or drug treatment for dyslipidemia)	<40 mg/dL (male)
	<50 mg/dL (female)
Elevated blood pressure (or hypertension history or drug therapy)	≥Systolic 130 mm Hg and/or diastolic 85 mm Hg
Elevated fasting glucose (or drug therapy for diabetes or hyperglycemia)	≥100 mg/dL

NOTE: Three abnormal findings out of the five listed above would support a diagnosis of metabolic syndrome.

Alberti KG, et al. *Circulation*. 2009;120(16):1640-1645.

bidity and mortality, Guo and associates proposed the 5-stage Cardiometabolic Disease Staging (CMDS) system (**Table 6.3**) for predicting the progressively increased risk for future T2D and all-cause and CVD mortality.[9] In order to demonstrate the progressive risk of the cardiometabolic disease spectrum, they validated the CMDS by using two large national cohorts, the CARDIA study for incident diabetes and the NHANES III linked mortality file for all-cause or CVD mortality.

Based on the 10-year follow-up period data from the CARDIA study, there were 203 cases of newly-diagnosed diabetes resulting in an overall crude cumulative diabetes incidence of 6.1%. The cumulative diabetes incidence across risk levels ranged across from 1.8%, 5.9%, 18.2%, and 41.8% at Stage level 0 to Stage 3, respectively (**Figure 6.3**). Among individuals with overweight or obesity, the cumulative diabetes incidence was 8.9% overall, and ranged from 2.2% 7.3%, 19.0%, and 41.0% at Stage levels 0 to Stage 3, respectively.[9] In addition to risk-stage–

associated increases in cumulative incidence of diabetes, the HRs for diabetes also increased exponentially from 2.83 at stage 1 to 23.5 at stage 3. The impact of risk stage on diabetes incidence was similar in both genders and in White and Black people.

Over a median follow-up of 173 months in the NHANES III cohort, there were 1012 ascertained all-cause mortality cases, resulting in a cumulative overall mortality rate of 14.7 per 1000 person-years. As with the progressive increases in cumulative diabetes incidence, the cumulative mortality rates also increased progressively with advancing CMDS risk stage (P <0.001 for trend). They ranged from 6.5 per 1000 person-years at stage 0 to 29.2 per 1000 person-years at stage 4 (**Figure 6.4**). In this cohort, there also were 404 cases of CVD-related deaths. The overall CVD cumulative mortality rate was 5.4 per 1000 person-years overall, and the rates also increased according to risk stage (P <0.001 for trend), ranging from 0.7 per 1000 person-years at stage 0 to 14.3 per 1000 person-years at stage 4.[9]

This study demonstrates that CMDS staging can discriminate a wide range of risk for diabetes, CVD mortality, and all-cause mortality independent of BMI, and can be used as a risk assessment tool to guide intervention. In particular, such a tool can be useful in a complications-centric approach to the treatment of obesity wherein the goal of weight loss is to ameliorate the complications of obesity. However, prospective interventional trials are needed to further validate the use of the CMDS will enhance patient outcomes and the cost-effectiveness of care.

A Medical Model for Management of Patients with Overweight/Obesity

Historically, the management of individuals with overweight/obesity focused primarily on weight loss and employed dietary/lifestyle interventions with the occasional addition of a very limited number of weight-reducing, modestly effective, pharmacologic agents. Bariatric surgery, although generally more effective than the other options, was generally reserved for more severe or refractory cases. However, there has been a gradual

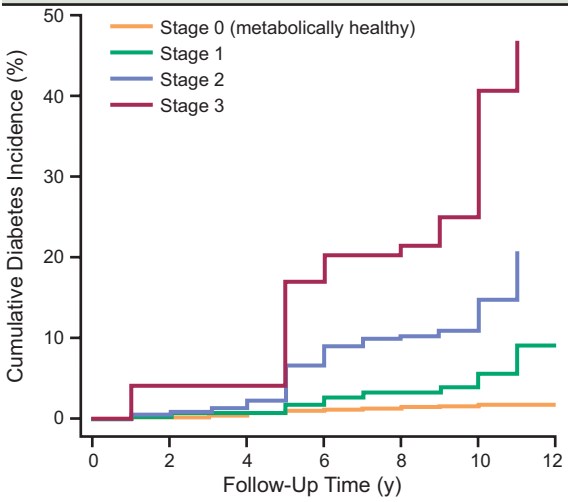
TABLE 6.3 — Cardiometabolic Disease Staging System (CMDS)

Stage	Descriptor	Criteria
0	Metabolically healthy	No risk factors
1	One or two risk factors	Have one or two of the following risk factors:
		Elevated waist circumference (≥112 cm in men, ≥88 cm in women)
		Elevated BP (SBP ≥130 mm Hg and/or DBP ≥85 mm Hg) or on anti-hypertensive medication
		Reduced serum HDL cholesterol (<1.0 mmol/L or 40 mg/dL in men; <1.3 mmol/L or 50 mg/dL in women) or on medication
		Elevated fasting serum triglycerides (≥1.7 mmol/L or 150 mg/dL) or on medication
2	Metabolic syndrome or prediabetes	Have only one of the following three conditions in isolation:
		Metabolic syndrome based on three or more of four risk factors:
		High waist circumference
		Elevated BP
		Reduced HDL-c
		Elevated triglycerides
		IFG (fasting glucose ≥5.6 mmol/L or 100 mg/dL)
		IGT (2-h glucose ≥7.8 mmol/L or140 mg/dL)

3	Metabolic syndrome + prediabetes	Have any two of the following three conditions:
		Metabolic syndrome
		IFG
		IGT
4	T2D and/or CVD	Have T2D and/or CVD:
		T2D (fasting glucose ≥126 mg/dL or 2-hour glucose ≥200 mg/dL or on antidiabetic therapy)
		Active CVD (angina pectoris or status post a CVD event, such as acute coronary artery syndrome, stent placement, coronary artery bypass, thrombotic stroke, nontraumatic amputation due to peripheral vascular disease)

Guo F, et al. *Obesity* (*Silver Spring*). 2014;22(1):110-118.

FIGURE 6.3 — Cumulative Diabetes Incidence as a Function of Increasing CMDS Risk Stage: CARDIA Study Cohort

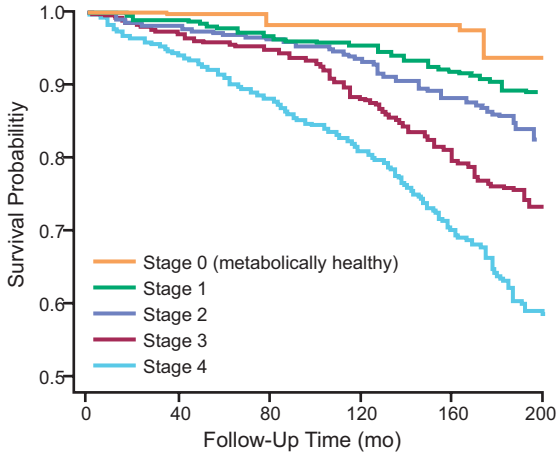


Guo F, et al. *Obesity (Silver Spring)*. 2014;22(1):110-118.

change in the understanding and appreciation of obesity, its complex pathophysiology, interrelationships with a broad spectrum of comorbidities, as well as increased mortality. As noted previously, obesity is a disease in its own right, a disease that cannot be defined for clinical management solely by specific increments in total body weight.

In contrast to earlier BMI-centric guidelines[3] (see **Table 6.4** for BMI-centric treatment recommendations), the AACE guidelines are based on a complications-centric model for treatment of patients with overweight or obesity (see **Figure 6.1** for an overview algorithm and **Figure 6.5** for therapy intensification).[1] The goal is to identify those patients who will benefit most from obesity treatment, namely, those who have obesity-related complications. Given that medications and surgical procedures have inherent risks for patients and increase the cost of health care delivery, it is important to develop and employ risk assessment steps in order to optimize the benefit/risk ratio for each patient.

FIGURE 6.4 — Survival Probability as a Function of Increasing CMDS Risk Stage: NHANES



Guo F, et al. *Obesity (Silver Spring)*. 2014;22(1):110-118.

There are several weight-loss medications currently in use (see *Chapter 9*). The new generation of anti-obesity drugs allows the provider to individualize therapy and use combination treatments in order to target the multiple pathways that contribute to the disease. Most importantly, the newer agents have been shown to not only result in significant weight loss but also to have significant beneficial effects on various cardiometabolic and anthropometric parameters.

In addition to the evolution of drug treatment, there have been new and refined options for dietary and lifestyle interventions (see *Chapter 8*) and further advances in bariatric surgery (see *Chapter 10*). Therefore, many conceptual and technological advances, including the complications-centric algorithm, expanding availability of unique new medications, and surgical interventions, have enabled a medical model for the identification, assessment, and management of patients with overweight/obesity.

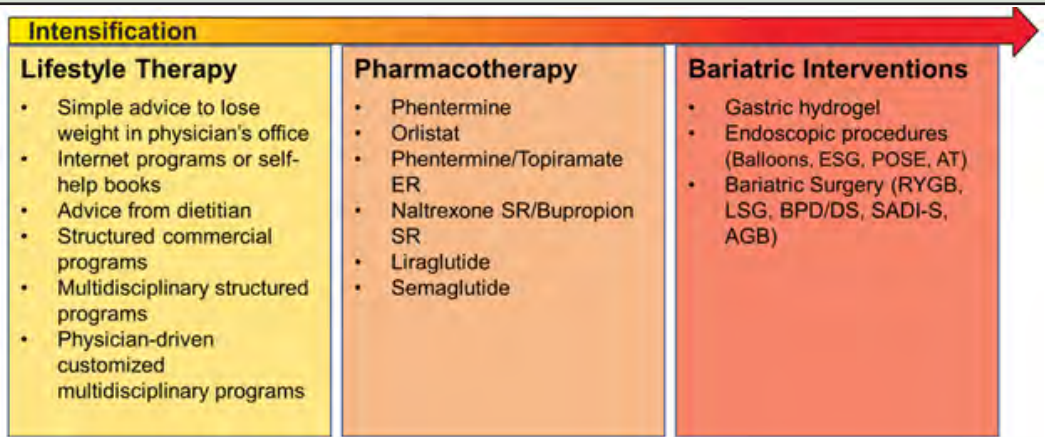
TABLE 6.4 — BMI-Centric Guide to Choosing Treatments for Obesity

Treatment	BMI Category				
	25-26.9	27-29.9	30-34.9	35-39.9	≥40
Diet, physical activity, behavior	+	+	+	+	+
Pharmacotherapy[a]	Not FDA approved	With weight-related comorbidities	+	+	+
Endoscopic interventions and gastric gels[b]	+ (Plenity)	+ (Plenity)	+ (Plenity, intragastric balloons, ESG, POSE, TPS [with comorbidities])	+ (Plenity, intragastric balloons, ESG, POSE, aspiration therapy, vBloc [with comorbidities], TPS)	+ (ESG, POSE, aspiration therapy, vBloc)
Surgery[b]	Not appropriate	Not appropriate	With T2D and inadequate glycemic control	With weight-related comorbidities	+

[a] See *Chapter 9* for available pharmacotherapy options.
[b] See *Chapter 10* for more details on endoscopic and surgical interventions.

ESG, endoscopic sleeve gastroplasty; POSE, primary obesity surgery endolumenal; TPS, transpyloric shuttle.

FIGURE 6.5 — Intensification of Therapies to Achieve Weight Loss Goals



AGB, Adjustable gastric banding; AT, aspiration therapy; BPD/DS, biliopancreatic diversion with or without duodenal switch; ESG, endoscopic sleeve gastroplasty; LSG, laparoscopic sleeve gastrectomy; POSE, Primary Obesity Surgery Endolumenal; RYGB, Roux-en-Y gastric bypass; SADI-S, Single Anastomosis Duodeno-Ileal Switch.

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Drug-Induced Weight Gain

A variety of prescription medications have been associated with weight gain. These drugs differ in their propensity to increase body weight.[1] The mechanism responsible for medication-induced weight gain has not been carefully studied for most of these agents but may be related to an increase in energy intake (eg, antipsychotics and steroid hormones), a decrease in energy expenditure (eg, β-adrenergic receptor blockers), a decrease in energy loss (eg, decreased glycosuria from diabetes therapy), or a combination of these factors.[2] This chapter will review weight gain associated with several classes of prescription medications, including antidiabetics, antihypertensives, anticonvulsants, steroid hormones and contraceptives, antidepressives and antipsychotics, and antihistamines.

Treatment Selection to Prevent Drug-Induced Weight Gain

Drug-induced weight gain is a preventable cause of obesity, and can be avoided by selecting alternative treatments that promote weight neutrality or even weight loss. The desired level of clinical efficacy for a chosen therapy should be balanced against side effects, including the likelihood of weight gain. Clinicians should use a shared decision making model - an approach where clinicians and patients take treatment decisions jointly, on the basis of best available evidence[3] - to inform patients about the available treatment options and to agree on a treatment plan. Clinicians should also communicate effectively with the patient's other healthcare providers, and not discontinue any vital medications without consulting the other prescribing providers first. In cases where there are no acceptable therapeutic alternatives, the minimal dose required to produce clinical efficacy may prevent or minimize drug-induced weight gain.

The patient's initial weight status, the presence of risk factors for CV disease, diabetes, and other obesity-related health complications, as well as the benefits of pharmacologic therapies warrant careful consideration when prescribing a first-line therapy or change in medication.[4] The expected length of treatment is also a factor, as some medications may be associated with weight loss in the short-term (<1 year), but with weight gain in the long-term (>1 year) and vice versa.[5]

Patients should be informed of potential drug-induced weight gain and educated on weight management techniques, such as proper nutrition, physical exercise, and behavioral modification. Individual patient risk profiles can also be assessed. For appropriate medication selection, physicians should consider the weight gain potential of various drugs.[6]

Table 7.1 provides a partial list of drugs and drug classes that contain medications associated with weight gain, weight neutrality, and weight loss.

Antidiabetic Medications

Many patients with T2D have overweight or obesity, both of which are associated with increased patient risk of CV events and mortality.[7] Unfortunately, weight gain is often associated with many diabetes therapies. Patients can gain as much as 10 kg after initiating treatment with insulin, sulfonylureas other insulin secretagogues, and the thiazolidinediones (TZDs). The causes of this weight gain are not fully understood but are thought to be due to drug-induced changes in the body's metabolic control, which result in a state of positive energy balance, eventually leading to weight gain.[8] Weight gain is of particular concern in patients with diabetes, because of the rise in insulin resistance associated with excess weight and obesity.[9] Taking into consideration weight gain as well as other side effects of antidiabetic medication, the AACE/ACE Diabetes Management Algorithm recommends metformin, GLP-1 receptor agonists (GLP-1 RAs), and SGLT2 inhibitors as the preferred therapies for T2D treatment. All three have been associated with weight-loss in patients with T2D.[10]

The most commonly used oral agent for the treatment of T2D is metformin. Metformin promotes weight loss by multiple mechanisms, including reducing hepatic glucose production and intestinal absorption of glucose, while improving insulin sensitivity. Due to the inconsistent effects of metformin on weight loss, the FDA has not approved it as a treatment for obesity and it is currently used off-label for weight loss by many providers.[11] The 2016 AACE/ACE Guidelines for the treatment of patients with obesity do recommend the use of metformin in select patients with obesity who are diagnosed with prediabetes and insulin-resistance and who do not respond to anti-obesity medications and lifestyle treatments.[12]

Similarly, dipeptidyl peptidase 4 (DPP-4) inhibitors are considered to be a weight-neutral class, and are ranked fourth in the hierarchy of recommended usage in the treatment algorithm for T2D.[10,13] DPP-4 inhibitors exert slightly less pronounced blood glucose reductions than metformin but have better GI tolerability.[14] They lower plasma glucose by enhancing insulin release and reducing glucagon secretion. DPP-4 inhibitors in combination with metformin have been shown to be safe and effective for patients with T2D.[15] A study comparing a DPP-4 inhibitor and metformin with pioglitazone in patients with T2D showed that the DPP-4 inhibitor/metformin treatment combination resulted in weight loss (-1.4 kg) while pioglitazone led to weight gain (3.0 kg).[15]

Newer drugs now exist that target pathways which actually promote weight loss, including the injectable agents exenatide, dulaglutide, liraglutide, semaglutide, tirzepatide, and oral semaglutide. The majority are subcutaneous injections which act by mimicking the GI incretin hormone glucagon-like peptide-1 (GLP-1), which is normally released in response to food intake. GLP-1 RAs enhance glucose-dependent insulin secretion, suppress glucagon, and slow gastric emptying. GLP-1 RAs also improve glycemic control, decrease food intake, and enhance satiety. A recent study has demonstrated a 7% reduction in mean body weight following treatment of patients with both T2D and a BMI ≥27 with 1.0 mg of semaglutide—a dose approved for T2D.[16] The newly-approved 2.0 mg weekly dose of subcutaneous

TABLE 7.1 — List of Select Drugs That Are Weight Gaining, Weight Neutral, and Weight Reducing for Each Type of Treatment

Weight Gain	Weight Neutral	Weight Loss
Antidepressants		
Nortriptyline Doxepin Amitryptyline, imipramine Phenelzine Paroxetine Escitalopram Citalopram Fluoxetine >1 year) Sertraline (>1 year) Mirtazapine	Bupropion	Bupropion Fluoxetine (<1 year) Sertraline (<1 year)
Antihypertensives		
Prazosin Doxazosin Terazosin Metoprolol tartrate Propranolol Atenolol	Carvedilol Nebivolol	
Antidiabetics		
Insulin Sulfonylureas Thiazolidinediones	Alpha-glucosidase inhibitors Acarbose Miglitol DPP-4 inhibitors	Metformin GLP-1 receptor agonists Sodium glucose cotransporter 2 (SGLT2) inhibitors Vidagliptin Sitagliptin Pramlintide
Anti-epileptics		
Gabapentin Pregabalin Valproic acid Vigabatrin Carbamazepine	Lamotrigine Levetiracetam Phenytoin	Topiramate Zonisamide Felbamate

Continued

TABLE 7.1 — *Continued*

Weight Gain	Weight Neutral	Weight Loss
Contraceptives and Hormones		
Depo-medroxy-progesterone acetate Megestrol acetate (not a contraceptive but falls in the class of hormones)	Copper IUDs and barrier contraceptive methods (not considered drugs but represent alternatives to weight gain–promoting contraceptive drugs)	
Antihistamines		
Diphenhydramine Cetirizine Hydroxyzine Fexofenadine Meclizine Cyproheptadine	Loratadine	
Antipsychotics		
Clozapine Olanzapine Risperidone Quetiapine Perphenazine Aripiprazole	Ziprasidone	
Mood Stabilizers		
Lithium	Ziprasidone	Topiramate
Steroids		
Glucocorticoids	Immunosuppressive agents	
Progestins		
Corticosteroids (ie, prednisone)		

semaglutide produces even greater weight loss than the 1.0 mg weekly dose.[17] Head-to-head comparison trials have demonstrated that subcutaneous semaglutide is superior to exenatide and dulaglutide for weight loss, while oral semaglutide 14 mg once daily is superior to subcutaneous liraglutide 1.8 mg daily.[18] Tirzepatide, a new GIP and GLP-1 RA approved for the treatment of T2D (May 2022), showed 11-13% weight loss from baseline in clinical trials of patients with T2D.[19-22] It also demonstrated superiority to semaglutide 1.0 mg once weekly at all three once-weekly doses (5.0 mg, 10.0 mg, and 15.0 mg) with respect to weight loss in a head-to-head comparison trial of patients with T2D.[20] In a study of patients with obesity but without T2D, tirzepatide demonstrated a pharmacologically unprecedented 20.9% weight loss from baseline at the 15.0 mg once-weekly dose.[23] Like subcutaneous liraglutide and semaglutide, which in addition to being approved for T2D have also been approved by the FDA for treatment of obesity (at the 3.0 mg once daily and 2.4 mg once weekly dose, respectively), subcutaneous tirzepatide received FDA approval for the treatment of obesity in 2023 (at a once-weekly maintenance dose of 5 mg, 10 mg, or 15 mg); see *Chapter 9* for more information.

Sodium glucose cotransporter 2 (SGLT2) inhibitors are another new class of drug for the treatment of patients with T2D. SGLT2 inhibitors reduce glucose reabsorption by the kidneys, resulting in increased urinary glucose excretion. Due to subsequent caloric loss, treatment with SGLT2 inhibitors may result in weight loss in addition to reduced hyperglycemia. Studies of SGLT2 inhibitors in patients with T2D have shown patient weight reductions from baseline of up to 4.7 kg.[7]

The most common classes of drugs which can promote weight gain include insulin therapy, sulfonylureas, and thiazolidinediones (TZDs). The weight gain observed with insulin therapy appears to be greater than the weight gain associated with oral hypoglycemic agents, although it is difficult to compare, as patients who require insulin therapy generally have more severe diabetes and may experience more drastic changes in energy conservation. The amount of weight gain associated with insulin therapy

is associated with the daily insulin dose and mean plasma insulin level.[24] Weight gain–associated with sulfonylurea medications, another class of antidiabetic drugs, is related to the resulting increased insulin secretion. TZDs are another class of commonly used oral antihyperglycemic agents, which are often associated with weight gain. These compounds, including rosiglitazone and pioglitazone, lower glucose concentrations by increasing peripheral insulin sensitivity. Pioglitazone is currently recommended as the preferred TZD for treatment of T2D.[4,15]

The Clinical Guidelines Subcommittee (CGS) of The Endocrine Society recommends weight-losing and weight-neutral medications as first- and second-line agents in the management of T2D.[4] Specific antidiabetic medications that are associated with weight gain, weight neutrality, and weight loss are outlined in **Table 7.1**.

Antihypertensive Medications

β-blockers have long been used for the treatment of hypertension[25] and have been shown to be efficacious at decreasing CV morbidity and mortality. However, in certain populations, such as in patients with diabetes and hypertension, therapy with traditional β-blockers has been associated with adverse effects on lipid and insulin balance, leading to weight gain. Increased body weight is a particular clinical problem in the vast majority of hypertensive patients.[9,26] Treatment with β-blockers can decrease the metabolic rate by as much as 10%.[25] An analysis of eight randomized controlled hypertension trials showed that changes in body weight was higher in those that received β-blockers, with a median difference of 1.2 kg between the β-blocker group and the control group.[26]

However, not all β-blockers are associated with weight gain. Selective β-blockers with a vasodilating component such as carvedilol and nebivolol appear to have less weight gain potential and less of an impact on glucose and lipid metabolism.[26,27] Unlike metoprolol tartrate, carvedilol was not found in comparison studies to be associated with significant weight gain in patients with hypertension.[9]

Treatments for hypertension that are not associated with weight gain or insulin resistance include angioten-

sin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and calcium channel blockers (CCBs).[28] Angiotensin is overexpressed in obesity, directly contributing to obesity-related hypertension, providing support for the use of ACE inhibitors. CCBs are also effective in the treatment of obesity-related hypertension and have not been associated with weight gain or adverse changes in lipids.

The Clinical Guidelines Subcommittee (CGS) of The Endocrine Society recommends the use of ACE inhibitors, ARBs, and CCBs rather than β-adrenergic blockers as first-line therapy for hypertension in patients with T2D and obesity.[9,25,29,30] Specific antihypertensive drugs that are associated with weight gain, weight neutrality, and weight loss are outlined in **Table 7.1**.

Anticonvulsant Medications

Pharmacologic treatment for epilepsy may be associated with substantial weight changes that may increase morbidity and impair adherence to the treatment regimen.[31] Anti-epileptic drugs (AEDs) known to cause weight gain include valproic acid, carbamazepine, and gabapentin. Valproic acid has been shown to cause weight gain in both adults and children.[32] A study of long-term weight gain in adult epileptic patients on valproic acid therapy showed marked weight gain (>10% of baseline weight) in 47% of patients.[33] Carbamazepine has also been associated with weight gain, although not as significant as valproic acid or gabapentin,[34] and is sometimes classified as a weight-neutral AED.[31] By contrast, topiramate is associated with weight loss during the first year of treatment, particularly in patients with overweight or obesity.[35] This makes topiramate an attractive alternative anticonvulsant in this patient population.

In clinical practice, it is critical to weigh patients regularly and AED selection should be based on each patient's profile without sacrificing therapeutic efficacy. The first step in treatment is to weigh all patients at each visit, calculate BMI, and react to weight changes. In some patients, waist circumference may be an independent measure of health risk.[31] The CGS of The Endocrine Society recommends considering weight gain potential

in choosing an AED for any given patient. Specific AEDs that are associated with weight gain, weight neutrality, and weight loss are outlined in **Table 7.1**.

Contraceptives, Hormones, and Steroids

Weight gain is a complaint of some women using oral, injectable, and transdermal contraceptives and may cause discontinuation of treatment.[36,37] Specifically, the use of the progestins depo-medroxyprogesterone acetate and megestrol acetate has been associated with weight gain. Megestrol acetate has been prescribed to induce weight gain in wasting illnesses, such as acquired immunodeficiency syndrome (AIDS) and cancer. Studies have found that women who used depo-medroxyprogesterone continuously for 1 or 2 years experienced more average weight gain than those who did not.[38,39]

Specifically, weight gain after 1 year of use may range from 0.63-8.04 kg and increase further with ongoing use. Although not every patient will gain weight, predicting which patients will experience substantial weight gain is not simple. Le and colleagues found that women who experience >5% weight gain increase within 6 months of depot medroxyprogesterone acetate (DMPA) use puts them at high risk for continued weight gain.[40]

Still, the research on oral contraceptives and weight gain is conflicting. Some studies show significant increases in body weight, total cholesterol, and triglycerides in patients before and after contraceptive use,[41] while others emphasize the lack of concrete changes in weight gain over menstrual cycles.[37] In 2011, the Cochrane Review conducted a meta-analysis of 49 trials of contraceptives and determined that the current data are not sufficient to establish an effect of oral contraceptives on weight.[42] In women with a BMI >27 with comorbidities or >30, the CGS of The Endocrine Society recommends using barrier methods or non-hormonal IUDs before contraceptives that may be associated with weight gain.[4] Specific contraceptives that are associated with weight gain, weight neutrality, and weight loss are outlined in **Table 7.1**.

In menopausal women taking hormone replacement therapy (HRT), drug-induced weight gain may contribute to the poor patient compliance and greater CV disease

risk. It is difficult to quantify the specific impact of HRT on body weight and fat distribution because menopause itself is associated with changes in body composition, energy metabolism, and physical activity. Weight gain has not been consistently observed as a side effect of HRT but rather varies considerably, not only with respect to weight change but also changes in fat distribution.[8,43]

Long-term anti-inflammatory treatment of asthma with systemic corticosteroids frequently leads to fluid retention and weight gain. Even inhaled corticosteroids, which act locally and are rapidly processed by the body, are associated with weight gain. A recent retrospective cohort study demonstrated that pregnant women with overweight or obesity were more at risk for asthma than women with normal weight, and that women who gained ≥20 kg had a 2.7-fold increased odds of asthma compared with those who maintained their weight.[44] Weight gain has also been widely reported with use of steroids to treat rheumatoid arthritis (RA).[45] Other RA treatment options are available that do not cause weight gain. For example, leflunomide, a disease-modifying antirheumatic drug (DMARDs), has been associated with weight loss following a 6 month treatment course.[46] The CGS of The Endocrine Society recommends the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and DMARDs where possible.[4]

Antipsychotic and Antidepressive Medications

Weight gain is a common adverse effect of psychotropic drugs such as antipsychotics, antidepressants, mood stabilizers, and anxiolytics.[6] Antidepressants vary considerably with respect to their long-term weight gain potential, often depending on the length of therapy.[5] Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have been associated with significant weight gain. Several reports suggest that weight gain with TCAs ranged from 0.57 kg (1.27 lb) to nearly 1.4 kg (3.1 lb) per month of treatment.[4] Newer drugs, such as selective serotonin reuptake inhibitors (SSRIs) are now the preferred treatment for patients with depression. However, it must be noted that some SSRIs have been associated with weight loss during short-term treatment,

but weight gain during long-term treatment.[5] Therefore, when choosing an antidepressant treatment, the duration of therapy is especially important.

The CGS of The Endocrine Society recommends carefully weighing patient response and desired clinical efficacy with the potential of the antidepressant to cause weight gain. For example, while the SSRI paroxetine is associated with weight gain, bupropion is a weight neutral antidepressant. Although bupropion does not have the same efficacy or side-effect profile as SSRIs, it may be of benefit in those with depression. However, bupropion therapy is associated with an elevated risk of anxiety and may worsen some forms of depression.[4] Specific antidepressants that are associated with weight gain, weight neutrality, and weight loss are outlined in **Table 7.1**.

Many antipsychotic agents have weight gain as a side effect,[47] which may impede patient compliance, and exacerbate existing health issues in already overweight patients.[47,48] Different types of antipsychotic medications have different effects on histamine receptors, anticholinergic effects, and serotonin antagonistic response. A study investigating the effectiveness of five antipsychotic medications found that a weight gain of >7% from baseline occurred in 30% of those taking olanzapine, 16% for quetiapine, 14% for risperidone, 12% for perphenazine, and 7% of those taking ziprasidone.[49]

Since most antipsychotics are associated with weight gain, the CGS of The Endocrine Society recommends considering more weight neutral alternatives such as ziprasidone and aripiprazole when clinically indicated.[4] These drugs have been shown in clinical studies to cause less weight gain than other antipsychotics.[47,50,51]

Other Medications That May Induce Weight Gain

Potent antihistamines may contribute to weight gain. Histamine is a neurotransmitter released by the posterior hypothalamus. Intravascular administration of histamine reduced food intake in animal studies, whereas histamine antagonism stimulates food intake. Commonly-prescribed allergy medications, such as the H_1-receptor antihistamines cetirizine, fexofenadine, and

desloratadine, stimulate appetite and may cause weight gain.[52] Although it is not known whether the weight gain potential of sedating vs nonsedating antihistamines differ, it appears that it is proportional to the potency of the antihistamine.[8] A recent study demonstrated that the chances of being overweight were increased in patients who were prescribed antihistamines. Antihistamine users were also shown to have significantly higher weight, waist circumference, and insulin concentration than non-users.[53] The CGS of The Endocrine Society recommends the use of milder, less centrally acting antihistamines, when possible.[4]

Treatments for human immunodeficiency virus (HIV) include administration of antiretroviral therapy and protease inhibitors. Although effective for suppressing HIV viral activity, such treatments are associated with changes in the deposition of fat tissue in the body.[54,55] One study of 10 HIV patients treated with protease inhibitor-containing regimens found that patients gained an average of 19 lb after a period of 6 months.[54]

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Dietary Interventions, Physical Activity, and Behavioral Approaches to the Treatment of Obesity

Dietary Interventions

In order to achieve weight loss, an energy deficit is required. There are multiple approaches in counseling a patient regarding achievement of this goal. The provider may create a specific caloric target, which typically ranges from 1200-1500 kcal/day for women and 1500-1800 kcal/day for men. The caloric goal may need to be adjusted for their baseline body weight and physical activity level. Another approach is to estimate the individual's specific requirements and reduce it by 500 kcal/day or approximately 30% energy deficit. Finally, an ad libitum approach is where a formal energy deficit target is not defined, however, lower caloric intake is achieved by restricting or eliminating one or more particular food groups (for example, carbohydrates).[1]

Dietary intervention alone shows average weight loss is maximal at 6 months with small losses maintained for up to 2 years. Weight loss with dietary interventions ranges from 4 kg to 12 kg at 6 months, then slow weight regain is observed with total weight loss at 1 year of 4 kg to 10 kg and at 2 years, 3 kg to 4 kg.

Very Low Calorie Diets (VLCDs)

VLCDs are defined as diets providing <800 kcal/day. VLCDs are designed to provide rapid weight loss while maintaining lean body mass. They can be effective at improving some of the parameters of diseases that are associated with obesity, including uncontrolled diabetes, OSA, and hypertension. They often consist of four to five high protein shakes per day in addition to vitamin and mineral supplements. The protein content is typically high and fat content relatively low. Typically, VLCDs are

prescribed for no more than 16 weeks and are followed by a re-feeding diet before returning to regular food.

VLCDs are safe and effective when used in appropriately selected individuals with obesity (BMI >30) and require close physician supervision. Patients need a thorough workup to ensure that they can endure such rapid weight change. Side effects may include fatigue, dizziness, hair loss, and increased risk of gallstones. VLCDs may induce weight loss of 20% to 25% of initial body weight during the first 12 to 16 weeks of treatment[2]; however, they are not well maintained. Patients typically regain 35% to 50% of the weight loss within the first year following treatment and regain all of the weight by years 3 to 5.[3] Thus, while VLCDs provide very good short-term weight loss and may be appealing for patients, one needs to consider the long-term success.

Protein-Sparing Modified Fast (PSMF)

Total fasting reduces or eliminates hunger and effectively induces rapid weight loss. However, its application is limited due to the significant protein catabolism coupled with undesirable physiologic effects. The Protein-Sparing Modified Fast (PSMF) was developed by Bistrian, Blackburn, and colleagues.[4] A total fast is modified with the addition of 1.5 g/kg of ideal body weight of animal protein from egg albumin, lean meat, or fish. By adding protein, the fasting-associated nitrogen loss declines and allows for preservation of normal liver, endocrine, and hematopoietic functions. Carbohydrates are prohibited on this diet and fat is restricted to the protein source. Patients also receive a daily multivitamin in addition to supplemented sodium chloride, potassium, and calcium. The PSMF is characterized by a fall in serum insulin and glucose concentrations, a rise in free fatty acid and ketone levels, and the appearance of ketonuria, similar to what happens in a total fast. Ketone bodies are important for protein sparing in total and semi-starvation, substituting for protein-derived glucose as a fuel for the brain. Weight loss ranges from 1 to 3 kg weekly, depending on the patient's age, height, weight, sex, and level of activity.[5] The PSMF should be restricted to patients who are at least 30% above their desirable weight with substantial increased risk of morbidity and mortality associated attributed to their obesity.[6]

Low Calorie Diets (LCDs)

Low calorie diets typically provide 1200 to 1500 kcal/day and are intended to produce a more modest weight loss, typically producing an average of 0.5 kg/week of weight loss. Most weight loss diets (**Table 8.1**) are considered low calorie diets. When comparing VLCDs vs LCDs, data have shown that VLCDs result in greater short-term weight loss (16.1% vs 9.7%) but similar weight losses after 1 year (6.3% vs 5%).[7]

Low Carbohydrate Diets

Low carbohydrate diets restrict carbohydrate intake to 50-100 g daily without limitations on fat and caloric intake. The consumption of high protein foods has been shown to promote satiety. Further, by limiting an entire food group, total daily caloric intake levels fall.

Low Energy Density Diets

Energy density is defined as the number of calories in a given weight of food. The principle behind low energy density diets is that for the same amount of calories a larger volume of food can be consumed when the food is low in energy density vs high density. Thus patients may be more satisfied for a lower number of calories. In a study by Ello-Martin and associates,[8] women with obesity were randomized to a diet focusing on reducing fat intake or one that emphasized both fat reduction and increased intake of water-rich foods (fruits and vegetables). Subjects assigned to increase their water-rich foods lost significantly more weight (8.9 kg vs 6.7 kg); but, at 12 months, weight-loss maintenance was not significantly different. However, those in the water-rich food group reported significantly less hunger.

TABLE 8.1 — Sample Dietary Compositions

- High protein (25% protein, 30% fat, 45% carbohydrate)
- High protein Zone™ type diet (5 meals/day: 40% carbohydrate, 30% protein, 30% fat)
- Low carbohydrate diet (<20 g/day)
- Low fat diet (10% to 25% of total calories from fat)
- Low glycemic diet
- Mediterranean style diet
- AHA style Step 1 diet (1500-1800 calories/day: <30% fat, <10% saturated fat)

Low Glycemic Index Diets

The Glycemic Index (GI) is a system that ranks carbohydrate-containing food according to its effect on blood sugar levels, with pure glucose ranking highest (100) on the GI scale. A food's GI is determined by measuring rises in blood glucose after consuming 50g of available carbohydrate of a particular food compared to the same amount of carbohydrate from a reference food (typically glucose). Based on their GI, foods items may be divided into high-GI (GI≥70), medium-GI (55 ≤ GI < 70), and low-GI (GI < 55) foods.[9] Carbohydrates that are easily digested, quickly absorbed into the blood stream, and cause a quick rise in glucose are termed high GI foods. The quick increase in blood sugar level after ingestion of high GI foods also leads to a sharp rise in insulin levels. Low GI foods contain carbohydrates that are digested less rapidly, which causes a slower, more sustained release of sugar into the blood stream and leads to a slower insulin response.[10]

Low GI diets have been shown to reduce glycated hemoglobin, fasting glucose, BMI, total cholesterol, and LDL in patients with T1D, T2D, or impaired glucose tolerance, and are therefore recommended for glycemic control and weight reduction in this population.[11] Flattening the postprandial glucose levels may lead to longer satiety and less hunger, which may aid in weight reduction. In a large systematic review of 101 randomized controlled trials comparing low glycemic diet with other diets in patients with overweight or obesity, it was demonstrated that low GI diets yield similar weight reduction results as other diets. However, in studies where the patients achieved a GI reduction of 20 points or more in their diet, weight reduction significantly exceeded other diets. This demonstrates the effectiveness of low glycemic diet on weight reduction and highlights the importance of diet adherence.[12]

Mediterranean Diet

The Mediterranean diet is considered to be the healthiest dietary pattern available to reduce the prevalence of overweight and obesity, and it has been ranked #1 in the Best Diet score in regards to body weight and adiposity.[13] Although no strict definition of what is

considered the Mediterranean diet exists, its characteristics include: high fat intake that comes predominantly from extra-virgin olive oil (a monounsaturated fat), high intake of low glycemic index carbohydrates, moderate intake of fish, small to moderate consumption of dairy and poultry, and low consumption of red meat.[14] The large scale PREDIMED study investigated the impact of the Mediterranean diet on the incidence of CVD in older patients who did not have CVD at baseline. After 4.8 years, the study revealed hazard ratios of 0.69 (95% CI, 0.53–0.91) for a Mediterranean diet with extra-virgin olive oil and 0.72 (95% CI, 0.54–0.95) for a Mediterranean diet with nuts, compared to the control reduced-fat diet.[15]

In the same study, long term effects of ad libitum consumption of a Mediterranean diet on body weight and waist circumference were analyzed. Compared to the control group, a reduction in body weight of –0.43 kg (95% CI –0.86 to –0.01; P=0.044) with the Mediterranean diet with extra-virgin olive oil and of –0.08 kg (–0.50 to 0.35; P=0.730) for the Mediterranean diet with nuts was observed. The reduction in waist circumference was –0.55 cm (–1.16 to –0.06; P=0.048) in the Mediterranean diet with olive oil group, and –0.94 cm (–1.60 to –0.27; P=0.006) in the nut group, compared with the control group.[16] These results demonstrate that even without combining the Mediterranean diet with energy restriction, the participants did not gain body weight and demonstrated a reduction in central adiposity.

Intermittent Fasting

Intermittent fasting (IF) is a term for dietary regimens where periods of restricted energy intake (fasting) are alternated with periods of normal feeding. These dietary patterns are also often referred to as intermittent energy restriction (IER). There is a substantial degree of variation in the IF regimens, from fasting periods lasting for multiple days, to so-called time-restricted feeding (TRF), where the eating time window is restricted to 8 hours a day for several days of the week.[17]

A recent systematic review and meta-analysis tested the effect of various types of intermittent fasting regimens on obesity-related health outcomes. The study identified

28/104 (27%) associations of IF with beneficial metabolic and anthropometric outcomes that were statistically significant. Of the IF regimens, modified alternate-day fasting and fasting once or twice per week were associated with statistically significant weight loss of more than 5% in adults with overweight or obesity.[18] Overall, the study results suggest that IF strategies can be effective in improving obesity-related health outcomes and promote weight reduction.

Meal Replacements

The use of meal replacements (defined as functional foods in the form of a drink or a bar) as part of an overall treatment strategy has been shown to be beneficial and to an extent proportional to the number of meal replacements used over a period of several years.[19] A partial meal replacement (PMR) plan typically prescribes a low calorie (>800 or ≤1600 kcal/day) diet whereby one or two meals are replaced by commercially available, energy-reduced product(s) that are vitamin and mineral fortified, and includes at least one meal of regular foods. By reducing the variety of foods in the diet and increasing dietary structure, meal replacements facilitate adherence to the daily calorie goal. Meal replacements may also help patients who find themselves in challenging situations where they would otherwise make an unhealthy food choice (eg, when in car running late to work, they may use meal replacement vs stopping at fast food restaurant). Furthermore, meal replacements are often very convenient and eliminate the need to make decisions about how and what type of food to eat.

A meta-analysis[20] revealed that subjects prescribed either both PMR or a standard calorie deficit treatment plans lost significant amounts of weight at both the 3-month and 1-year evaluation time points, however there was greater weight loss in subjects receiving the PMR plan. The PMR group lost approximately 7% to 8% body weight and the RCD group lost approximately 3% to 7% body weight.

Evaluation of factors associated with 1-year weight-loss success from the Look AHEAD study demonstrated that the number of meal replacements consumed in the first 6 months was significantly related to weight loss at

week 26. Further, participants in the highest quartile of meal replacement use had four times greater odds of reaching the 7% weight-loss goal and 4.1 times greater odds of reaching the 10% weight-loss goal than participants in the lowest quartile.

Comparison of Macronutrient Content

There are multiple diet approaches available, each with specific regulations around nutrient content. In four meta-analyses of diet comparison, each summarizing 13 to 24 trials, the only consistent finding was that adherence—the degree to which participants continued in the program or met program goals for diet and physical activity—was most strongly associated with weight loss and improvement in disease-related outcomes.[21] Macronutrient content may influence dietary adherence via the satiating properties of protein, carbohydrates, and fat. However, dietary content is only one of many factors influencing adherence. The assumption that one diet is optimal for all persons fails to acknowledge the variation in adherence influenced by food preferences, cultural or regional traditions, food availability, and food intolerances.

Sacks and colleagues compared weight-loss diets with different compositions of fat, protein, and carbohydrates.[22] The study randomly assigned 811 adults with overweight or obesity to one of four diets; the targeted percentages of energy derived from fat, protein, and carbohydrates in the four diets were 20, 15, and 65%; 20, 25, and 55%; 40, 15, and 45%; and 40, 25, and 35%. The diets consisted of similar foods and patients were followed for 2 years. The primary outcome was the change in body weight between the low fat vs high fat and average protein vs high protein and in the comparison of highest and lowest carbohydrate content. At 6 months, participants assigned to each diet had lost an average of 6 kg, which represented 7% of their initial weight; they began to regain weight after 12 months.

By 2 years, weight loss remained similar in those who were assigned to a diet with 15% protein and those assigned to a diet with 25% protein (3.0 and 3.6 kg, respectively); in those assigned to a diet with 20% fat and those assigned to a diet with 40% fat (3.3 kg for

both groups); and in those assigned to a diet with 65% carbohydrates and those assigned to a diet with 35% carbohydrates (2.9 and 3.4 kg, respectively) Among the 80% of participants who completed the trial, the average weight loss was 4 kg. Ultimately, all of the reduced-calorie diets resulted in clinically meaningful weight loss, regardless of which macronutrients they emphasized.

Ultimately, the specific diet itself does not determine the success with weight loss, but rather the ability of the patient to adhere to the defined diet is of utmost importance.[23] Furthermore, all approaches can lead to meaningful weight loss if a reduction in dietary energy is achieved.

Limiting Consumption of Ultra-Processed Foods

Ultra-processed foods have been defined as "formulations mostly of cheap industrial sources of dietary energy and nutrients plus additives, using a series of processes"[24] that are being widely consumed due to high availability and low cost. A recent randomized controlled trial investigated the effect of consumption of ultra-processed food on energy intake. Subjects were admitted for 28 days and were randomized into two groups of 10 people, with each group receiving either ultra-processed or unprocessed diet for two weeks, followed by two weeks on the alternate diet. Ultra-processed and unprocessed meals were matched for total calories and other nutritional parameters, but the participants were allowed to consume the meals in ad libitum quantities within a 60-minute window, 3 times a day. During the ultra-processed diet consumption phase, the consumption of calories increased by 508 ± 106 kcal/day (P=0.0001) and there was a strong correlation between the energy intake and weight change (r = 0.8; P <0.0001).[25]

This suggests that a diet consisting of overconsumption of ultra-processed foods leads to excessive energy intake which may lead to weight gain. Another large multinational prospective cohort study of 348,748 participants has also found a positive association between weight gain and high consumption of ultra-processed diet. It also found that higher intake of ultra-processed food was associated with 15% greater risk (95% CI 1.11–1.19) of developing overweight in subjects with

regular weight at baseline, and 16% greater risk (95% CI 1.09–1.23) of developing obesity in participants with overweight at baseline.[26]

Considering Food Order

In addition to diet composition, the order of intake of nutrient groups has an effect on postprandial sugar and hormone levels. In a pilot study of 11 subjects with T2D, it was found that the blood glucose levels after a meal decreased by 28.6% (P=0.001), 36.7% (P=0.001), and 16.8% (P=0.03) at 30, 60, and 120 min, respectively, in subjects who consumed carbohydrates after vegetables and proteins compared to subjects who consumed carbohydrates first. A reduction in postprandial insulin levels at 60 min and 120 min after the meal were observed in the group that consumed carbohydrates last.[27] Another study investigated the effect of consumption order of carbohydrates on the appetite-stimulating hormone ghrelin. In this study, 16 subjects with overweight or obesity and T2D consumed carbohydrate-first meals, carbohydrate-last meals, and sandwich meals where the food groups were ingested all at once. The study demonstrated changes in ghrelin levels from baseline of -11.45% ± 3.86% and 4.13 ± 4.38% (P = 0.003) in the carbohydrate-last vs carbohydrate-first groups 180 mins postmeal.[28] Timing the carbohydrate ingestion can lead to improvements in glycemia and the associated hormone excursions.

Diet Composition Relative to Changes in Cardiometabolic Parameters

The effects of low-carbohydrate diets (≤45% of energy from carbohydrates) vs low-fat diets (≤30% of energy from fat) on metabolic risk factors were compared in a meta-analysis.[21] Compared with participants on low-fat diets, those on low-carbohydrate diets experienced a statistically significantly lower reduction in total cholesterol (-2.7 mg/dL; 95% CI: 0.8, 4.6), and LDL cholesterol (-3.7 mg/dL; 95% CI: 1.0,6.4), but a greater increase in HDL cholesterol (3.3 mg/dL; 95% CI 1.9,4.7) and a greater decrease in triglycerides (-14.0 mg/dL; 95% CI: -19.4, -8.7). Reductions in body weight, waist circumference, and other metabolic risk factors were not significantly different between the two diets.

Foster and colleagues compared patients prescribed a low-carbohydrate diet (<20 g/d for 3 months with subsequent increase in their carbohydrate content once desired weight achieved) compared with a low-fat diet (limited energy intake 1200-1800 kcal/day, <30% fat).[29] Weight loss was approximately 11 kg (11%) at 1 year and 7 kg (7%) at 2 years. There were no differences in weight. During the first 6 months, the low-carbohydrate diet group had greater reductions in DBP, triglyceride levels, and very-LDL cholesterol levels, and lesser reductions in LDL cholesterol levels. The low-carbohydrate diet group had greater increases in HDL cholesterol levels at all time points.

Further, Sacks and associates compared four diets with varying nutrient composition; as mentioned above, the targeted percentages of energy derived from fat, protein, and carbohydrates in the four diets were 20, 15, and 65%; 20, 25, and 55%; 40, 15, and 45%; and 40, 25, and 35%.[22] He concluded that all the diets reduced risk factors for CV disease and diabetes at 6 months and 2 years. At 2 years, the two low-fat diets and the highest-carbohydrate diet decreased LDL cholesterol levels more than did the high-fat diets or the lowest-carbohydrate diet (low-fat vs high-fat, 5% vs 1%; highest-carbohydrate vs lowest-carbohydrate, 6% vs 1%). The lowest-carbohydrate diet increased HDL cholesterol levels more than the highest-carbohydrate diet (9% vs 6%, $P = 0.02$). All the diets decreased triglyceride levels similarly, by 12% to 17%. All the diets except the one with the highest carbohydrate content decreased fasting serum insulin levels by 6% to 12%; the decrease was larger with the high-protein diet than with the average-protein diet (10% vs 4%, P=0.07).

Some tips for counseling patients on diet are shown in **Figure 8.1**, along with visual aids to help patients to make portion sense (**Figure 8.2**).

Physical Activity

Physical activity is an essential component of a weight-loss treatment program. Physical activity influences the composition of weight loss so that a higher proportion of the weight loss is loss of fat as opposed

FIGURE 8.1 — Simple Tips to Counsel Patients

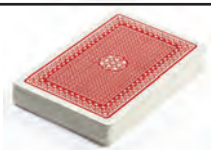
1. The Plate Method: Patient should be encouraged to reduce the size of their plate to a 9-inch dinner plate. Half of the plate should be filled with nonstarchy vegetables (broccoli, cauliflower, lettuce, tomatoes, etc), a quarter of the plate with a lean source of protein (lean chicken, turkey, fish), and the remaining quarter with whole grains (brown rice, potato, whole grain breads).

2. Avoid liquid calories (regular soda, juice, coffee with cream) and focus on water, seltzer water, and other noncaloric alternatives.
3. Replace regular sugar with noncaloric sweeteners.
4. Avoid skipping meals: plan small regular meals throughout the day in order to keep your hunger controlled. Consider using a meal replacement if unable to plan a healthy meal (such as a protein shake or high protein bar).
5. Replace all white bread with whole wheat/whole grain alternatives.
6. Swap regular salad dressings, mayonnaise, and butter with low-fat or fat-free alternatives.
7. Avoid high fat, high calorie, high carbohydrate snacks (cookies, pastries, cakes).
8. Snack on fruits, low fat dairy (yogurt, cottage cheese).

to fat-free mass (or lean muscle) which is metabolically desirable.[30] Exercise may help offset the reduction in resting metabolic rate that results from weight loss itself. Further engaging in physical activity may help facilitate dietary adherence.

The AHA/ACC/TOS Guidelines for the Management of Overweight and Obesity in Adults[1] recommend at least 150 minutes of aerobic activity per week (equal to at least 30 minutes per day, most days of the week). This level of activity produces an energy expenditure of approximately 1000 kcal per week. Physical

FIGURE 8.2 — Visual Aids Make "Portion Sense"

Visual Cue	Approximate Portion Size
	~1 cup Food[a]: green salad, frozen yogurt, medium piece of fruit, baked potato
	~½ cup Food[a]: cut fruit, cooked vegetables, pasta, rice
	~¼ cup Food[a]: dried fruit (eg, raisins)
	~3 ounces Food[a]: meat, poultry
	~3 ounces Food[a]: grilled fish
	~1½ ounces Food[a]: natural cheese

Tools to help patients understand proper portion size.
[a] Food = one FGP serving of food(s) listed.

activity becomes even more critical during the weight-loss maintenance phase. Members of the National Control Weight Registry report maintaining their weight loss by engaging in approximately 1 hour of physical activity per day, expending an average of 2825 calories per week.[31] In order to maintain weight loss, higher intensity activity (at least 200 to 300 minutes per week) is recommended.[32]

The aim of physical activity is not purely to increase CV activity (eg, walking, running) but it is also important to include resistance training exercises. The Centers for Disease Control and Prevention (CDC) recommend that adults engage in muscle-strengthening activities at least 2 days per week. Resistance training is an effective technique to improve muscle strength and endurance, prevent and modify chronic medical conditions, and modify coronary risk factors. Further, strength training can help preserve fat-free mass during weight loss to enhance metabolic rate.

It is often difficult for patients to achieve physical activity goals and time is often a limiting barrier. Research has demonstrated that continuous vs intermittent activity of the same total duration produces equivalent improvements in CV health, weight, and fasting or postprandial lipemia.[33] Therefore, one may want to counsel patients to focus on achieving small bouts of exercise, multiple times per day (10 minutes of a brisk walk, three to four times daily) as a means to achieve their goal and improve compliance.

Behavioral Modification

Behavioral modification is a critical component in successfully treating obesity and can be used to support any type of dietary intervention. The goal of behavioral treatment is to target maladaptive eating behaviors that contribute to obesity. Various components of a behavioral treatment program may include the following.

Self-Monitoring of Dietary Intake

Individuals with obesity have been shown to underestimate their food intake;[34] thus behavioral treatment programs focus on teaching participants to accurately record the type, amount, and total calories of the foods they consume throughout the day. They are also taught how to read food labels and use measuring tools to help improve the accuracy of their food records. Data have shown that individuals who regularly record their food intake lose significantly more weight than those who do so inconsistently.[35]

Trigger or Stimulus Control

Techniques to help control a patient's environment is crucial in helping support their goal of eating healthy and exercising. As an example, patients may be taught to store food out of sight, limit the number of places they eat to the kitchen or dining table, and refrain from eating while engaging in other activities (eg, working on computer, watching television).

Problem-Solving Techniques

In order to be successful, patients need to be taught problem-solving techniques for when they encounter barriers that limit their ability to be consistent with a healthy diet and exercise plan. The goal is to plan solutions in advance such that the patient can overcome the challenge with ease. As an example, a patient may travel for work and not have access to their usual planned meals; however, with proper education and support, they can create solutions that allow them to overcome an uncertain situation.

Cognitive Restructuring

Individuals attempting to lose weight often exhibit catastrophic thinking that leads them to abandon their weight control efforts. As an example, they may overeat one evening and decide to give up altogether. However, by teaching them to replace these thoughts with more rationale responses, they can recognize a setback as a temporary lapse and continue to move forward.

Relapse Prevention

Techniques for long-term success must focus on relapse prevention, particularly focusing on high-risk situations that may create a set-back (eg, vacations, illness, or periods of high stress). Behavioral therapy focuses on teaching patients to plan for these events and incorporate them into the long-term weight management plan.

Behavioral treatment may be offered individually or in group sessions (usually 10 to 15 individuals who all begin the treatment program at the same time) and the sessions often last from 60 to 90 minutes. A group format provides social support, and individuals can help one another develop strategies to overcome barriers around achieving the diet and exercise goals. Group sessions are often held weekly during the active weight-loss phase and

may taper to biweekly meetings that can help individuals focus on weight maintenance.

Intensive Lifestyle Intervention

The Diabetes Prevention Program (DPP) was designed to determine whether a lifestyle intervention directed at reducing body mass and increasing activity levels, or the medication metformin, would delay or prevent development of diabetes in a high-risk population (for more information on DPP, see *Chapter 4*).[36] The DPP lifestyle intervention was delivered by individual lifestyle coaches. Participants received a 16-week core curriculum over the first 6 months and then had at least one contact monthly for the remainder of the study (at least one in-person visit every 2 months with phone visits as needed to maintain once per month contact) (**Table 8.2**). Participants who received behavioral treatment achieved a weight loss on average of 7 kg at the end of 1 year (vs 0.1 kg for placebo).[37] Although on average, they regained one third of their weight in years 2 to 3, they were able to reduce their risk of developing T2D by 58% compared with participants treated in the placebo group. Further,

TABLE 8.2 — Comparison of Lifestyle Intervention Features of Diabetes Prevention Program and Look AHEAD Trial

	DPP	Look AHEAD
Intervention format	Individual sessions	Group plus individual sessions
Frequency of follow-up	16 sessions in the first 6 months with minimum of one in-person follow-up every 2 months thereafter	24 sessions in the first 6 months; 18 sessions in months 7-12; minimum of monthly individual sessions years 2-4
Refresher groups/campaigns	3 times/year after first 6 months	2-3 times/year in years 2 and beyond
Supervised activity sessions	2 times/week throughout the trial	Periodically in refreshers or campaigns

even though all groups eventually received some amount of lifestyle intervention, at 10 years, the cumulative incidence of diabetes was lowest in the lifestyle intervention group; this intervention delayed onset of diabetes by 4 years relative to 2 years in the metformin group.[38]

The ongoing Look AHEAD Study is designed to evaluate the effect of an ILI in people with overweight and T2D and its effect on CV outcomes. Subjects were randomly assigned to ILI or usual care (ie, diabetes support and education [DSE]).[39] The Look AHEAD intervention is delivered in a group plus individual format by intervention teams that include registered dietitians, behavioral psychologists, and exercise specialists. Participants are offered weekly sessions with three group sessions and one individual session per month in the first 6 months and two group sessions and one individual session per month during months 7 through 12, for a total of 42 sessions the first year. In years 2 to 4, participants are offered a minimum of monthly individual sessions and one additional contact by group, phone, mail, or e-mail (**Table 8.2**). Subjects in the ILI lost 8.6% of their weight at year 1 compared with 0.7% for DSE. At year 4, ILI participants lost an average of 4.7% of initial weight compared with 1.1% for DSE.

Commercially Available Lifestyle Interventions with Evidence-Based Findings

Weight Watchers

Weight Watchers is a commercially available weight-loss program that emphasizes behavioral modifications. Johnston and colleagues randomized patients to either a self-help program vs enrollment in the Weight Watchers program.[40] The Weight Watchers program allowed for three different avenues to access treatment: either weekly meetings, use of a mobile application, or online Weight Watchers tools. Weights were evaluated at baseline, 3 months, and 6 months. Patients enrolled in the Weight Watchers program lost an average of 10.1 lb at 6 months vs 1.3 lb for the self-help group. Importantly, those participants who accessed all of the Weight Watchers platforms more frequently (attended 50% of meetings and used the mobile app and online tools at least 2 times per

week) lost on average 19 lb, those using two platforms lost 9.5 lb, and those only utilizing one platform lost 9.3 lb.

Jenny Craig

The Jenny Craig weight management program involves one-to-one behavioral counseling, as well as packaged prepared meal plans. Rock and associates evaluated the use of the Jenny Craig program (weekly in person or telephone-based counseling) for 2 years to see how it compared with usual care[41] (where participants received two individualized weight-loss counseling sessions and monthly contacts). The mean weight loss was 7.4 kg (or 7.9% of initial weight) at 24 months for the center-based group, 6.2 kg (or 6.8%) for the telephone-based group, and 2 kg (or 2.1%) for the usual care group.

NutriSystem

NutriSystem is a commercially available portion-controlled diet program which provides entrees and snacks to encourage weight loss. Foster and colleagues evaluated participants with obesity and T2D (mean BMI 39, mean A1C 7.5)[42] who were randomly assigned to the portion-controlled diet (NutriSystem) or a DSE program. After the initial 3 months, the NutriSystem group continued on the portion-controlled diet for the remaining 3 months, and the DSE group crossed over to the portion-controlled diet for the remaining 3 months. At 3 months, the NutriSystem lost significantly more weight (7.1% ± 4%) than the DSE group (0.4% ± 2.3%). From 3 to 6 months, the change in weight for both groups was statistically significant. After 3 months, the NutriSystem group had greater reductions in A1C than the DSE group (-0.88 ± 1.1 vs 0.03 ± 1.09; P <0.001). From 3 to 6 months the NutriSystem group had no further change in A1C, while the DSE group showed a significant reduction. The data suggest that patients with obesity and T2D can have significant improvements in weight and glycemic control with the use of a commercially available portion-controlled diet.

Other Commercially Available Interventions

There are a plethora of commercially available lifestyle intervention programs and diets.[13] Some programs

promote weight-loss through very low-calorie meal replacements, lower than Weight Watchers, Jenny Craig, or NutriSystem. These regimens result in short-term efficacy, but their long-term efficacy and sustainability are unclear.[43] A large systematic review and meta-analysis collated various commercial weight-loss programs and concluded that 57% of participants lost <5% of their initial body weight, which is not a clinically significant weight-loss outcome, and there were high rates of attrition.[44] Although the study concluded that the weight-loss programs do not produce clinically significant results, this conclusion has been challenged with a view that for patients with overweight or obesity even a modest weight decrease under 5% is beneficial.[45] Overall, there are a multitude of commercial weight-loss programs available on the market, but for most there is a lack of efficacy data.

Use of Remote and Mobile Technologies in Behavioral Weight-Loss Programs

Typical behavioral weight-loss programs involve weekly or twice-monthly, face-to-face counseling sessions and can be very effective as described above. However, it can be time and resource intensive and may not be convenient for the patient or provider. Mobile devices have been used successfully to provide dietary guidance and self-monitor weight and other health-related variables.[46] Electronic solutions can deliver a weight loss of up to 5 kg at 6 to 12 months, which is greater than that resulting from no or minimal intervention offered on the internet or in print.[1]

Appel and associates compared two behavioral weight-loss interventions in a primary care setting using remote vs in-person support.[47] Patients were randomized to remote weight-loss support via telephone, a study specific website and email, or offered in-person group and individual sessions along with the other three remote means of support. The groups were evaluated over 24 months. The data showed both groups clinically significant weight loss (-4.6 kg for remote support vs -5.1 kg for in-person) and it did not differ significantly between the groups. The data support the notion that remote support can provide a meaningful alternative weight-loss solution.

Harvey-Benino evaluated an internet-based behavioral obesity treatment program.[48] Subjects were either randomized to an internet-based solution, in-person, or a combination of internet/in-person program (hybrid). Evaluation of the weight loss at 6 months was -5.5 kg, 8 kg, and 6 kg for the internet, in-person, and hybrid, respectively. Although weight loss was greater for the in-person program, meaningful weight loss was achieved via remote solutions at a fraction of the cost ($372 vs $706). Further, the addition of in-person to the internet solution did not appear to improve weight-loss outcomes.

Long-term weight maintenance is often one of the most challenging aspects of obesity treatment. Radcliff and colleagues evaluated the use of a telephone vs face-to-face extended-care lifestyle maintenance program after an initial weight-loss program. After 12 months of treatment, weight regain was evaluated in both groups compared with a control. Weight regain was 1.7 kg, 2.1 kg, and 3.1 kg for the in-person, telephone, and control group, respectively. Both interventions were helpful in keeping weight off, but the telephone format had a lower overall cost.

Intellihealth/Evolve

Intellihealth is a healthcare technology company whose stated mission is to scale and broaden access to effective medical weight management. The approach combines behavioral changes and pharmacotherapy to achieve clinically significant weight loss and sustained weight maintenance. The obesity treatment software platform and app, Evolve, train and support providers to deliver specialized obesity treatment, support patients with education and resources, and enable remote patient monitoring (RPM), among other features. Participation in the online program (formerly known as BMIQ), when combined with population health management (without pharmacotherapy), produced a statistically significant greater weight loss as compared to usual care or the online program only. After 12 months, greater than 5% weight-loss was achieved by 32.3%, 14.9% and 20.8% of participants in the combination program, usual care, and the online-only program, respectively.[49] The clinical decision support and medication decision support delivered

through Evolve provide a structured weight-management intervention for patients as well as obesity treatment recommendations for healthcare providers. The platform aims to bring obesity care to more people by providing online tools for both patients and healthcare providers.

Telemedicine

The SARS-CoV-2 pandemic and the associated quarantine orders have negatively impacted people with obesity, with many reporting increased depression, anxiety, stress eating, and decrease in exercise.[50] In order to provide continued care for patients, healthcare providers pivoted to telemedicine instead of in-person visits. A retrospective investigational study explored the effect of virtual visits on weight loss in patients with obesity. The effects of in-person visits, video visits, and hybrid visits were compared. After 6 months, the median percent weight change was not significantly different between the three modes of visits, with -4.3%, -5.6%, and -5.8% in in-person, hybrid and video groups respectively. A similar pattern was observed for the percent of patients who achieved ≥5% weight loss with 46.4%, 55.3%, and 59.3% for in-person, hybrid, and video groups, respectively.[51] These results warrant a discussion on incorporating telemedicine visits into the treatment of obesity beyond the pandemic. It seems likely that telemedicine will be just as effective and potentially more convenient than in-person treatment which may help facilitate long-term follow-up which is critical for maintaining weight loss.

Summary

Ultimately, the treatment of obesity requires a long-term intervention. Patients increasingly rely on technology and mobile-based solutions for many of their day-to-day operations. The use of internet-based solutions as a tool in obesity treatment appears to provide a cost-effective alternative to traditional weight-loss interventions.

Comprehensive Lifestyle Interventions

The best diet and behavioral treatment programs typically result in a 10% weight loss during the first 6

months of treatment. Key components to success include three critical components:

- Choosing a diet that appeals to the patients' preferences so that they can easily adhere to it.
- Incorporating significant physical activity.
- Providing a behavioral treatment plan to reinforce the necessary strategies to maintain weight loss.

Long-term, ongoing contact between the patient and practitioner enhances weight-loss maintenance.

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Pharmacologic Treatment

The development and approval of new antiobesity drugs is particularly challenging. In addition to safety concerns, the FDA criteria for a drug to be approved for treatment of obesity are quite stringent. A new agent must induce statistically significant placebo-adjusted weight loss of ≥5% at 1 year or that ≥35% of patients should achieve >5% weight loss (which must be at least twice that induced by placebo). In addition, the FDA also requires that the medication shows evidence of improvement in metabolic biomarkers, including BP, lipids, and glycemia.

The search for safe and effective pharmacologic weight-loss agents began in the late 19th century with the discovery that sheep thyroid extract increased metabolic rate and induced significant weight loss. However, the use of thyroid hormone treatment in euthyroid patients increased the risk of cardiac arrhythmias and cardiac arrest. Subsequently, many different classes of pharmacologic agents, such as centrally acting amphetamine derivatives and 5-HT–releasing agents appeared (and then disappeared) over the next half century.[1-3] As a result, very few approved weight-loss drugs were available prior to 2012 (**Table 9.1**).

Centrally acting amphetamine derivatives (desoxyephedrine, phentermine, and diethylpropion) were among the earliest pharmacologic agents used for weight loss.[3] However, growing concerns about CV risk and abuse potential led to a decline in their use by the early 1970s. Although still available in many countries, phentermine and diethylpropion were largely superseded in the 1970s and 1980s by the 5-HT–releasing agents fenfluramine and dexfenfluramine. In the early 1990s, evidence of superior efficacy over either compound given alone led to the widespread use in the United States of the combined treatment with phentermine and fenflu-

TABLE 9.1 — Obesity Medications Available Prior to 2012

Medication	FDA Date of…	
	Approval	Withdrawal
Phentermine	5/1959	–
Diethylpropion	8/1959	–
Benzphetamine	10/1960	–
Fenfluramine	6/1973	9/1997
Phendimetrazine	9/1982	–
Dexfenfluramine	4/1996	9/1997
Orlistat	4/1999	–
Sibutramine	11/1997	10/2008
Rimonabant	6/2006[a]	10/2008

[a] Withdrawn by FDA; approved in Europe but subsequently withdrawn.

Powell AG, et al. *Clin Pharmacol Ther*. 2011;90(1):40-51.

ramine (fen-phen). Within only a few years, reports of cardiac valvulopathy associated with fenfluramine and dexfenfluramine (particularly in combination with phentermine) resulted in withdrawal of these two agents from the market. Although fenfluramine and dexfenfluramine were withdrawn due to safety concerns, phentermine as monotherapy was considered safe and was not withdrawn from the market. Phentermine continued to be the most commonly prescribed drug.

Despite an inauspicious history, the pharmacologic management of obesity is at an exciting crossroad. Research has identified many new therapeutic targets. Currently available treatment options in the United States include phentermine, orlistat, a fixed-dose combination of phentermine and topiramate ER, a fixed-dose combination of naltrexone SR and bupropion SR, liraglutide, semaglutide, and tirzepatide. Semaglutide, which was approved in June 2021, and tirzepatide, which was approved in November 2023, have demonstrated a strikingly significant weight reduction induced by a therapeutic agent, with one third of patients achieving efficacy comparable to metabolic and bariatric surgeries. Notably, lorcaserin, a selective 5-HT2C receptor agonist

which has been previously been used, was withdrawn from the market in February 2020 due to increased risk of various cancers.

Currently, seven antiobesity medications are approved by the FDA:

- Phentermine
- Orlistat
- A fixed-dose combination of phentermine and topiramate ER
- A fixed-dose combination of naltrexone SR and bupropion SR
- Liraglutide
- Semaglutide
- Tirzepatide

The choice of which antiobesity pharmacotherapy to initiate must be individualized to the patient taking into consideration their goals, their unique challenges with weight loss, the presence of any co-existing medical conditions, and any contraindications to specific medications or drug-drug interactions. Once a medication is initiated, patients should be assessed at regular intervals (preferably at least monthly for the first three months) to assess its efficacy, which is typically defined as ≥5% total body weight loss at three months, and to assess its safety. If a medication is not effective, or if it is causing intolerable side effects, it should be discontinued and a different medication started. If a patient is successful with any given medication but reaches a weight loss plateau (typically defined as no weight loss over 1-3 months), the medication should not be discontinued abruptly as it may lead to weight regain. Instead, consider increasing the dose of that medication if possible or adding on a different medication which may target a different pathway and lead to additional weight loss. Given that obesity is a chronic disease, any medication that is started for the treatment of obesity should be considered a long-term medication and patients will require long-term treatment and follow-up to ensure weight loss maintenance. Clinical trials, including STEP 4 and SURMOUNT-4 (see the semaglutide and tirzepatide sections below)

support the idea that discontinuing medications at the patient's desired goal weight may lead to weight regain, and therefore is typically not recommended.

Table 9.2 provides summaries of the prescribing information for these medications. The rest of this chapter is dedicated to sections discussing the currently available agents. These sections include discussion of the currently published trials that support the safety and efficacy of each drug. However, it is important to keep in mind that this is a rapidly developing field, with many other studies in the pipeline, especially for the newer agents (ie, GLP-1 receptor agonists, GIP/GLP-1 receptor agonists).

Phentermine

Phentermine, approved in 1959, has historically been the most commonly prescribed antiobesity agent in the United States. Phentermine is a sympathomimetic amine with pharmacologic activity similar to the prototype drugs of this class (eg, amphetamines). It is believed to suppress appetite. The approved duration of treatment is only 3 months because of a lack of understanding of the chronic nature of obesity, and because the safety data for phentermine came from a short-term study. Phentermine is approved for use in adolescents 17 years of age and older.[4]

Efficacy

The efficacy of continuous vs intermittent phentermine was evaluated in an early 36-week, double-blind, placebo-controlled study in 108 women who had overweight or obesity. Patients were randomized into three groups: one group received phentermine continuously for 36 weeks, another group received placebo continuously, and the third group alternated phentermine and placebo every 4 weeks (**Figure 9.1**).[5] The mean weight loss was -12.2 and -13.0 kg in patients who received phentermine continuously and intermittently, compared with -4.8 kg in the group treated with placebo. Attrition was 41% and data were presented for completers only. Statistical differences were not reported. Individual responses to therapy were variable but irrespective of the method employed, weight loss diminished with duration of treatment.

Furthermore, there seemed to be no advantage in taking phentermine continuously.

Studies investigating the use of phentermine alone for weight loss published in the 1960s and 1970s typically presented only completer analyses and had high dropout rates leading to an overstatement of efficacy.[6] A more recent study by Aronne and colleagues investigating the differences in weight loss using phentermine alone vs in combination reported weight loss of 5.1% at 28 weeks.[7]

Safety

The most common treatment-emergent adverse events (TEAEs) with phentermine include:

- Dizziness
- Dry mouth
- Difficulty sleeping
- Irritability
- Nausea
- Vomiting
- Diarrhea
- Constipation.

Prescribing, Dosing, and Administration

The recommended dosage of phentermine is 15 mg to 37.5 mg orally once daily before breakfast or 1 to 2 hours after breakfast, or 8 mg up to three times daily 30 minutes before meals (**Table 9.2**). Dosage should be individualized to obtain an adequate response (in this case, appetite suppression) with the lowest effective dose. For example, a sufficient dose for some patients may be as low as a half tablet of the 8 mg daily tablet. Other patients may benefit from taking a half tablet of 37.5 mg twice daily. Administration in the late evening should be avoided because it may lead to insomnia.

Consider prescribing phentermine to patients who would benefit from appetite suppression.

Phentermine is not recommended for use in pediatric patients ≤16 years of age. Phentermine is a schedule IV controlled substance.

TABLE 9.2 — Summaries of Prescribing Information for Currently Available Obesity Medications

	Phentermine[1,2] (Adipex-P, Lomaira)	Orlistat[3] (Xenical)	Phentermine/ Topiramate E[4] (Qsymia)	Naltrexone SR/ Bupropion SR[5] (Contrave)	Liraglutide[6] (Saxenda)	Semaglutide[7] (Wegovy)	Tirzepatide[8] (Zepbound)
Estimated % weight loss drug minus placebo, ITT data	5.1%: 28 weeks[9] 15 mg qd	3.1%: 1 year[10] 120 mg tid	6.6%: 1 year[11] 7.5 mg phen/ 46 mg top ER qd	4.8%: 56 weeks[12] 8 mg nal/90 mg bup 2 tabs bid	4.5%: 56 weeks[6] 3 mg qd	12.4%: 68 weeks[7] 2.4 mg per week	17.8%: 72 weeks[8] 15 mg per week
Available formulations	8 mg, 15 mg, 30 mg, 37.5 mg	Capsules: 60 mg, (over-the-counter), 120 mg	Capsules: 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, 15/92 mg	Tablets: 8 mg naltrexone HCl/90 mg bupropion HCl	Prefilled pen for subcutaneous injection (mg): 0.6, 1.2, 1.8, 2.4, 3.0 once daily in the abdomen, thigh, or upper arm	Pre-filled pen for subcutaneous injection (mg): 0.25, 0.5, 1, 1.7, 2.4 once weekly in the abdomen, thigh, or upper arm	Pre-filled pen for subcutaneous injection (mg): 2.5, 5, 7.5, 10, 12.5, 15 once weekly in the abdomen, thigh, or upper arm
Dosage[a]/ administration	For 15 mg, 30 mg, 37.5 mg one tablet daily	1 capsule 3 times per day before	Once daily in morning. Avoid evening	Week 1: 1 morning tablet; Week 2: 1 morning	Subcutaneous injection once daily into the	Subcutaneous injection once weekly into	Subcutaneous injection once weekly into the

	For 8 mg, 1 tablet up to 3 times daily (avoiding dosing too late to avoid insomnia)	meals	dose to prevent insomnia. Start with phen/top ER 3.75/23 mg daily for 14 days then increase to 7.5/46 mg daily; evaluate weight loss at 12 weeks–if <3%, discontinue or escalate to 11.25/69 mg once daily for 14 days, followed by 15/92 mg once daily	tablet, 1 evening tablet; Week 3: 2 morning tablets, 1 evening tablet; Week 4 and onward: 2 morning tablets, 2 evening tablets A total daily dosage of 2 tablets twice daily reached at start of Week 4 Not to be taken with high-fat meal	abdomen, thigh, or upper arm, irrespective of meals. Recommended dose is 3 mg daily, to be initiated at 0.6 mg/day for 1 week, then increased at weekly intervals until 3 mg is reached	the abdomen, thigh, or upper arm, irrespective of meals. Recommended dose is 1.7 mg or 2.4 mg weekly (2.4 mg only in pediatric patients). Initiate with 0.25 mg weekly and increase dose every 4 weeks as tolerated until the maximum dose is achieved	abdomen, thigh, or upper arm, irrespective of meals. Recommended dose is 5 mg, 10 mg, or 15 mg weekly. Initiation with a dose of 2.5 mg weekly is recommended; the dose should then be increased every 4 weeks as tolerated. The recommended maintenance dosages are 5, 10 or 15 mg.

Continued

TABLE 9.2 — *Continued*

	Phentermine[1,2] (Adipex-P, Lomaira)	Orlistat[3] (Xenical)	Phentermine/ Topiramate E[4] (Qsymia)	Naltrexone SR/ Bupropion SR[5] (Contrave)	Liraglutide[6] (Saxenda)	Semaglutide[7] (Wegovy)	Tirzepatide[8] (Zepbound)
Discontinuation criteria	Not specified	Not specified	7.5/46 mg daily: <3% weight loss at 12 weeks – discontinue or increase dose 15/92 mg daily: <5% weight loss at 12 weeks Discontinue 15/92-mg dose gradually to prevent possible seizure	<5% weight loss after 12 weeks at maintenance dose	<4% weight loss after 16 weeks at maintenance dose	Unable to tolerate the 1.7 mg once weekly dose	Not specified
Indication(s)	Short-term (a few weeks) adjunt in a	For obesity management,	Adjunct to a reduced-calorie diet and in-	Adjunct to a reduced-calorie diet and in-	Adjunct to reduced calorie diet and in-	In combination with a reduced calorie diet and	In combination with a reduced-calorie diet and

	regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial BMI ≥30 or ≥27 in the presence of other risk factors (eg, controlled hypertension, diabetes, hyperlipidemia); Approved for use in adults	including weight loss and maintenance when used in conjunction with a reduced-calorie diet in patients with an initial BMI ≥30, or ≥27 in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia); Also indicated to re-	creased physical activity for chronic weight management in adults with initial BMI of ≥30, or ≥27 in the presence of ≥1 weight-related comorbidity (eg, hypertension, T2D, or dyslipidemia)	creased physical activity for chronic weight management in adults with initial BMI of ≥30, or ≥27 in the presence of ≥1 weight-related comorbidity (eg, hypertension, T2D, or dyslipidemia)	creased physical activity for chronic weight management in: • adult patients with initial BMI of ≥30 or ≥27 in the presence of ≥1weight-related comorbid condition (eg, hypertension, T2D, or dyslipidemia) • pediatric patients aged 12 years and older with	increased physical activity: • to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in adults with established cardiovascular disease and either obesity or overweight • to reduce excess body weight and	increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition

Continued

TABLE 9.2 — *Continued*

	Phentermine[1,2] (Adipex-P, Lomaira)	Orlistat[3] (Xenical)	Phentermine/ Topiramate ER[4] (Qsymia)	Naltrexone SR/ Bupropion SR[5] (Contrave)	Liraglutide[6] (Saxenda)	Semaglutide[7] (Wegovy)	Tirzepatide[8] (Zepbound)
Indications (*continued*)	and adolescents ≥17 years of age	duce the risk for weight regain after prior weight loss; Approved for use in pediatric patients ≥12 years of age			body weight >60 kg and an initial BMI corresponding to 30 for adults (obesity) by international cut-offs	maintain weight reduction long term in: – adults and pediatric patients aged 12 years and older with obesity – adults with overweight in the presence of at least one weight-related comorbid condition	

Contraindications	• Pregnancy • Nursing • History of CVD (eg, CAD, stroke, arrhythmias, CHF, uncontrolled hypertension • During or within 14 days following administration of MAOIs • Hyperthyroidism • Glaucoma • Agitated states • History of drug abuse	• Pregnancy • Nursing • Chronic malabsorption syndrome • Cholestasis • Known hypersensitivity to orlistat or to any component of this product	• Pregnancy • Nursing • Glaucoma • Hyperthyroidism • Use during or within 14 days of taking MAOIs	• Pregnancy • Nursing • Uncontrolled hypertension • Seizure disorder or history of seizures • Use of other bupropion-containing products • Bulimia or anorexia nervosa • Chronic opioid or opioid agonist (eg, methadone) or partial agonists (eg, buprenorphine) use or acute	• Pregnancy • Nursing • Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 • Patients with a prior serious hypersensitivity reaction to liraglutide or to any of the product components	• Pregnancy • Nursing • Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 • Known hypersensitivity to semaglutide or any of the excipients • History of pancreatitis	• Pregnancy • Nursing • Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 • Known hypersensitivity to tirzepatide or any of the excipients • History of pancreatitis

Continued

TABLE 9.2 — *Continued*

	Phentermine[1,2] (Adipex-P, Lomaira)	Orlistat[3] (Xenical)	Phentermine/ Topiramate ER[4] (Qsymia)	Naltrexone SR/ Bupropion SR[5] (Contrave)	Liraglutide[6] (Saxenda)	Semaglutide[7] (Wegovy)	Tirzepatide[8] (Zepbound)
Contraindications (*continued*)	• Known hypersensitivity, or idiosyncrasy to sympathomimetic amines			opiate withdrawal • Patients undergoing an abrupt discontinuation of alcohol, benzodiazepines, barbiturates and antiepileptic drugs • Use during or within 14 days of taking MAOIs • Known allergy to bupropion naltrexone, or any other component of this drug	• History of pancreatitis		

Most frequently reported side effects	Dizziness, drymouth, difficulty sleeping, constipation, irritability	Bloating, diarrhea, fecal urgency, fecal incontinence	Paresthesia, dizziness, dysgeusia, insomnia constipation, dry mouth	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea	Nausea, diarrhea, constipation, vomiting, injection site reactions, headache, hypoglycemia (when used with insulin secretagogues or insulin), dyspepsia, fatigue, dizziness, abdominal pain, increased lipase, upper abdominal pain, pyrexia, gastroenteritis	Nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia (when used with insulin secretagogues or insulin), flatulence, gastroenteritis, gastroesophageal reflux disease	Nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, injection site reactions, fatigue, hypersensitivity reactions, eructation, hair loss, gastroesophageal reflux disease, flatulence, abdominal distension, dizziness, hypotension

Continued

TABLE 9.2 — *Continued*

	Phentermine[1,2] (Adipex-P, Lomaira)	Orlistat[3] (Xenical)	Phentermine/ Topiramate ER[4] (Qsymia)	Naltrexone SR/ Bupropion SR[5] (Contrave)	Liraglutide[6] (Saxenda)	Semaglutide[7] (Wegovy)	Tirzepatide[8] (Zepbound)
Warnings/ precautions	• Rare cases of primary pulmonary hypertension and/or serious regurgitant cardiac valvular disease • Risk of abuse and dependence • Concomitant alcohol use • Impairment in the ability to perform potentially hazardous activities	• Rare reports of liver injury with hepatocellular necrosis or acute hepatic failure • Increased levels of urinary oxalate, with rare cases of nephrolithiasis and oxalate nephropathy	• Fetal toxicity • Increased heart rate • Suicide, mood, and sleep disorders • Acute myopia and glaucoma • Cognitive impairment • Metabolic acidosis • Creatinine elevation • Risk of hypoglycemia	• Suicidal behavior and ideation • Risk of seizure may be minimized by adhering to dosing schedule and avoiding coadministration with high-fat meal • Increased blood pressure and heart rate • Hepatotoxicity	• Risk of thyroid C-cell tumors • Acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis • Acute gallbladder disease: substantial or rapid weight loss can increase risk of	• Risk of thyroid C-cell tumors • Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis • Acute gallbladder disease: substantial or rapid weight loss can increase the risk of cholelithiasis	• Risk of thyroid C-cell tumors • Acute kidney injury • Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis • Acute gallbladder disease: substantial or rapid weight loss can increase the risk

	• Reduction in the doses of antidiabetic agents in some patients	with renal failure • Cholelithiasis	with diabetic agents • Risk of hypokalemia in patients on potassium-wasting diuretics	• Angle-closure glaucoma • Use of antidiabetic medications: weight loss may cause hypoglycemia	cholelithiasis • Serious hypoglycemia can occur when used with an insulin secretagogue (eg, sulfonylurea) • Increased heart rate • Renal impairment • Hypersensitivity reactions • Suicidal behavior and ideations	• Hypoglycemia: concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia • Acute kidney injury • Hypersensitivity reactions • Diabetic retinopathy complications in patients with T2D	of cholelithiasis and cholecystitis • Hypoglycemia: concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia • Severe gastrointestinal disease • Hypersensitivity reactions

Continued

TABLE 9.2 — *Continued*

	Phentermine[1,2] (Adipex-P, Lomaira)	Orlistat[3] (Xenical)	Phentermine/ Topiramate ER[4] (Qsymia)	Naltrexone SR/ Bupropion SR[5] (Contrave)	Liraglutide[6] (Saxenda)	Semaglutide[7] (Wegovy)	Tirzepatide[8] (Zepbound)
Warnings/ precautions (*continued*)						• Heart rate increase • Suicidal behavior and ideation	• Suicidal behavior and ideations • Diabetic retinopathy complications in patients with T2D
REMS program	No	No	Yes	No	No	No	No
Schedule IV controlled substance	Yes	No	Yes	No	No	No	No

bid, twice a day; qd, once a day; REMS, Risk Evaluation and Mitigation Strategies; tid, three times a day.

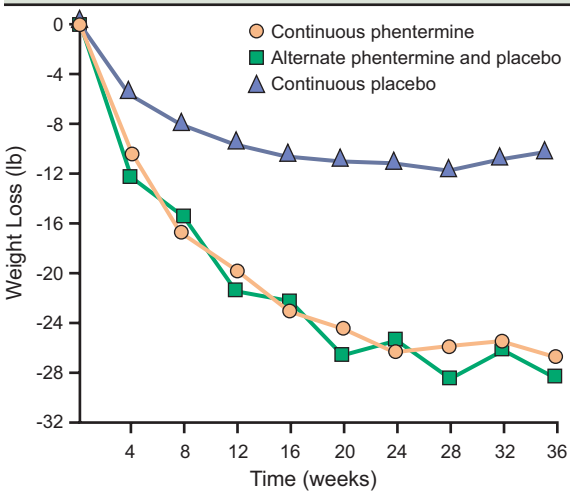
[a] For dosing in patients with renal or hepatic impairment, see the prescribing information.

[1] Adipex-P [package insert]. Parsippany, NJ: Teva Pharmaceuticals USA, Inc; 09/2020.

[2] Lomaira [package insert]. Newtown, PA: KVK-Tech, Inc; 09/2016.

[3] Xenical [package insert]. Montgomery, AL: H2-Pharma, LLC; 08/2017.
[4] Qsymia [package insert]. Campbell, CA: Vivus, Inc; 03/2022.
[5] Contrave [package insert]. Brentwood, TN: Currax Pharmaceuticals LLC; 11/2021.
[6] Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk; 04/2023.
[7] Wegovy [package insert]. Plainsboro, NJ; Novo Nordisk Inc; 07/2024.
[8] Zepbound [package insert]. Indianapolis, IN; Lilly USA; 10/2024.
[9] Aronne LJ, et al. *Obesity (Silver Spring)*. 2013;21(11):2163-2171.
[10] Yanovski SZ, Yanovski JA. *JAMA*. 2014;311(1):74-86.
[11] Gadde KM, et al. *Lancet*. 2011;377(9774):1341-1352.
[12] Greenway FL, et al. *Lancet*. 2010;376(9741):595-605.

FIGURE 9.1 — Weight Loss With Continuous or Intermittent Treatment With Phentermine



Munro JF, et al. *Br Med J*. 1968;1(5588):352-354.

Orlistat (Xenical)

Orlistat is indicated for the treatment of obesity, including weight loss and weight maintenance, when used in conjunction with a reduced-calorie diet. It also is indicated to reduce the risk for weight regain after prior weight loss. Orlistat is approved for use in adults and children and adolescents 12 years of age or older. Unlike the other weight-loss agents which reduce appetite and/or enhance energy expenditure, orlistat inhibits pancreatic and gastric lipases, thereby reducing fat absorption from the gut.[8]

Efficacy

The efficacy of orlistat was demonstrated in a 4-year, double-blind, prospective study in which 3305 patients were randomized to lifestyle changes plus either orlistat 120 mg or placebo three times daily.[9] Patients had a BMI ≥30 and normal (79%) or impaired (21%) glucose tolerance (IGT). Mean weight loss after 4 years was significantly greater with orlistat (5.8 vs 3.0 kg with placebo; P <0.001) and similar between orlistat recipients with

impaired or normal glucose tolerance at baseline (**Figure 9.2**). In addition to causing significant weight loss after 4 years relative to placebo, the cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat, corresponding to a risk reduction of 37.3% (P <0.0032).

Safety

Most common TEAEs with orlistat (5% and at least twice that of placebo) include:

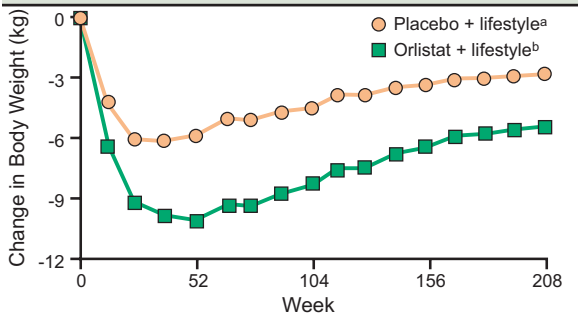
- Oily spotting
- Flatus with discharge
- Fecal urgency
- Fatty/oily stool
- Oily evacuation
- Increased defecation
- Fecal incontinence.[8]

Prescribing, Dosing, and Administration

Orlistat is available in a 60 mg capsule (over the counter) and a 120 mg capsule (prescription). The recommended dosage of orlistat is one capsule three times a day with each main meal containing fat during or up to 1 hour after the meal (**Table 9.2**).[8]

- Advise patients to take a nutritionally balanced, reduced-calorie diet that contains approximately 30% of calories from fat.

FIGURE 9.2 — Effects of Orlistat as an Adjunct to Lifestyle Modification Diet on Weight Loss and Incidence of Diabetes in At-Risk Patients with Obesity



Torgerson JS, et al. *Diabetes Care.* 2004;27(1):155-161.

- Distribute the daily intake of fat, carbohydrate, and protein over three main meals.
- Advise patients to take a multivitamin containing fat-soluble vitamins to ensure adequate nutrition.

Phentermine/Topiramate ER (Qsymia)

This fixed-dose combination formulation of phentermine and topiramate ER (phen/top ER) was approved by the FDA in 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults who have obesity (BMI ≥30) or overweight (BMI ≥27) and at least one weight-related comorbid condition (eg, hypertension, dyslipidemia, or T2D). Phentermine is also approved by the FDA as monotherapy for the treatment of obesity, as above. Topiramate is FDA approved as monotherapy for the treatment of epilepsy (1996) and for migraine prophylaxis (2004).

Although the exact mechanism of action is not known, the effect of phentermine on body weight is likely mediated by release of catecholamines in the hypothalamus, resulting in reduced appetite and decreased food consumption, but other metabolic effects may also be involved. The precise mechanism of action of topiramate on body weight is also not known, although it may be due to its effects on both appetite suppression and satiety enhancement induced by a combination of pharmacologic effects with various neurotransmitters.[10,11] The combination of phentermine with topiramate has been shown to have a greater weight-loss benefit than either medication alone while mitigating the side-effect profile.

Efficacy

The efficacy of phen/top ER on weight loss was assessed in two 1-year randomized, double-blind, placebo-controlled studies (EQUIP and CONQUER),[10,12] and a 2-year extension trial (SEQUEL).[13] Both studies included a 4-week titration period followed by 52 weeks of treatment. The SEQUEL study was a placebo-controlled, double-blind, 52-week extension (for a total of 108 weeks of treatment) in patients who completed the CONQUER study.[13] During these studies, a well-balanced, reduced-calorie diet to result in an approximate 500 kcal/day decrease in caloric intake was recommended

to all patients, and patients were offered nutritional and lifestyle modification counseling. The two co-primary efficacy outcomes in these studies after 1 or 2 years of treatment were:

- Percent weight loss from baseline
- Treatment response defined as achieving ≥5% weight loss from baseline.

The efficacy results from these trials of phen/top ER are summarized in **Table 9.3**.

The EQUIP trial included only patients with class II and III obesity (BMI ≥35 with no upper limit), while the CONQUER trial included patients with both overweight and obesity (BMI 27-45) with ≥2 significant comorbidities, including elevated BP or requirement for ≥2 antihypertensive medications; triglycerides >200-400 mg/dL or treatment with ≥2 lipid-lowering agents; elevated FPG (>100 mg/dL) or diabetes; and/or waist circumference ≥102 cm for men or >88 cm for women.[10] Patients with T2D were excluded from participating in the EQUIP study while diabetic patients were neither specifically included nor excluded in the CONQUER study.

EQUIP

This trial randomized a total of 1267 patients to receive placebo, phen/top ER 3.75/23 mg, or phen/top ER 15/92 mg once daily.[10] Overall, mean age was 42.7 years, BMI was 42.0, mean waist circumference was 120.8 cm, and 83% were female, with a substantial representation of Black patients (16% to 18%). There were no significant between-group differences in any baseline variable. A total of 59.9% of randomized patients completed the study regardless of whether they continued taking their assigned treatment (52.9% placebo, 61.0% phen/top ER 3.75/23 mg, 66.4% phen/top ER 15/92 mg; (P <0.0001 for difference), while 53.7% reported taking the assigned study drug/placebo for the full intended treatment period (46.9% placebo, 57.3% phen/top ER 3.75/23 mg, 58.8% phen/top ER 15/92 mg; P = 0.0003 for difference). The most common reasons for discontinuation were lost to follow-up or withdrawal of consent (more common in placebo than active treatment groups)

TABLE 9.3 — Summary of Primary Efficacy Endpoints From Three Randomized, Placebo-Controlled Trials of Combination Treatment With Phentermine/Topiramate ER in Patients with Overweight/Obesity

	Placebo	Phentermine/Topiramate ER (mg/mg)		
		3.75/23	7.5/46	15/92
EQUIP: Patients with Obesity (BMI ≥35 kg/m^2)/1-Year				
mITT-LOCF population (n)	498	234	—	498
Weight loss from baseline (kg)	-1.6	-5.1[a]	—	-10.9[a]
Patients losing ≥5% baseline weight (%)	17	45[a]	—	67[a]
Patients losing ≥10% baseline weight (%)	7	19[a]	—	47[a]
CONQUER: Patients with Obesity or Overweight (BMI 27-45 kg/m^2) with ≥2 Risk Factors/1-Year				
mITT-LOCF population (n)	979	—	488	981
Weight loss from baseline (kg)	-1.2	—	-7.8[a]	-9.8[a]
Patients losing ≥5% baseline weight (%)	21	—	62[a]	70[a]
Patients losing ≥10% baseline weight (%)	7	—	37[a]	48[a]

SEQUEL: Patients with Overweight and Obesity (BMI 27-45 kg/m^2) with ≥2 Risk Factors/2-Year Double-Blind, Placebo-Controlled Extension Study of CONQUER Trial				
Patients who continued original blinded treatment (*n*)	227	—	153	295
Weight loss from baseline (kg) difference from placebo	-2.1	—	-9.6[a]	-10.9[a]
Patients losing ≥5% baseline weight (%)	30.0	—	75.2[a]	79.3[a]
Patients losing ≥10% baseline weight (%)	11.5	—	50.3[a]	53.9[a]

[a] $P < 0.0001$ vs placebo.

[1] Allison DB, et al. *Obesity (Silver Spring)*. 2012;20(2):330-342.
[2] Gadde KM, et al. *Lancet*. 2011;377(9774):1341-1352.
[3] Garvey WT, et al. *Am J Clin Nutr*. 2012;95(2):297-308.

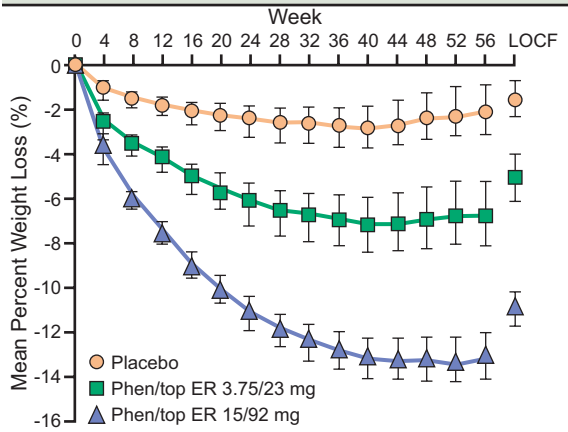
or AEs (more common in active treatment than placebo groups). Overall, discontinuations were lower in patients receiving active treatments.

Treatment with each phen/top ER dosage resulted in statistically significant weight loss from baseline compared with placebo during 56 weeks of treatment (**Figure 9.3**). The percent weight loss from baseline was significantly greater with phen/top ER 15/92 mg than with phen/top ER 3.75/23 mg. In addition, a significantly greater proportion of patients randomized to either dosage of phen/top ER achieved weight loss of either ≥5% or ≥10% (**Table 9.3**). In this study in which all patients had obesity, a separate analysis showed that these results did not differ significantly according to baseline BMI.[10]

CONQUER

In this trial, a total of 2487 patients were randomized to treatment with placebo (n = 979), phen/top

FIGURE 9.3 — EQUIP Study: Time Course of Weight Change During 52 Weeks of Treatment With Phentermine/Topiramate ER in Patients with a BMI ≥35 kg/m^2



Data from ITT-LOCF population.

Allison DB, et al. *Obesity (Silver Spring)*. 2012;20(2):330-342.

ER 7.5/46 mg (n = 488), or phen/top ER 15/92 mg (n = 981) once daily. Baseline patient characteristics were similar across treatment groups[12]: 70% patients were women and 86% were White. Overall, 11% of patients were Black. The mean age for the whole group was 51.1 years, mean body weight was 103.1 kg, and BMI was 36.6. At baseline, 52% of patients had hypertension, 36% had hypertriglyceridemia, 68% had IGT or IFG (including T2D), and 16% had T2D. Overall, half of patients had ≥3 protocol-specified comorbidities, and virtually all (98%) had abdominal obesity. A total of 38% of patients prematurely discontinued the study drugs (43% placebo, 31% phen/top ER 7.5/46 mg, and 36% in the phen/top ER 15/92 mg groups). However, 69% of all randomized patients had an endpoint (week 56) assessment.

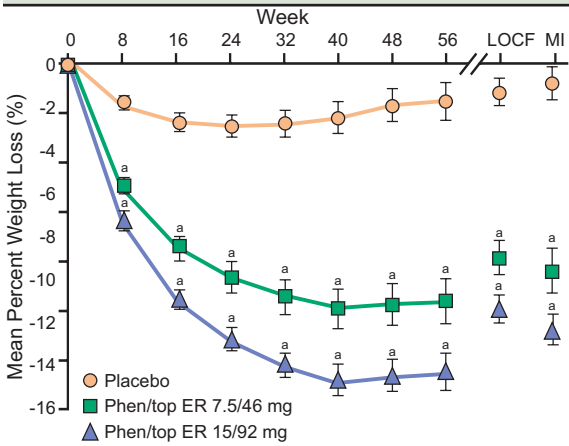
Compared with placebo, both dosages of phen/top ER resulted in and maintained significantly greater weight losses throughout the 56-week course of treatment (**Figure 9.4**). The reductions from baseline body weight with both dosages of phen/top ER were significantly greater than with placebo (**Table 9.3**). In addition, the reduction with phen/top ER 15/92 mg was significantly greater compared with phen/top ER 7.5/46 mg. Significantly more patients who received either phen/top ER dosages achieved a ≥5% and/or ≥10% weight reduction from baseline compared with placebo. Significantly more patients achieved these goals with the phen/top ER 15/92 mg dosage compared with the lower dosage.

Long-Term Efficacy

SEQUEL

The study was a placebo-controlled, double-blind, 108-week extension study in which volunteers who had completed the CONQUER study continued with their original randomly assigned treatment: placebo (n = 227), phen/top ER 7.5/46 mg (n = 153), or phen/top ER 15/92 mg (n = 295) to complete a total of 108 weeks of treatment. All patients participated in a lifestyle-modification program. Baseline demographic, anthropometric, and clinical characteristics, including comorbidities, were similar among patients in all three treatment arms of the

FIGURE 9.4 — CONQUER: Time Course of Weight Change During 52 Weeks of Treatment With Phentermine/Topiramate ER in Patients with Overweight or Obesity (BMI 27-45 kg/m^2) With ≥2 Risk Factors



Data from ITT-LOCF population.

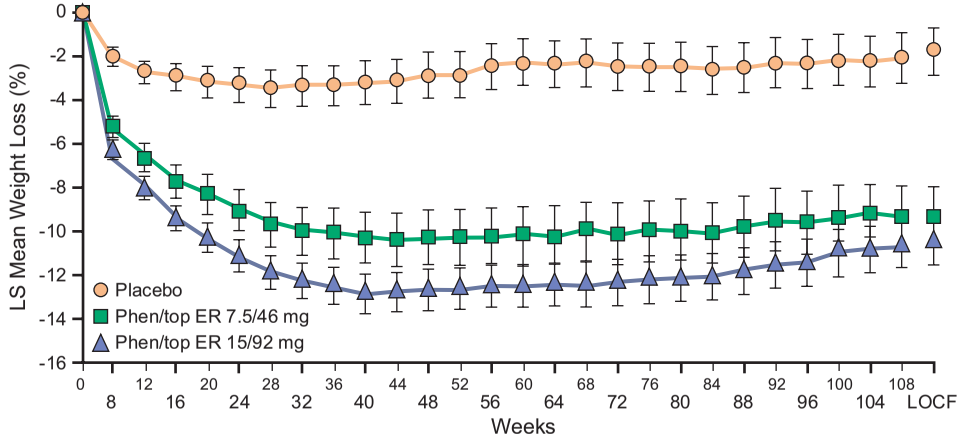
[a] P <0.0001.

Gadde KM, et al. *Lancet*. 2011;377(9774):1341-1352.

study.[13] Overall, 84.0% of patients completed the extension study, including 86.3% of those assigned to placebo, 82.5% of those assigned to phen/top ER 7.5/46 mg, and 83.1% of those in the phen/top ER 15/92 mg group.

Patients in both active treatment arms experienced significantly greater percentage weight losses compared with those in the placebo arm, and these weight losses were maintained at all time points during 108 weeks of treatment compared with placebo (**Figure 9.5**). At week 108, the mean percentage changes from baseline in body weight were significantly greater (P <0.0001) in the phen/top ER groups compared with placebo (-1.8%, -9.3%, and -10.5% with placebo, phen/top ER 7.5/46 mg, and phen/top ER 15/92 mg, respectively). In addition, significantly greater proportions of patients treated with each dosage of phen/top ER achieved weight losses of ≥5% and ≥10% compared with placebo-treated patients (**Table 9.3**).

FIGURE 9.5 — SEQUEL: Time Course of Weight Change During 108 Weeks of Treatment With Phentermine/Topiramate ER in Patients with Overweight/Obesity



Data from overall study completer population.

Garvey WT, et al. *Am J Clin Nutr.* 2012;95(2):297-308.

Secondary Efficacy Endpoints

All three of these trials also assessed changes from baseline in metabolic, CV, and anthropomorphic risk factors associated with obesity.

In the EQUIP trial, patients treated with phen/top ER 15/92 mg had significantly greater changes compared with those in the placebo group in:

- SBP and DBP
- Heart rate
- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides
- Fasting glucose
- Waist circumference (**Table 9.4**).

Patients in the phen/top ER 3.75/23 mg group experienced numerically, but not always significantly different changes, except the changes in SBP and waist circumference were significant.[10]

In the CONQUER study, phen/top ER 15/92 mg compared with placebo showed significant changes in:

- BP
- Waist circumference
- Concentrations of lipids
- Fasting glucose and insulin (**Table 9.4**).[12]

Improvements in risk factors were most pronounced in patients with pre-existing comorbid diseases. In patients with hypertension at baseline, there were greater reductions in SBP with both dosages of phen/top ER than with placebo, and more patients had their antihypertensive drugs withdrawn in the phen/top ER 7.5/46 mg group. Patients with diabetes at baseline had greater reductions in A1C with both dosages. Patients with prediabetes had greater reductions in fasting blood glucose and fewer patients progressed to T2D.

In the SEQUEL study, treatment with phen/top ER 15/92 mg compared with placebo resulted in significantly greater changes from baseline in:

- Lipid parameters and triglycerides
- Fasting glucose and insulin
- Waist circumference (**Table 9.4**).[13]

In the phen/top ER 7.5/46 mg group, changes were significantly greater compared with placebo in LDL cholesterol, triglycerides, fasting insulin, A1C, and waist circumference. Among patients without diabetes at baseline, the annualized incidence rates for progression to T2D were 3.7%, 1.7%, and 0.9% in the placebo, phen/top ER 7.5/46 mg, and phen/top ER 15/92 mg treatment groups, respectively. These findings indicate a 54% reduction in the progression to T2D.

Safety

In the 1-year clinical trials with phen/top ER, AEs that occurred at a rate of ≥5% and at a rate at least 1.5 times placebo included paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth (**Table 9.5**). Dose-related trends in the incidences of such AEs were noted. Other less frequent events occurring more commonly with the highest phen/top ER dosage included:

- Depression
- Irritability
- Alopecia
- Anxiety
- Disturbance in attention
- Hypoesthesia.

Serious AEs were similar across treatment groups. Most AEs reported were mild in severity and the rates of serious AEs were similar across treatment groups.[11]

In the 1-year placebo-controlled clinical studies, the rates of discontinuations due to AEs were:

- Phen/top ER 3.75/23 mg: 11.6%
- Phen/top ER 7.5/46 mg: 11.6%
- Phen/top ER 15/92 mg: 17.4%
- Placebo: 8.4%.

TABLE 9.4 — Summary of Mean Changes From Baseline in Metabolic and CV Risk Factors and Waist Circumference in Randomized, Placebo-Controlled Trials With Fixed-Dose Combination Treatment With Phentermine/Topiramate ER in Patients with Overweight/Obesity

	EQUIP:[1] Patients with Obesity (BMI ≥35 kg/m^2)			CONQUER:[2] Patients with Obesity or Overweight (BMI 27-45 kg/m^2) With ≥2 Risk Factors			SEQUEL:[3] 2-Year Double-Blind, Placebo-Controlled Extension of CONQUER Trial		
		Phen/Top ER (mg/mg)			Phen/Top ER (mg/mg)			Phen/Top ER (mg/mg)	
	Placebo	3.75/23	15/92	Placebo	7.5/46	15/92	Placebo	7.5/46	15/92
Change From Baseline	(*n* = 498)	(*n* = 234)	(n = 498)	(*n* = 994)	(*n* = 498)	(*n* = 995)	(*n* = 227)[a]	(*n* = 153)[a]	(*n* = 295)[a]
Total cholesterol (%)	-3.5	-5.4	-6.0	-3.3	-4.9	-6.3	NA	NA	NA
LDL cholesterol (%)	-5.5	-7.7	-8.4	-4.1	-3.7	6.9	-10.7	-4.6	-5.6
HDL cholesterol (%)	0.0	+0.5	+3.5	+1.2	+5.2	+6.8	+4.7	+7.3	+11.9
Triglycerides (%)	+9.1	+5.2	-5.2	+4.7	-8.6	-10.6	+0.4	-12.5	-13.7
Systolic BP (mm Hg)	+0.9	-1.8	-2.9	-2.4	-4.7	-5.6	-3.2	-4.7	-4.3
Diastolic BP (mm Hg)	+0.4	-0.1	-1.5	-2.7	-3.4	-3.8	-3.9	-3.7	-3.5

Heart rate (bpm)	-0.2	-0.3	+1.2	-0.1	+0.1	+1.7	+0.4	+1.3	+1.7
Fasting glucose (mg/dL)	+1.9	+0.8	-0.6	+0.13	-0.01	-0.07	+3.7	+0.1	-1.2
Fasting insulin (mU/mL)	NA	NA	NA	+5.1	-24.0	-27.6	-2.6	-5.3	-5.2
A1C (%)	NA	NA	NA	+0.1	0	-0.1	+0.2	+0.01	0.0
Waist circumference (cm)	-3.1	-5.6	-10.9	-2.4	-7.6	-9.2	-3.6	-9.8	-10.6

Highlighted results indicate significantly better results with phentermine/topiramate ER compared with placebo.

[a] The results from this trial are from patients who continued their original, blinded-study treatments from baseline to week 108, including a 4-week titration period.

[1] Allison DB, et al. *Obesity (Silver Spring)*. 2012;20:330-342.

[2] Gadde KM, et al. *Lancet*. 2011;377:1341-1352.

[3] Garvey WT, et al. *Am J Clin Nutr*. 2012;95(2):297-308.

TABLE 9.5 — Summary of Adverse Events With Incidence ≥1% Leading to Treatment Discontinuation in the EQUIP and CONQUER Clinical Trials

		Phentermine/Topiramate ER (mg/mg) (%)		
AE Leading to Discontinuation	**Placebo (%) (n = 1561)**	**3.75/23 (n = 240)**	**7.5/46 (n = 498)**	**15/92 (n = 1580)**
Blurred vision	0.5	2.1	0.8	0.7
Headache	0.6	1.7	0.2	0.8
Irritability	0.1	0.8	0.8	1.1
Dizziness	0.2	0.4	1.2	0.8
Paresthesia	0.0	0.4	1.0	1.1
Insomnia	0.4	0.0	0.4	1.6
Depression	0.2	0.0	0.8	1.3
Anxiety	0.3	0.0	0.2	1.1

Qsymia [package insert]. Campbell, CA: Vivus, Inc; 03/2022.

The most common AEs that led to discontinuation of treatment are shown in **Table 9.5**.

In the SEQUEL study, the most common treatment emergent AEs were upper respiratory tract infection, constipation, paresthesia, sinusitis, and dry mouth.[11] The types of TEAEs that occurred between weeks 56 and 108 were similar to those reported in the overall CONQUER population sample from weeks 0 to 56. However, the incidence of individual TEAEs was markedly lower in the second year (weeks 56 to 108) than in the first year (weeks 0 to 56). The incidences of serious AEs from weeks 0 to 108 were 6.2% with placebo, 5.9% with both phen/top ER 3.75/23 mg and phen/top ER 7.5/46 mg, and 8.1% with phen/top ER 15/92 mg. The percentage of patients who discontinued due to AEs by week 108 was also similar across treatment groups (3.1%, 4.5%, and 4.4% in the placebo, phen/top ER 7.5/46 mg, and phen/top ER 15/92 mg groups, respectively).

Prescribing, Dosing, and Administration

Phen/top ER is available in four dosage levels of phentermine and topiramate ER (**Table 9.2**). The lowest-dose formulation contains phentermine 3.75 mg and topiramate ER 23 mg, the mid-level formulation contains phentermine 7.5 mg and topiramate ER 46 mg, and the highest dosage formulation contains phentermine 15 mg and topiramate ER 92 mg. Another dosage level containing phentermine 11.25 mg and topiramate ER 69 mg is recommended for use during dosage titration, ie, during a 14-day period while escalating to the maintenance dose of 15/92 mg. The dosages of the individual component agents are considerably lower than the previously approved maximum recommended doses for other indications. This was by design in order to minimize AEs.

Consider prescribing phen/top for patients requiring appetite suppression and enhanced satiety. Additionally, consider this medication for patients who also have migraines, as the topiramate may help with migraine prophylaxis.

Phen/top ER should be taken once daily in the morning with or without food. Avoid dosing in the evening due to the possibility of insomnia. Gradual dose titration is required (**Table 9.2**).[11]

All dosage formulations of phen/top ER are controlled in Schedule IV of the Controlled Substances Act because they contain phentermine, a Schedule IV drug. Topiramate ER is not controlled as a Schedule IV drug. The FDA requires a Risk Evaluation and Mitigation Strategy to inform women of reproductive potential about the increased risk of orofacial clefts in fetuses exposed to phen/top during the first trimester of pregnancy.

Naltrexone SR/Bupropion SR (Contrave)

Bupropion is a norepinephrine and dopamine reuptake inhibitor that was approved by the FDA as an antidepressant (1989) and for smoking cessation (1997). Naltrexone is an opioid antagonist that was approved by the FDA for the treatment of opioid dependence (1984) and the treatment of alcohol use disorder (1994). The fixed-dose formulation of naltrexone SR/bupropion SR (nal/bup) was developed based on preclinical evidence that this combination has complementary actions in the CNS that result in reduced food intake. Bupropion stimulates hypothalamic POMC neurons, with downstream effects to reduce food intake and increase energy expenditure. Naltrexone blocks opioid receptor-mediated POMC autoinhibition, augmenting POMC firing in a synergistic manner. Given the known individual effects of naltrexone and bupropion on addiction (alcohol and nicotine, respectively), a fixed combination of nal/bup was hypothesized to induce weight loss through sustained modulation of CNS reward pathways. Nal/bup was approved by the FDA for the treatment of obesity in 2014.

Efficacy

The efficacy of nal/bup was assessed in several clinical trials that used various dosage combinations.[14-17] An early dose-ranging study in a total of 419 patients with uncomplicated obesity randomized patients to 24 weeks of treatment with bupropion SR (400 mg/day), immediate-release naltrexone (48 mg/day), or placebo, and three combination therapy groups consisting of immediate-release naltrexone, 16, 32, or 48 mg/day, plus bupropion SR (400 mg/day), with a 24-week exten-

sion. A minimal diet and exercise component was also included.[14] Weight loss with combination therapy was statistically significant vs monotherapy for all three nal/bup combinations with the exception of nal/bup 48/360 mg vs bupropion. Weight loss with nal/bup continued after week 24.

Subsequent, four 56-week phase 3 trials (Contrave Obesity Research I [COR-I], Contrave Obesity Research II [COR-II], Contrave Obesity Research Behavioral Modification [COR-BMOD], and Contrave Obesity Research-Diabetes [COR-Diabetes])[15-18] enrolled patients with obesity (BMI 30-45) or overweight and obesity (BMI 27-45) with dyslipidemia and/or hypertension to 56 weeks of treatment with fixed-dose combination formulations of nal/bup or placebo. All patients in the COR-I, COR-II, and COR-Diabetes trials were also prescribed a mild hypocaloric diet and exercise. All patients in the COR-BMOD trial were prescribed an energy-reduced diet and 28 group behavioral modification sessions. The co-primary endpoints in all of these trials were percentage change in weight and the proportion of participants who lost ≥5% weight at week 56. All trials included a ~3-week dose escalation period. The efficacy results from these trials of nal/bup are summarized in **Table 9.6**.

COR-I

In the COR-I study, 1742 patients were randomized in a 1:1:1 ratio to receive placebo, nal/bup 16/360 mg or nal/bup 32/360 mg.[15] Throughout the study, decreases in body weight were greater with nal/bup (**Figure 9.6**). At week 56, the mean changes in body weight with both nal/bup 16/360 mg (-5.0%) and nal/bup 32/360 mg (-6.1%) were significantly greater (P <0.0001) than with placebo (-1.3%). The change with nal/bup 32/360 mg was significantly greater (P <0.0099) than with nal/bup 16/360 mg (**Table 9.6**). In addition, significantly greater (P <0.0001) proportions of patients in both nal/bup groups had a decrease in body weight of ≥5% and ≥10% compared with those who received placebo (**Figure 9.6**).

TABLE 9.6 — Summary of Primary Efficacy Endpoints From Four Randomized, Placebo-Controlled Trials of Combination Treatment With Naltrexone ER/Bupropion ER in Patients with Overweight/Obesity

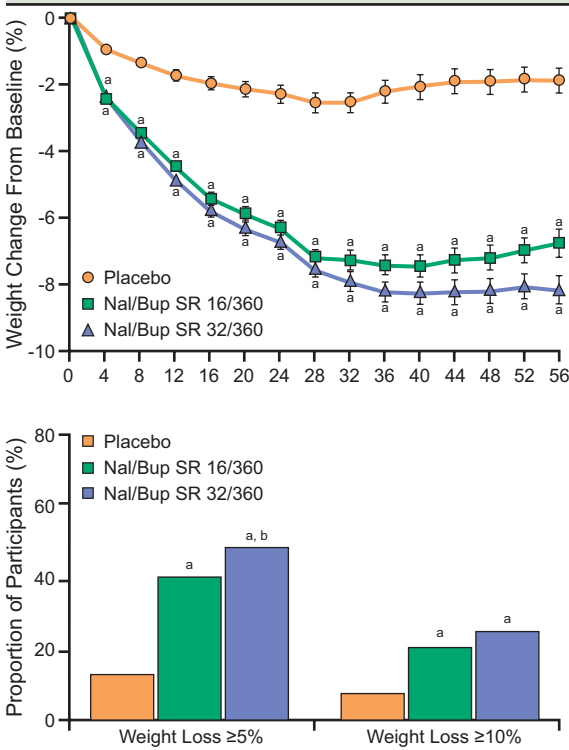
	Patients with Obesity (BMI 30-45 kg/m^2) or Overweight/Obesity (BMI 27-45 kg/m^2) With Dyslipidemia and/or Hypertension / 56 Weeks										
	COR-I[a,1]			COR-II[a,2]			COR-BMOD[a,3]			COR-Diabetes[a,4]	
		Nal/Bup SR (mg/mg)			Nal/Bup SR (mg/mg)			Nal/Bup SR (mg/mg)			Nal/Bup SR (mg/mg)
	Placebo	16/360	32/360	Placebo	16/360[b]	32/360	Placebo	16/360[b]	32/360	Placebo	32/360
mITT-LOCF population	*n* = 511	*n* = 471	*n* = 471	*n* = 456	—	*n* = 825	*n* = 202	—	*n* = 591	*n* = 159	*n* = 265
Weight loss from baseline (%)	-1.3	-5.0[c]	-6.1[c,d]	-1.2	—	-6.4[e]	-7.3	—	-11.5[e]	-1.8	-5.0[e]
Patients losing ≥5% baseline weight (%)	16	39[c]	48[c]	17.1	—	50.5[e]	42.5	—	66.4[e]	18.9	44.5[e]

Patients losing ≥10% baseline weight (%)	7	20[c]	25[c]	5.7	—	28.3[e]	20.2	—	41.5[e]	5.7	18.5[e]

[a] The trial included an approximate 3-week dose escalation period.
[b] Not included in these trials.
[c] $P < 0.0001$ vs placebo.
[d] $P < 0.0099$ for nal/bup SR 32/360 mg vs nal/bup SR 16/360 mg.
[e] $P < 0.001$ vs placebo.

[1] Greenway FL, et al; COR-I Study Group. *Lancet*. 2010;376(9741):595-605.
[2] Apovian CM, et al; COR-II Study Group. *Obesity (Silver Spring)*. 2013;21(5):935-943.
[3] Wadden TA, et al. *Obesity (Silver Spring)*. 2011;19(1):110-120.
[4] Hollander P, et al; COR-Diabetes Study Group. *Diabetes Care*. 2013;36(12):4022-4029.

FIGURE 9.6 — COR-I Trial: Change From Baseline in Body Weight and Proportion of Patients Achieving ≥5% or ≥10% Loss of Body Weight During 56 Weeks of Treatment



Data from mITT-LOCF population.

This trial included an approximate 3-week dose escalation period.

[a] $P<0.0001$ vs placebo.

[b] $P<0.0099$ for nal/bup SR 32/360 mg vs nal/bup SR 16/360 mg.

Modified from Greenway FL, et al; COR-I Study Group. *Lancet*. 2010;376(9741):595-605.

COR-II

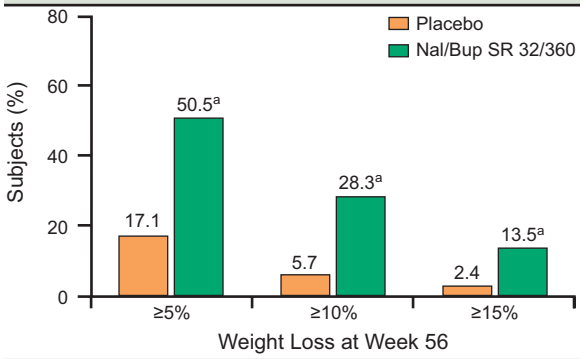
The COR-II study randomized 1496 patients in a 2:1 ratio to nal/bup 32/360 mg or placebo for up to 56 weeks.[16] Patients in the nal/bup 32/360 mg arm with a <5% weight loss at visits between weeks 28 and 44 inclusive were re-randomized (double-blind, 1:1 ratio)

to continue receiving nal/bup 32/360 mg or escalate to nal/bup 48/360 mg for the remainder of the study. In the mITT-LOCF population, weight loss was significantly greater for nal/bup 32/360 mg vs placebo at week 28 (6.5% vs 1.9%; P <0.001), and was maintained with continued double-blind treatment through week 56 (6.4% vs 1.2; P <0.001). In addition, nal/bup 32/360 mg was associated with significantly larger proportion of participants achieving ≥5%, ≥10%, and ≥15% weight loss both in the mITT-LOCF and "completer" populations vs placebo at weeks 28 and 56 (**Figure 9**.7).

COR-BMOD

Given that intensive behavioral modification programs (BMOD) have been shown to significantly increase weight loss compared with treatment by weight loss medication,[19,20] the COR-BMOD trial was designed to assess the efficacy of nal/bup 32/360 mg added to a BMOD program compared with BMOD alone.[17] A total of 793 participants (BMI = 36.5 ± 4.2) were randomly assigned in a 1:3 ratio to placebo + BMOD (n = 202);

FIGURE 9.7 — COR-II Trial: Proportion of Patients Achieving ≥5%, ≥10%, or ≥15% Loss of Body Weight During 56 Weeks of Treatment



Data from mITT-LOCF population.

This trial included an approximate 3-week dose escalation period.

[a] P <0.001 vs placebo.

Modified from Apovian CM, et al; COR-II Study Group. *Obesity (Silver Spring)*. 2013;21(5):935-943.

or nal/bup 32/360 mg + BMOD (n = 591). All participants also were prescribed an energy-reduced diet. Throughout the study, decreases in body weight in the mITT-LOCF population were significantly (P <0.001) greater with nal/bup 32/360 mg + BMOD compared with placebo + BMOD (**Figure 9.8**). At week 56, the mean changes in body weight were significantly greater with nal/bup + BMOD than with BMOD alone (-11.5 % and -7.3%, respectively; P <0.001) (**Table 9.6**). Similarly, significantly greater (P <0.001) proportions of patients in the nal/bup + BMOD group had a decrease in body weight of ≥5% and ≥10% compared with those who received placebo + BMOD (**Figure 9.8**).

COR-Diabetes

The efficacy and safety of nal/bup in patients with overweight and diabetes was assessed in the COR-Diabetes trial.[18] 505 individuals with overweight/obesity and T2D with or without background oral antidiabetes drugs were randomized 2:1 to 32 mg/360 mg nal/bup or placebo. In the modified ITT population, nal/bup resulted in significantly greater weight reduction (-5.0% vs -1.8%; P <0.001) and proportion of patients achieving ≥5% weight loss (44.5% vs 18.9%, P <0.001) compared with placebo (**Figure 9.9**).

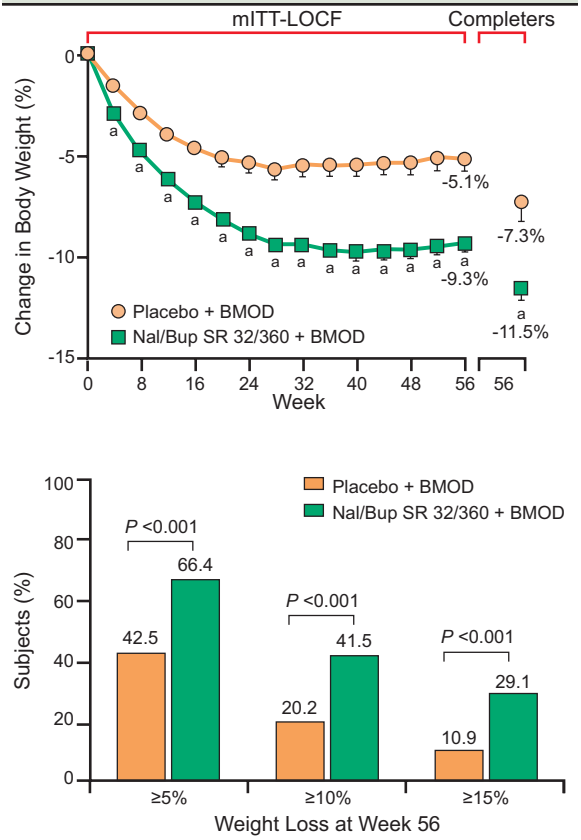
Secondary Efficacy Endpoints

In addition to the primary efficacy endpoints, the COR-I, COR-II, COR-BMOD, and COR-Diabetes studies also assessed several secondary efficacy endpoints, including changes from baseline in CV, metabolic, and anthropometric risk factors associated with obesity. The results are summarized in **Table 9.7**.

In the COR-1 trial, patients who received either nal/bup 16/360 mg or nal/bup 32/360 mg had significantly greater changes compared with placebo in lipid parameters (HDL-cholesterol, and triglycerides), SBP and DPB, HOMA-IR, and waist circumference. In addition, changes with nal/bup 32/360 mg were significantly greater for fasting glucose and fasting insulin.

In the COR-II study, changes from baseline in all but DBP and fasting glucose were significantly different from the results with placebo.

FIGURE 9.8 — COR-BMOD Trial: Change From Baseline in Body Weight and Proportion of Patients Achieving ≥5%, ≥10%, or ≥15% Loss of Body Weight During 56 Weeks of Treatment



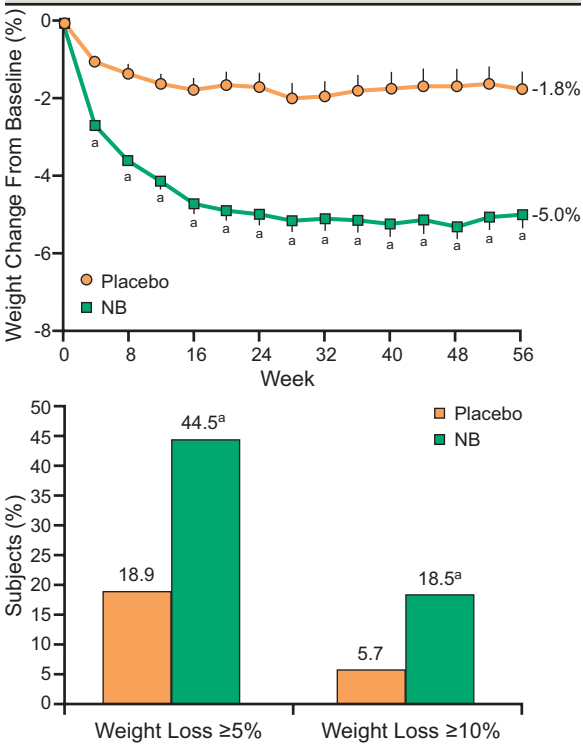
Data from mITT-LOCF population.

This trial included an approximate 3-week dose escalation period.

[a] $P < 0.001$ vs placebo.

Modified from Wadden TA, et al. *Obesity (Silver Spring)*. 2011; 19(1):110-120.

FIGURE 9.9 — COR-Diabetes Trial: Change From Baseline in Body Weight and Proportion of Patients Achieving ≥5% or ≥10% Loss of Body Weight During 56 Weeks of Treatment



Data from mITT-LOCF population. This trial included an approximate 3-week dose escalation period.

[a] $P < 0.001$.

Adapted from Hollander P, et al. *Diabetes Care*. 2013;36:4022-4029.

In the COR-BMOD trial, there were significant changes with nal/bup + BMOD compared with placebo + BMOD in HDL cholesterol, triglycerides, fasting insulin, HOMA-IR, and waist circumference. Changes in BP were not assessed.

In COR-Diabetes, nal/bup treatment was associated with improvements in glycemic control and select

cardiovascular disease (CVD) risk factors, as shown by significantly greater A1C reduction, percent of patients achieving A1C <7% (53 mmol/mol), and improvement in triglycerides and HDL cholesterol compared with placebo. Nal/bup was associated with higher incidence of nausea, constipation, and vomiting. No difference was observed between groups in the incidence of depression, suicidal ideation, or hypoglycemia.

Safety

Nal/bup was generally well-tolerated in the four 56-week, randomized, placebo-controlled trials. Nausea, generally mild to moderate and transient, typically occurring during the dose-escalation period, was the most frequent AE (29.8%, 29.2%, 34.1%, and 32.5% in COR-I, COR-II, COR-BMOD, and COR-Diabetes respectively). Other AEs reported noticeably more frequently by patients treated with nal/bup included headache, constipation, dizziness, vomiting, and dry mouth (**Table 9.8**). Treatment with nal/bup was not associated with increased reports of depressive or suicidal events compared with placebo.

Prescribing, Dosing, and Administration

Nal/bup is available as film-coated, extended-release tablets containing 8 mg naltrexone HCl and 90 mg bupropion HCl, and should be taken in the morning and evening. Nal/bup dosing should initially be started as one tablet daily in the morning and escalated by 1 tablet per week during the first 4 weeks, arriving at a total daily dosage of two tablets twice daily from week 4 onwards (**Table 9.2**).

Total daily doses greater than two tablets twice daily (32 mg/360 mg mg per day) are not recommended. Nal/bup should not be taken with a high-fat meal because of a resulting significant increase in bupropion and naltrexone systemic exposure. Nal/bup should be discontinued if ≥5% weight loss is not achieved by week 12.[21]

Consider prescribing nal/bup to help with appetite suppression and decreased cravings. Providers can also consider prescribing this medication for patients who are also trying to quit smoking, or who are trying to cut back on alcohol intake.

TABLE 9.7 — Summary of Mean Changes From Baseline in Metabolic and Cardiovascular Risk Factors and Waist Circumference in 56-Week Randomized, Placebo-Controlled Trials With Fixed-Dose Combination Treatment With Naltrexone SR/Bupropion SR

	COR-I[1]			COR-II[2]			COR-BMOD[3]			COR-Diabetes[4]	
		Nal/Bup SR (mg/mg)			Nal/Bup SR (mg/mg)			Nal/Bup SR (mg/mg)			Nal/Bup SR (mg/mg)
Change From Baseline	Placebo (n = 511)	16/360 (n = 471)	32/360 (n = 471)	Placebo (n = 456)	16/360[a] —	32/360 (n = 702)	Placebo (n = 193)	16/360[a] —	32/360 (n = 482)	Placebo (n = 159)	32/360 (n = 265)
LDL cholesterol (%)	-0.5	-1.5	-2.0	-2.1	—	-6.2	+10.0	—	+7.1	0.0	-1.4
HDL cholesterol (%)	+0.8	+7.6	+8.0	-0.9	—	+3.6	+2.8	—	+9.4	-0.3	+3.0
Triglycerides (%)	-3.1	-8.0	-12.7	-0.5	—	-9.8	-8.5	—	-16.6	-0.8	-11.2
SBP (mm Hg)	-1.9	+0.3	-0.1	-0.5	—	+0.6	NA	—	NA	-1.1	0.0

DBP (mm Hg)	-0.9	+0.1	0.0	+0.3	—	+0.4	NA	—	NA	-1.5	-1.1
Fasting glucose (mg/dL)	-0.7	-1.9	-2.6	-1.3	—	-2.8	0.0	—	-1.5	-4.0	-11.9
Fasting insulin (mU/mL)	-4.6	-11.8	-17.1	+3.5	—	-11.4	-15.5	—	-28.0	-10.4	-13.5
HOMA-IR (%)	-5.9	-14.3	-20.2	+1.2	—	-13.8	-16.6	—	-29.9	-14.7	-20.6
Waist circum-ference (cm)	-2.5	-5.0	-6.2	-2.1	—	-6.7	-6.1	—	-9.1	-2.9	-5.0

Highlighted results indicate significant difference with naltrexone SR/bupropion SR (Nal/Bup) compared with placebo.

[a] Not included in these trials.

[1] Greenway FL, et al; COR-I Study Group. *Lancet*. 2010;376(9741):595-605.
[2] Apovian CM, et al; COR-II Study Group. *Obesity (Silver Spring)*. 2013;21(5):935-943.
[3] Wadden TA, et al. *Obesity (Silver Spring)*. 2011;19(1):110-120.
[4] Hollander P, et al; COR-Diabetes Study Group. *Diabetes Care*. 2013;36(12):4022-4029.

TABLE 9.8 — Adverse Reactions With an Incidence of at Least 2% Among Patients Treated With Naltrexone SR/Bupropion SR and More Commonly Than Placebo

Adverse Reaction	Naltrexone SR/ Bupropion SR 32 mg/360 mg *N* = 2545 (%)	Placebo *N* = 1515 (%)
Nausea	32.5	6.7
Constipation	19.2	7.2
Headache	17.6	10.4
Vomiting	10.7	2.9
Dizziness	9.9	3.4
Insomnia	9.2	5.9
Dry mouth	8.1	2.3
Diarrhea	7.1	5.2
Anxiety	4.2	2.8
Hot flush	4.2	1.2
Fatigue	4.0	3.4
Tremor	4.0	0.7
Upper abdominal pain	3.5	1.3
Viral gastroenteritis	3.5	2.6
Influenza	3.4	3.2
Tinnitus	3.3	0.6
Urinary tract infection	3.3	2.8
Hypertension	3.2	2.2
Abdominal pain	2.8	1.4
Hyperhidrosis	2.6	0.6
Irritability	2.6	1.8
Blood pressure increased	2.4	1.5
Dysgeusia	2.4	0.7
Rash	2.4	2.0
Muscle strain	2.2	1.7
Palpitations	2.1	0.9

Contrave [package insert]. Brentwood, TN: Currax Pharmaceuticals LLC; 11/2021.

Liraglutide (Saxenda)

Liraglutide is a glucagon-like peptide-1 (GLP-1) that is an GLP-1 analogue of human GLP-1, a gut-derived incretin hormone. Liraglutide binds and activates the GLP-1 receptor (ie, is a GLP-1 receptor agonist), a cell-membrane embedded signaling receptor that is expressed in multiple brain regions that regulate appetite and caloric intake. Liraglutide additionally acts on pancreatic β cells to potentiate glucose-dependent insulin secretion and inhibit glucagon secretion, and in the gastrointestinal tract to inhibit gastric emptying.[22] Native GLP-1 has a short elimination half-life (1 to 2 minutes), whereas liraglutide has a half-life of about 13 hours and therefore can be administered once a day by subcutaneous injection. Liraglutide 1.8 mg daily has been approved for the treatment of T2D, having a significant effect on improving A1C, weight, blood pressure, and lipids. Since many patients on liraglutide experienced a dose-dependent weight loss, it appeared to be an attractive treatment option for obesity. Liraglutide 3.0 mg was subsequently approved by the FDA for the treatment of obesity in 2014. Liraglutide 3.0 mg is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 or greater or 27 or greater in the presence of at least one weight-related comorbid condition. In December 2020, the FDA approved the use of liraglutide for chronic weight management in patients aged 12 and older who have obesity, as defined by specific BMI cut-offs for age and sex that correspond to a BMI 30 or higher for adults, and who weigh more than 60 kg (132 pounds).

Efficacy

In dose-ranging studies, liraglutide 3 mg was found to result in greater weight loss compared to placebo or orlistat. Liraglutide reduced blood pressure and reduced the prevalence of prediabetes. An 84-week, open-label extension following this study switched liraglutide/placebo recipients to liraglutide 2.4 mg after 1 year, then to 3 mg. In the ITT-LOCF population, the mean weight loss from randomization to year 1 was significantly greater with all liraglutide doses compared with placebo and was dose-dependent.

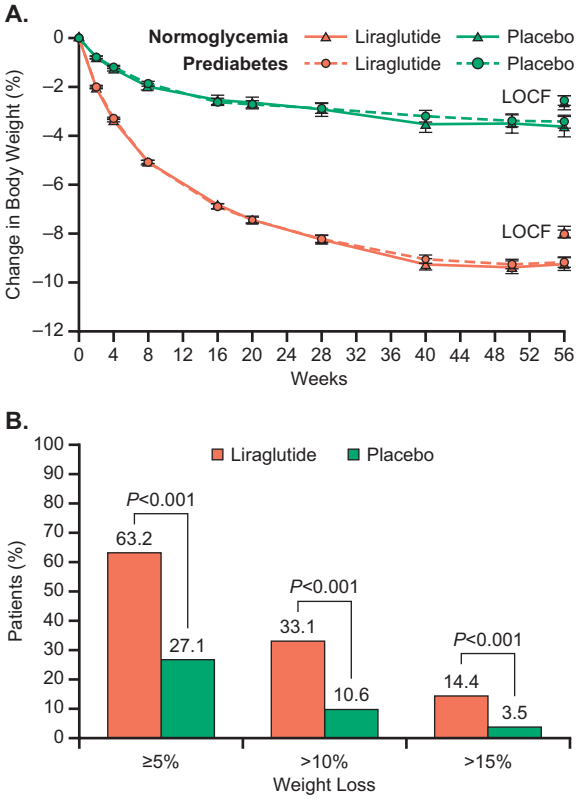
Weight loss for those on liraglutide 3 mg for 2 years was also significantly greater than with orlistat. In addition to weight loss, mean change in waist circumference was significantly greater with liraglutide 3 mg vs placebo. With liraglutide 3 mg, the 2-year prevalence of prediabetes and metabolic syndrome decreased by 52% and 59%, with improvements in BP and lipids.[23] Greater weight loss was also observed in pediatric patients aged between 12 and 18, with 3 mg subcutaneous once-daily injection resulting in greater weight loss compared to placebo measured by change from baseline in the BMI standard deviation score.[24]

SCALE Obesity and Pre-diabetes

The efficacy of liraglutide 3 mg as an adjunct to diet and exercise on weight loss was examined in a 56-week trial. 3731 participants with obesity (BMI ≥30) or overweight (BMI ≥27) with ≥1 comorbidity (excluding T2D) were randomized to once-daily subcutaneous treatment with liraglutide 3 mg or placebo in combination with a 500 kcal/day deficit diet and exercise. Randomization was stratified by pre-diabetes status (according to ADA 2010 criteria) and BMI. The co-primary endpoints included change in body weight and the proportions of patients with ≥5% and >10% weight loss from baseline. After 56 weeks of treatment, patients receiving liraglutide 3 mg showed significantly greater loss of body weight of 8% from baseline compared with those receiving placebo (2.6%; P <0.0001) (**Figure 9.10**). Proportions of patients losing ≥5%,>10%, and >15% of body weight with liraglutide 3 mg were 63.2%, 33.1%, and 14.4% respectively, compared with 27.1%, 10.6%, and 3.5%, respectively, in patients who received the placebo (P <0.001 for all comparisons) (**Figure 9.10**).

In conjunction with weight loss, treatment with liraglutide 3 mg reduced waist circumference by -8.19 cm compared with -3.94 cm with placebo (P <0.0001). Furthermore, treatment with liraglutide 3 mg improved blood glucose levels. In fact, in the studies, liraglutide expressed a specific effect on preventing diabetes, converting nearly 70% of the subjects with prediabetes to normoglycemia, blood pressure, and lipids levels (**Table**

FIGURE 9.10 — SCALE Obesity and Prediabetes: Mean Percentage Change in Body Weight and Proportion of Patients Achieving ≥5%, >10%, and >15% Weight Loss



Pi-Sunyer X, et al. *N Engl J Med.* 2015;373(1):11-22.

9.9). Loss of body weight was independent of prediabetes status at screening and baseline BMI.[25]

SCALE Diabetes

This trial was a 56-week, randomized, placebo-controlled, double-blind clinical trial that demonstrated the effect of liraglutide 3 mg on weight loss and involved 846 adults with obesity or overweight and T2D. All treatment groups followed a reduced-calorie diet and increased

TABLE 9.9 — Changes From Randomization to Week 56 in Measures of Glycemic Control, Lipids, and Cardiovascular Biomarkers

	SCALE Obesity and Prediabetes (Obesity or Overweight With Comorbidities Without Diabetes)		SCALE Diabetes (Patients With Type 2 Diabetes)	
	Liraglutide 3 mg (*n* = 2487)	Placebo (*n* = 1244)	Liraglutide 3 mg (*n* = 423)	Placebo (*n* = 212)
Waist circumference (cm)	-8.2	-4.0	-6.0	-2.8
Systolic blood pressure (mm Hg)	-4.3	-1.5	-3.0	-0.4
Diastolic blood pressure (mm Hg)	-2.7	-1.8	-1.0	-0.6
Heart rate (bpm)	2.6	0.1	2.0	-1.5
Total cholesterol (mg/dL)	-3.2	-0.9	-1.4	2.4
LDL cholesterol (mg/dL)	-3.1	-0.7	0.9	3.3
HDL cholesterol (mg/dL)	2.3	0.5	4.8	1.9
Triglycerides (mmol l–1)	-13.0	-4.1	-14.5	-0.7

Changes from randomization to week 56 are means (SD) and estimated treatment differences from an analysis of covariance, both using the full analysis set with the last observation carried forward. Least squares mean adjusted for treatment, country, sex, prediabetes status at screening, baseline BMI stratum.

Saxenda [package insert]. Liraglutide injection. Plainsboro, NJ: Novo Nordisk; 04/2023.

physical activity program. Like in SCALE Obesity and Pre-diabetes, the co-primary endpoints were change in body weight and the proportions of patients achieving ≥5% and >10% weight loss from baseline. At 56 weeks, adults treated with liraglutide 3 mg achieved significantly greater mean weight loss of 5.9% compared with 2.0% with placebo (P <0.0001) (**Figure 9.11**). More patients achieved a weight loss of 5% or more in the liraglutide 3 mg (54.3%) and liraglutide 1.8 mg (40.4%) groups, compared to the placebo (21.4%; P <0.001 for either liraglutide group vs placebo).

Liraglutide treatment also significantly increased the proportion of patients achieving >10% weight loss: 25.2% in the liraglutide 3 mg group (compared to 6.7% with the placebo; P <0.001) and 15.9% in the liraglutide 1.8 mg group (P <0.001 vs the placebo). Waist circumference was also significantly reduced with liraglutide 3 mg (-6 cm) compared with placebo (-2.8 cm, P ≤0.0004). Liraglutide 3 mg reduced systolic blood pressure by 3.0 mm Hg compared with 0.4 mm Hg with placebo (P <0.05), although no significant difference was observed in diastolic blood pressure. Compared with baseline, liraglutide 3 mg significantly improved total cholesterol (-4%) and fasting lipid levels, including VLDL, HDL, and triglycerides (-13%, +3% and -14%, respectively). Liraglutide 3 mg also improved levels of CRP by -27% compared with placebo (P ≤0.0002). In addition, treatment with liraglutide 3 mg provided statistically significantly greater improvements in CV disease risk factors, such as blood pressure and cholesterol, compared with placebo in combination with diet and physical activity (**Table 9.9**).[26]

SCALE Maintenance

The efficacy of liraglutide in maintaining weight loss achieved with a low-calorie diet was examined in the SCALE maintenance study. Four hundred twenty-two adult patients with overweight/obesity who lost ≥5% of their initial weight during a caloric restriction period were randomly assigned to receive subcutaneous liraglutide 3 mg/day or placebo for 56 weeks. Diet and exercise counseling were provided throughout the trial. Participants lost a mean 6% of screening weight during

the caloric restriction period. From randomization to week 56, weight decreased an additional mean 6.2% with liraglutide and 0.2% with placebo (P <0.0001) (**Figure 9.12**). Significantly more participants receiving liraglutide (81.4%) maintained the ≥5% run-in weight loss compared with those receiving placebo (48.9%; P <0.0001). Similarly, more patients in the liraglutide group lost ≥5% of their randomization weight than in the placebo group (50.5 vs 21.8%; P <0.0001). These results suggest that liraglutide, in conjunction with diet and exercise, maintained weight loss achieved by caloric restriction and induced further weight loss over 56 weeks. Improvements in some CV disease risk factors, such as BMI, waist circumference, and glycemic parameters, were also observed compared to placebo.[27]

Liraglutide for Treatment of Obesity in Adolescents

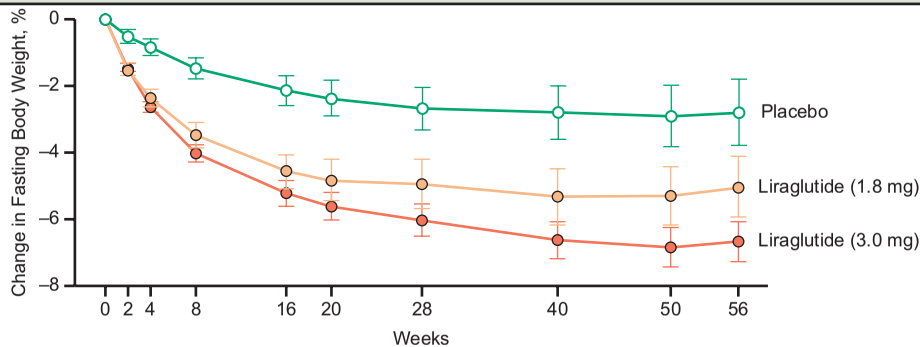
The efficacy of liraglutide 3 mg as an adjunct to diet and exercise on weight loss was examined in a double-blind, 56-week trial in 251 adolescents (12 to <18 years of age) with obesity and a poor response to lifestyle therapy alone. Following a 12-week lifestyle run-in period, 125 patients were given 3.0 mg subcutaneous liraglutide once daily, while 126 patients were given placebo. Liraglutide was superior to placebo with regard to the change from baseline in the BMI standard-deviation score (SDS) at week 56, with an estimated treatment difference (ETD) of -0.22 (95% CI; P <0.002).

Proportions of patients achieving ≥5% and ≥10% body weight reduction were numerically higher with liraglutide than with placebo (43.3% vs 18.7% for ≥5% weight loss, and 26.1% vs 8.1% for ≥10% weight loss). In addition, patients taking liraglutide lost, on average, 2.65% of their body weight while patients receiving the placebo gained an average 2.37% of their body weight. At week 56, there was no substantial difference between treatment groups in the change in glycemic and cardiometabolic variables or in overall weight-related quality of life.[24]

Safety

Liraglutide was well-tolerated in clinical studies (**Table 9.10**). In the SCALE Obesity and Prediabetes trial, the most common AEs with liraglutide 3 mg were

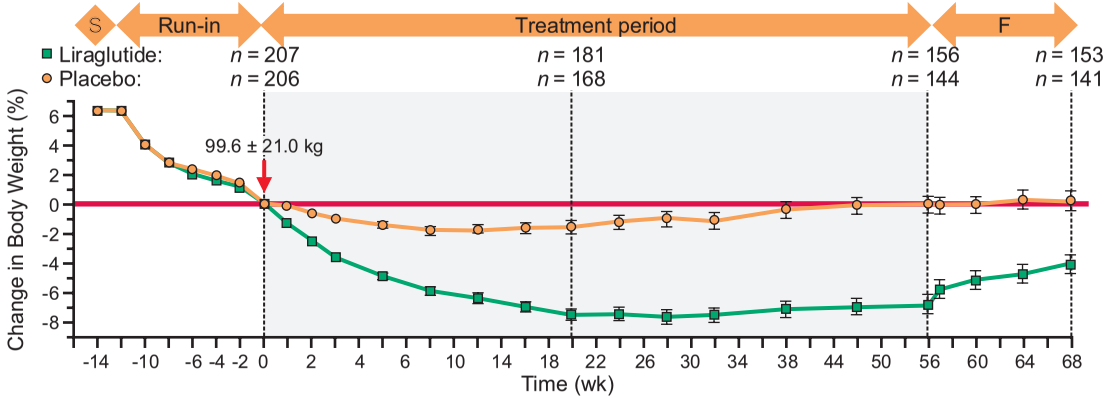
FIGURE 9.11 — SCALE Diabetes: Fasting Body Weight Change from Baseline



No. of patients									
Placebo	211	205	193	165	154	137	124	116	116
Liraglutide (1.8 mg)	204	192	182	179	176	172	165	160	158
Liraglutide (3.0 mg)	412	400	385	365	352	337	329	320	317

Davies MJ, et al. *JAMA*. 2015;314(7):687-699.

FIGURE 9.12 — Mean Percentage Change in Body Weight in the SCALE Maintenance Trial



Mean ± SD weight at run-in (week -12): 105.9 ± 22.1 kg.

Wadden TA, et al. *Int J Obes (Lond)*. 2013;37(11):1443-1451.

nausea and diarrhea, with most events being mild/moderate in intensity and transient in duration. In the SCALE diabetes trial, the most frequently reported side effects were gastrointestinal disorders, and occurred in 65% of people treated with liraglutide 3 mg compared with 39% with placebo. In the SCALE maintenance trial, GI disorders were also reported more frequently with liraglutide (74%) than placebo (45%), but most events were transient, and mild or moderate in severity. Discontinuations due to AEs occurred in 9.9% of liraglutide-treated patients and 3.8% of placebo-treated patients, and were mostly due to GI events.

In the pediatric study, the most commonly reported mild-to-moderate AEs were gastrointestinal events, including nausea, vomiting, and diarrhea, which were reported in 64.8% of patients taking liraglutide and 36.5% of patients taking placebo. Additionally, hypoglycemia occurred in 15% of patients receiving liraglutide compared to 4% of patients receiving placebo. Discontinuation due to AEs occurred in 10.4% of liraglutide-treated adolescent patients and 0% in placebo-treated patients. The incidence of serious AEs in the trial was low and deemed not related to the liraglutide treatment.[24]

The prescribing information for liraglutide includes a black box warning about a potential risk of thyroid C-cell tumors, including medullary thyroid carcinoma (MTC). An increased risk is suspected based on studies in rats and mice; however, these studies used much higher (supratherapeutic) doses of GLP-1 receptor agonists. Furthermore, rodents express much higher levels of GLP-1 receptors in the thyroid than primates; this, combined with the supratherapeutic doses in the rodent studies, makes the significance of the rodent findings to humans unclear.[26,28] Nevertheless, liraglutide is currently contraindicated in patients with a personal or family history of MTC, and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2).

Prescribing, Dosing, and Administration

Liraglutide is administered subcutaneously once per day (at any time of day, although timing should be consistent) with or without food in the abdomen, thigh, or upper arm (**Table 9.2**).[25] Use of liraglutide with

insulin or insulin secretagogues can increase the risk of hypoglycemia; the doses of the concomitant medications may need to be reduced or discontinued. The liraglutide dose is titrated over the first 5 weeks of treatment, starting at 0.6 mg daily and increasing to 3.0 mg daily from week 5 onwards, in order to reduce the risk of gastrointestinal symptoms. Treatment should also be discontinued in patients who have not lost at least 4% of baseline body weight at 16 weeks, because it is unlikely they will achieve any meaningful weight loss with further treatment.

Consider the use of liraglutide for appetite suppression and increased satiety. Also consider using for patients with concomitant T2D.

Semaglutide (Wegovy)

Semaglutide (1.7 mg or 2.4 mg) is another pharmacological treatment option for chronic weight management, receiving FDA approval in 2021. Similar to liraglutide, semaglutide is a GLP-1 receptor agonist, and ie, GLP-1 mimic, which targets various areas of the brain and GI tract to regulate appetite and food intake. Semaglutide is a subcutaneous injection and is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with obesity (BMI ≥30) or overweight (BMI ≥27) and who have at least one weight-related comorbid condition, (eg, hypertension, dyslipidemia, or T2D).[29] In December 2022, semaglutide 2.4 mg also received FDA approval (as an adjunct to a reduced calorie diet and increased physical activity) for chronic weight management in pediatric patients 12 years of age and older with obesity, ie, an initial BMI of ≥95th percentile standardized for age and sex.[29] In March 2024, semaglutide 2.4 mg received FDA approval to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke), in adults with established cardiovascular disease and either obesity or overweight.

Like liraglutide, semaglutide also increases glucose-dependent insulin secretion from pancreatic β cells and improves insulin sensitivity throughout the body, works on the appetite center in the brain to reduce appetite, and acts in the gastrointestinal tract to slow gastric emptying

TABLE 9.10 — Adverse Reactions With an Incidence of at Least 2% Among Patients Treated With Liraglutide and More Commonly Than Placebo

Adverse Reaction	Liraglutide 3 mg *N* = 3384 (%)	Placebo *N* = 1941 (%)
Gastrointestinal		
Nausea	39.3	13.8
Diarrhea	20.9	9.9
Constipation	19.4	8.5
Vomiting	15.7	3.9
Dyspepsia	9.6	2.7
Abdominal pain	5.4	3.1
Upper abdominal pain	5.1	2.7
GERD	4.7	1.7
Abdominal distension	4.5	3.0
Eructation	4.5	0.2
Flatulence	4.0	2.5
Dry mouth	2.3	1.0
Metabolism and Nutrition		
Hypoglycemia in T2D	23.0	12.7
Decreased appetite	10.0	2.3
Nervous System		
Headache	13.6	12.6
Dizziness	6.9	5.0
General Disorders and Administration Site Conditions		
Fatigue	7.5	4.6
Injection site erythema	2.5	0.2
Injection site reaction	2.5	0.6
Asthenia	2.1	0.8

Continued

TABLE 9.10 — *Continued*

Adverse Reaction	Liraglutide 3 mg *N* = 3384 (%)	Placebo *N* = 1941 (%)
Infections and Infestations		
Gastroenteritis	4.7	3.2
Urinary tract infection	4.3	3.1
Viral gastroenteritis	2.8	1.6
Investigations		
Increased lipase	5.3	2.2
Psychiatric Disorders		
Insomnia	2.4	1.7
Anxiety	2.0	1.6

Saxenda [package insert]. Liraglutide injection. Plainsboro, NJ: Novo Nordisk; 04/2023.

and increase satiety. Unlike liraglutide, which is administered daily, semaglutide has an elimination half-life of one week and is therefore administered as a subcutaneous injection of 1.7 mg or 2.4 mg once-weekly. Semaglutide is also available in the United States and other countries for treatment of patients with T2D as semaglutide 0.5 mg, 1.0 mg, or 2.0 mg weekly injection and in an oral formulation as semaglutide 14 mg daily.

Efficacy

The efficacy and safety of semaglutide 2.4 mg were investigated in the phase 3 Semaglutide Treatment Effect in People with Obesity (STEP) program – the largest placebo-controlled clinical trial program for obesity management without a focus on T2D.[30] Results from four 68-week STEP trials demonstrate that semaglutide is superior to the placebo in weight reduction.[31] The first three STEP studies were randomized, double-blind, placebo-controlled trials which included a 16-week dose escalation period prior to reaching 2.4 mg, while STEP 4 was a double-blind, placebo-controlled, randomized withdrawal trial, in which patients receiving semaglutide either continued with the treatment or switched to a placebo after week 20.[29] The approval of semaglutide

2.4 mg for weight management in pediatric patients was based on results from STEP TEENS, a trial that enrolled participants 12 to <18 years of age. In the STEP program, the reduction of body weight has been observed with semaglutide treatment irrespective of age, sex, race, ethnicity, BMI at baseline, body weight (kg) at baseline, or level of renal function impairment. The efficacy of semaglutide for cardiovascular risk reduction was assessed in the SELECT trial, while its efficacy for management of body weight and heart failure (HF) symptoms in patients with obesity-related HF with preserved ejection fraction (HFpEF) was tested in the STEP HFpEF trial. The efficacy of semaglutide on the progression of renal impairment in patients with chronic kidney disease (CKD) and T2D was evaluated in the FLOW trial.

STEP 1

STEP 1 was a double-blind trial that enrolled 1961 adult patients with a BMI ≥30 or BMI ≥27 with at least one weight-related comorbid condition, who did not have diabetes. Patients were randomized in a 2:1 ratio to either semaglutide or placebo. The once-weekly injections were combined with reduced-calorie diet (500-kcal deficit per day relative to the energy expenditure estimated at the time they underwent randomization) and increased physical activity (150 minutes per week of physical activity encouraged). The co-primary endpoints were percent change in body weight and ≥5% weight loss at week 68.

The change in body weight from baseline to week 68 was −14.9% in the semaglutide group as compared with −2.4% with placebo, with an ETD of −12.4 % (P <0.0001) (**Figure 9.13A**). The semaglutide-treated group also demonstrated greater mean weight loss: −15.3 kg compared with −2.6 kg in the placebo group (ETD, −12.7 kg; 95% CI, −13.7 to −11.7). The proportions of patients achieving ≥5%, ≥10%, and ≥15% body weight reduction with semaglutide were 86.4%, 69.1%, and 50.5% respectively, all significantly higher than in the placebo group (31.5%, 12%, and 4.9% respectively; P <0.001) (**Figure 9.13B**). Greater reduction in the secondary endpoints of waist circumference, BMI, and systolic and diastolic blood pressure were also observed with semaglutide. Semaglutide treatment showed beneficial

changes in glycated hemoglobin, fasting plasma glucose, c-reactive protein, and fasting lipid levels.[32]

STEP 2

The efficacy of semaglutide at 2.4 mg and 1 mg (the maximum dose approved for treatment of T2D at the time) in patients with a BMI ≥27 and T2D was evaluated in STEP 2. This double-blind 68-week trial randomly assigned 1210 adult participants to semaglutide 2.4 mg, semaglutide 1.0 mg, or placebo. The once-weekly injections were combined with a reduced-calorie diet (500-kcal deficit per day relative to the energy expenditure estimated at the time they underwent randomization) and increased physical activity (150 minutes per week of physical activity recommended). As in STEP 1, the co-primary endpoints were percent change in body weight and ≥5% weight reduction at week 68. The changes in weight compared to baseline in the semaglutide 2.4 mg, semaglutide 1.0 mg, and placebo groups were -9.6%, -6.9% and -3.5% respectively; with an ETD of -6.2% compared to the placebo, semaglutide 2.4 mg was significantly more effective (P <0.0001) (**Figure 9.14A**).

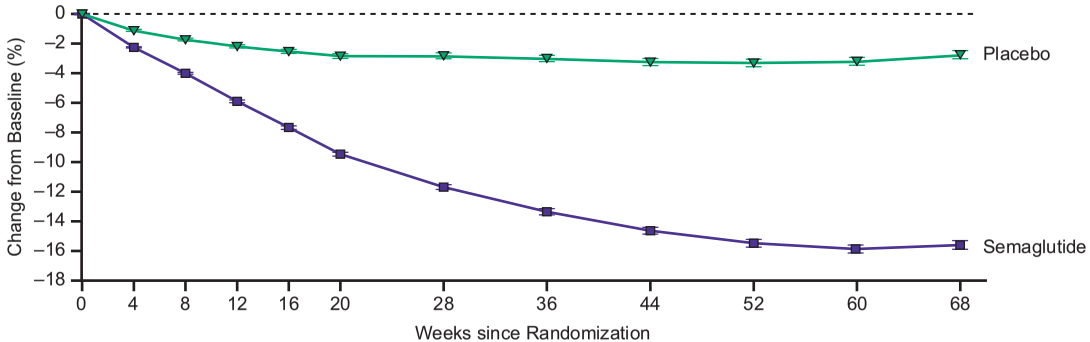
The proportions of patients losing ≥5% of body weight with semaglutide 2.4 mg, semaglutide 1.0 mg, and placebo injections at week 68 were reported as 68.8%, 57.1% and 28.5% respectively (P <0.001 for semaglutide 2.4 mg vs placebo) (**Figure 9.14B**). Semaglutide 2.4 mg was also superior to the placebo in the confirmatory secondary endpoints of ≥10% weight loss (45.6% vs 28.7%; P <0.0001) (**Figure 9.14B**) and ≥15% weight loss (25.8% vs 13.7%; P <0.0001) (**Figure 9.14B**). Furthermore, 67.5% of patients treated with 2.4 mg semaglutide achieved a target A1C of 6.5% or less, compared to 60.1% of patients treated with 1.0 mg of semaglutide and 15.5% in the placebo group. Overall, the study has demonstrated that the once-weekly injection of semaglutide 2.4 mg is more effective at reducing body weight in patients with obesity and T2D than the lower dose of semaglutide 1.0 mg or placebo.[33]

STEP 3

The efficacy of semaglutide in combination with intensive therapy has been evaluated in STEP 3, a

FIGURE 9.13 — STEP 1: Change in Body Weight from Baseline and Proportion of Patients Achieving ≥5%, ≥10%, and ≥15% Weight Loss

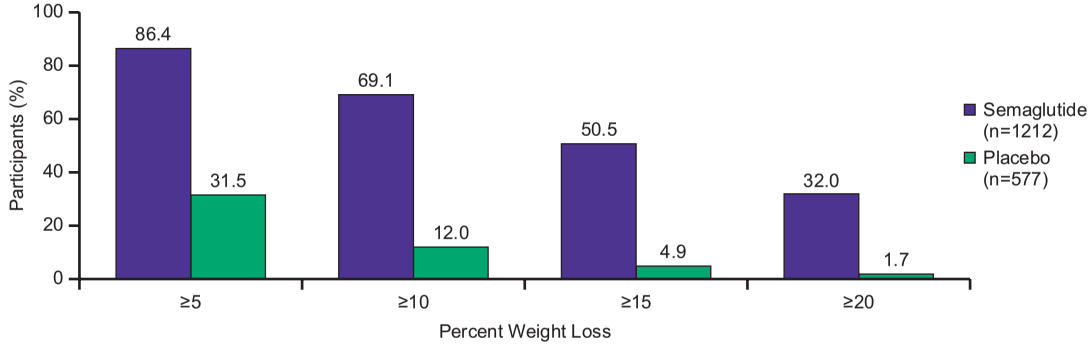
A. Body Weight Change from Baseline by Week, Observed In-Trial Data



No. at risk

Placebo	655	649	641	619	615	603	592	571	554	549	540	577
Semaglutide	1306	1290	1281	1262	1252	1248	1232	1228	1207	1203	1190	1212

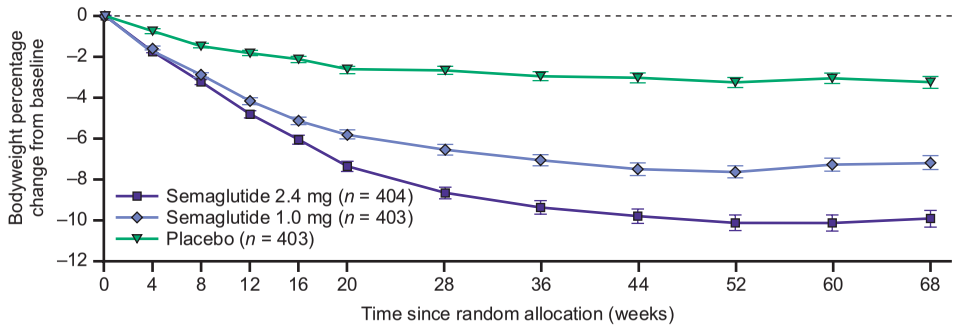
B. In-Trial Data at Wk 68



Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989.

FIGURE 9.14 — STEP 2: Change in Body Weight from Baseline and Proportion of Patients Achieving ≥5%, ≥10%, ≥15%, and ≥20% Weight Loss

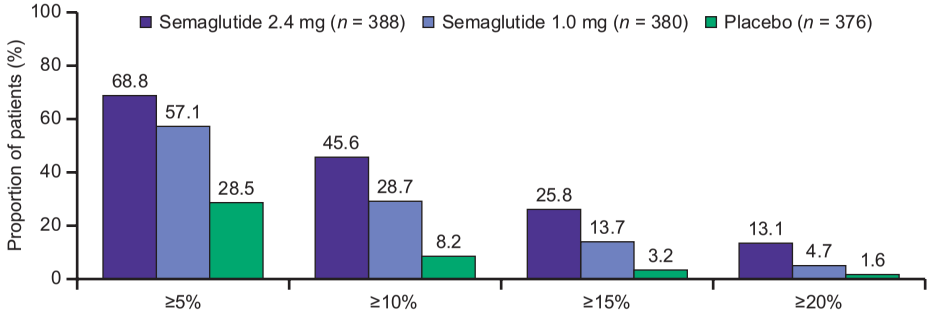
A.



Number of patients

Semaglutide 2.4 mg	404	395	397	390	388	392	386	383	381	381	378	388
Semaglutide 1.0 mg	403	394	392	385	383	383	378	377	373	370	374	380
Placebo	403	398	394	389	387	383	381	377	371	367	366	376

B.



Davies M, et al. *Lancet*. 2021;397(10278):971-984.

double-blind trial enrolling 611 adult patients with a BMI ≥30 (or BMI ≥27 with at least one weight-related comorbid condition) who did not have diabetes. Patients were randomized in a 2:1 ratio to either semaglutide 2.4 mg or placebo. The once-weekly injections were combined with a reduced-calorie diet (500-kcal deficit per day relative to the energy expenditure estimated at the time they underwent randomization) for the first 8 weeks and intense behavioral therapy for entire 68-week duration of the study. The behavioral therapy consisted of 30 individual counselling sessions with a registered dietician. Like in STEP 1 and STEP 2, the co-primary endpoints were percentage change in body weight and ≥10% weight loss by week 68.

The change in body weight from baseline to week 68 was −16% in the semaglutide group compared with −5.7% with placebo (ETD −10.3%; P <0.001) (**Figure 9.15A**). Proportions of patients achieving a weight loss of ≥5%, ≥10% and ≥15% with semaglutide at week 68 were 86.6%, 75.3%, and 55.8% respectively - significantly higher than in the placebo group (47.6%, 15%, and 13.2% respectively; P <0.001 for all comparisons) (**Figure 9.15B**). Semaglutide also demonstrated superiority to the placebo in the secondary efficacy endpoints of waist circumference change (difference -8.3 cm; P <0.001) and systolic blood pressure change (difference -3.9 mm Hg; P = 0.001). Improvements were also observed in diastolic blood pressure, BMI and glycated hemoglobin parameters.[34]

STEP 4

The fourth study of the STEP program investigated the effect of continuing or withdrawing semaglutide treatment on weight loss maintenance. STEP 4 was a double-blind trial recruiting 902 adult patients with a BMI ≥30 (or BMI ≥27 with at least one weight-related comorbid condition) and without diabetes. All patients received subcutaneous once-weekly injections of semaglutide during the run-in period of 20 weeks (including 16 weeks of dose escalation), after which they were randomly assigned to continue to receive semaglutide 2.4 mg or placebo for the remaining 48 weeks of the trial. The primary endpoint was percent change in body weight from week 20 to week 68.

At week 20, the participants exhibited a mean weight loss of -10.6%. At week 68, the semaglutide group reported an additional -7.9% weight change (from week 20) and an overall change of -17.4%, while the placebo group gained 6.9% in body weight between weeks 20 and 68, and showed an overall weight change of -5.0% at 68 weeks (**Figure 9.16A**). The proportions of patients who lost ≥5%, ≥10%, ≥15%, or ≥20% of body weight between weeks 20 and 68 with continued semaglutide (88.7%, 79.0%, 63.7%, and 39.6% respectively) were higher than in the placebo-switch group (47.6%, 20.4%, 9.2%, and 4.8% respectively) (**Figure 9.16B**).[35]

STEP TEENS

The efficacy and safety of semaglutide in adolescents was assessed in STEP TEENS, a double-blind trial that enrolled a total of 201 patients 12 to <18 years of age with obesity (defined as a BMI ≥95th percentile for age and sex) or overweight (defined as a BMI ≥85th percentile for age and sex); patients with overweight were required to have at least one coexisting weight-related condition, but only one enrolled patient did not have obesity.[36] Eligible patients were randomized (2:1) to receive either subcutaneous semaglutide 2.4 mg once weekly or a matching placebo for 68 weeks, in addition to a lifestyle intervention. The primary endpoint was percentage change in BMI from baseline, assessed at week 68.

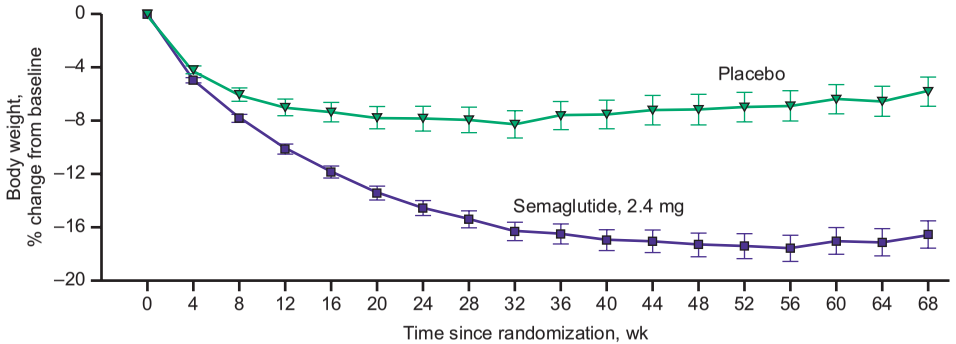
Patients in the semaglutide group achieved a significantly greater change in BMI from baseline at week 68 (-16.1%) compared to those in the placebo group (0.6%; P <0.001) (**Figure 9.17A**).[36] Significantly more patients in the semaglutide group (73%) achieved the secondary confirmatory endpoint of 5% or greater reduction in body weight, compared to patients who received the placebo (18%; P <0.001) (**Figure 9.17B**). Compared to patients in the placebo group, numerically more patients in the semaglutide group achieved a BMI reduction of ≥5%, and body weight reduction of ≥10%, ≥15%, and ≥20% (**Figure 9.17B**).

SELECT

The SELECT trial, a multicenter, double-blind, randomized, placebo-controlled study, assessed the efficacy

FIGURE 9.15 — STEP 3: Change in Body Weight from Baseline and Proportion of Patients Achieving ≥5%, ≥10%, ≥15%, and ≥20% Weight Loss

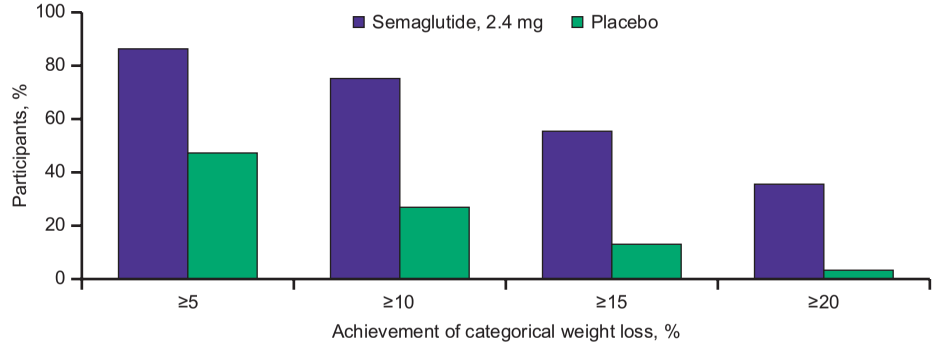
A. Change from baseline by week in body weight



No. of participants

Semaglutide, 2.4 mg	407	398	396	385	389	385	370	380	363	373	364	364	356	367	343	365	346	373
Placebo	204	200	197	190	194	194	185	189	180	189	180	184	172	183	170	180	166	189

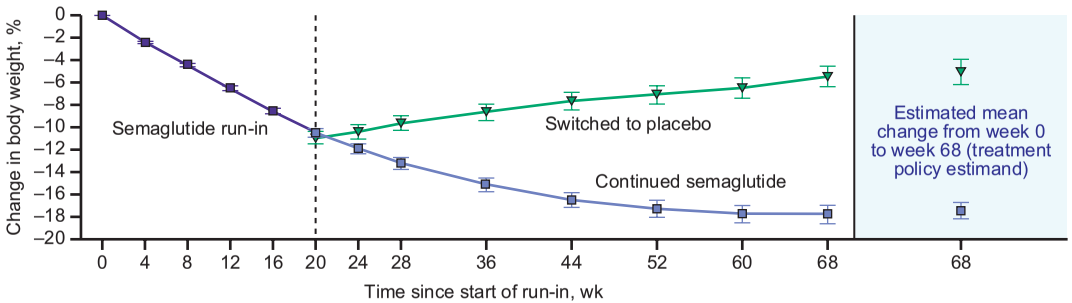
B. Weight loss at week 68



Wadden TA, et al. *JAMA*. 2021 ;325(14):1403-1413.

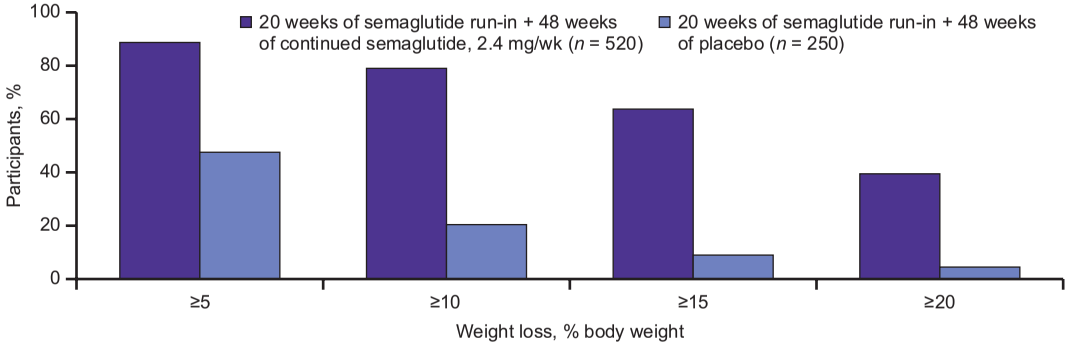
FIGURE 9.16 — STEP 4: Change in Body Weight from Baseline and Proportion of Patients Achieving ≥5%, ≥10%, ≥15%, and ≥20% Weight Loss

A. Mean percent change in body weight during the entire trial (weeks 0–68; observed in-trial data)



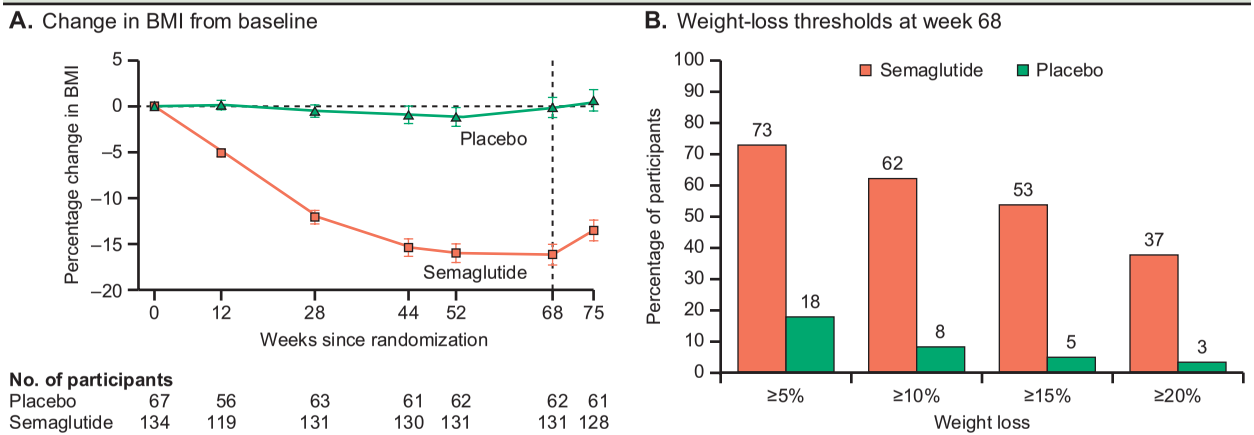
No. of participants										
Semaglutide run-in	803	803	803	802	801					
Continued semaglutide						535	527	531	525	523	521	516	520	535
Switched to placebo						268	267	265	258	260	254	246	250	268

B. Proportion of participants achieving thresholds of weight loss during the entire trial (weeks 0–68; observed in-trial data)



Rubino D, et al. *JAMA*. 2021;325(14):1414-1425.

FIGURE 9.17 — STEP TEENS: Change in BMI from Baseline and Weight Loss Thresholds at Week 68



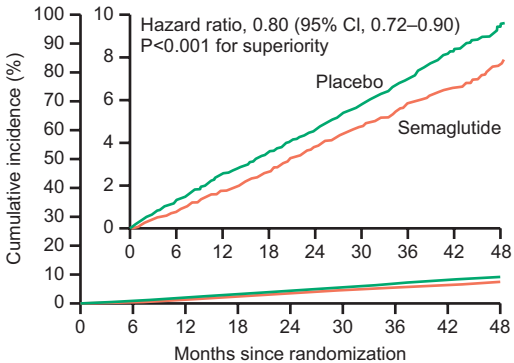
The I bars in panel A represent the standard errors.

Weghuber D, et al. *N Engl J Med*. 2022;387(24):2245-2257.

of semaglutide for the prevention of major adverse cardiovascular events (MACE) in patients without T2D.[37] Semaglutide was previously shown to significantly reduce the risk of MACE in a population of patients with T2D in the SUSTAIN-6 trial.[38] In SELECT, a total of 17,604 patients ≥45 years of age with CVD and a BMI of ≥27 but no T2D were randomized (1:1) to receive a once-weekly subcutaneous dose of semaglutide 2.4 mg (gradually escalated from 0.25 mg to 0.5, 1.0, 1.7, and 2.4 mg every 4 weeks over the first 16 weeks of the trial) or a matching placebo. A composite of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke was the primary cardiovascular endpoint in the trial.

In the semaglutide group (n = 8803), a primary endpoint event occurred in 569 patients (6.5%), compared to 701 patients (8.0%) in the placebo group (n = 8801) (P <0.001) (**Figure 9.18**).[37] Semaglutide thus reduced the risk of a primary endpoint event by 20%. However, semaglutide did not demonstrate superiority to the placebo for the first secondary endpoint in the statistical testing hierarchy – death from CV causes: 223 (2.5%) vs 262

FIGURE 9.18 — SELECT: Cumulative Incidence of Primary Cardiovascular Composite Endpoint Events



No. at Risk

Placebo	8801	8652	8487	8326	8164	7101	5660	4015	1672
Semaglutide	8803	8695	8561	8427	8254	7229	5777	4126	1734

Lincoff AM, et al. *N Engl J Med*. Published online November 11, 2023. doi: 10.1056/NEJMoa2307563.

(3.0%) patients in the semaglutide and placebo groups, respectively; $P = 0.07$. Therefore, superiority was not assessed for other secondary endpoints, including heart failure and death from any cause. Semaglutide also resulted in numerical body weight and waist circumference reduction from baseline, compared to the placebo. A limitation of this study is that it only evaluated the effects of semaglutide on subjects with pre-existing CVD and excluded those without known atherosclerotic disease, therefore the cardioprotective effect on this group is unknown.

STEP HFpEF

The efficacy of semaglutide was also assessed in patients with obesity-related HFpEF, an increasingly prevalent condition with limited treatment options. The double-blind STEP HFpEF trial enrolled a total of 529 patients with HFpEF and a BMI of ≥30, randomizing them (1:1) to receive a once-weekly subcutaneous injection of either semaglutide 2.4 mg or a matching placebo for 52 weeks.[39] The dual primary endpoints, assessed at week 58, were the change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) and the change from baseline in body weight. The KCCQ-CSS is a 23-item, standardized instrument that assesses HF symptoms (eg, fatigue, edema, dyspnea), functional (physical and social) limitation, and quality of life.[39,40] The scores range from 0 to 100; higher scores indicate fewer symptoms and limitations.

At week 58, semaglutide resulted in significant improvement from baseline in both the KCCQ-CSS score (16.6 points vs 8.7 points with the placebo; $P < 0.001$) and weight change (-13.3% vs -2.6% with the placebo; $P < 0.001$).[39] Patients in the semaglutide group also achieved significant improvements in the confirmatory secondary endpoints of change from baseline in the 6-minute walk distance (21.5 meters vs 1.2 meters with the placebo; $P < 0.001$) and change from baseline in the CRP level (-43.5%, compared to -7.3% with the placebo; $P < 0.001$).

Other STEP Trials

Two other STEP trials have been published to date: STEP 5 and STEP 6. The double-blind, randomized STEP 5 trial compared the long-term (104-week)

efficacy of semaglutide 2.4 mg once-weekly to that of a placebo in adult patients with BMI ≥30 or BMI ≥27 and at least one weight-related comorbidity (excluding T2D).[41] Semaglutide demonstrated superiority to the placebo, with a greater change in body weight from baseline (-15.2% vs -2.6%) (P <0.0001) and with more patients achieving ≥5% weight loss from baseline (77.1% vs 34.4%) (P <0.0001) at week 104. The STEP 6 trial assessed the efficacy of semaglutide for weight management in adult patients from East Asia (Japan and South Korea) with a BMI ≥27 and ≥2 weight-related comorbidities or BMI ≥35 with ≥1 weight-related comorbidity.[42] Patients were randomized to receive a 68-week course of semaglutide 2.4 mg (or a matching placebo) or semaglutide 1.7 mg (or a matching placebo) once-weekly. Semaglutide was superior to the placebo in this population, achieving significantly greater body weight reduction from baseline at both the 2.4 mg (-13.2%) and the 1.7 mg (-9.6%) dose compared to the placebo (-2.1%) (P <0.0001 for both comparisons).

FLOW

The efficacy of semaglutide as an adjunct to standard care on the progression of renal impairment in patients with CKD and T2D was assessed in FLOW, an international, randomized, double-blind, parallel-group, placebo-controlled superiority trial.[43] The study randomized (1:1) a total of 3,533 patients to either semaglutide 1.0 mg weekly or a matching placebo. The primary endpoint was major CKD events, defined as a composite of onset of kidney failure, a ≥50% reduction in the eGFR from baseline, or death from causes related to the kidney or CV events. Three key confirmatory secondary endpoints were pre-specified, including the annual rate of change in eGFR from randomization to the end of the trial, MACE (defined as a composite of non-fatal myocardial infarction, nonfatal stroke, or death from CV causes), and death from any cause.

FLOW met its primary objective, with semaglutide reducing the risk of a primary endpoint event by 24% compared to the placebo (P = 0.0003). The risk of kidney-specific components of the primary endpoint was reduced by 21%, and that of CV death by 29%. The

mean annual change in eGFR was lower in the semaglutide group compared to the placebo group (-2.19 vs -3.36 ml/min/1.73 m^2) (P <0.001), as were the risk of MACE (by 18%) (P = 0.029) and the risk of death by any cause (by 20%) (P = 0.01).

Safety

Semaglutide was generally well tolerated in clinical trials (**Table 9.11**). In STEP 1, 74.2% of patients in the semaglutide-treated group reported transient mild-to-moderate GI AEs, compared to 47.9% in the placebo group; these occurred primarily during the dose-escalation period. Gallbladder-related disorders (mostly cholelithia-

TABLE 9.11 — Adverse Reactions With an Incidence of at Least 2% Among Patients Treated With Semaglutide and More Common Than With Placebo

Adverse Reaction	Semaglutide 2.4 mg *N* = 2116 (%)	Placebo *N* = 1261 (%)
Nausea	44	16
Diarrhea	30	16
Vomiting	24	6
Constipation	24	11
Abdominal pain	20	10
Headache	14	10
Fatigue	11	5
Dyspepsia	9	3
Dizziness	8	4
Abdominal distension	7	5
Eructation	7	<1
Hypoglycemia in T2D	7	2
Flatulence	6	4
Gastroenteritis	6	4
GERD	5	3
Gastritis	4	1
Viral gastroenteritis	4	3
Hair loss	3	1

Wegovy [package insert]. Plainsboro, NJ: Novo Nordisk Inc; 07/2023.

sis) were reported in 2.6% and 1.2% of participants in the semaglutide and placebo groups, respectively.[32] In STEP 2, 63.5% of patients receiving semaglutide 2.4 mg, 57.5% receiving semaglutide 1.0 mg, and 34.3% receiving placebo reported transient mild-to-moderate GI AEs.[33] In STEP 3, 82.2% of patients in the semaglutide-treated group and 63.2% in the placebo group reported transient mild-to-moderate GI AEs. Serious AEs were reported in 9.1% and 2.9% of patients in the semaglutide and placebo groups, respectively. In STEP 4, 84% of participants reported AEs during the run-in period of the trial, with 71.4% reporting GI tract disorders.[35] In STEP TEENS, the frequency of AEs was comparable in the semaglutide and placebo groups (79% vs 81%, respectively) as was the frequency of serious AEs (11% vs 9%); however, GI AEs were numerically more common in the semaglutide group (62%) compared to the placebo group (42%).[36]

In the SELECT trial of semaglutide safety and efficacy in a population of patients with CVD, serious AEs occurred at a significantly lower frequency in the semaglutide group (33.4%) than in the placebo group (36.4%; P <0.001).[37] Among serious AEs, those that were significantly less common with semaglutide compared to placebo included cardiac disorders (11.5% vs 13.5%; P <0.001), infections and infestations (7.1% vs 8.4%; P = 0.001), and surgical and medical procedures (4.9% vs 6.2%; P <0.001). By contrast, AEs leading to permanent discontinuation of the study agent were more common with semaglutide (16.6%) than with placebo (8.2%; P <0.001).

In the STEP HFpEF trial, AEs were numerically more common with placebo (26.7%) than with semaglutide (13.3%).[39] Although the rates of GI AEs were similar in the semaglutide and placebo group (2.7% vs 2.6%, respectively), numerically more AEs led to discontinuation in the semaglutide group (13.3%) compared to the placebo group (5.3%), and GI disorder was more common as a cause of discontinuation with semaglutide (9.5%) than with placebo (5.3%).

The safety profile of semaglutide in the FLOW trial was similar to that observed in the other trials of semaglutide.[43] Serious AEs occurred in a numerically lower proportion of patients in the semaglutide group (49.6%) compared to the placebo group (53.8%).

The prescribing information for semaglutide comes with a black box warning about a potential risk of thyroid C-cell tumors, which was determined from studies in rodents that used much higher doses of GLP-1 receptor agonists. Since rodents express much higher levels of GLP-1 receptors in the thyroid than primates, and the doses used in rodent studies were supratherapeutic, the significance of these findings to humans is not clear.[29,36] Like liraglutide, semaglutide is contraindicated in patients with a history (including family history) of MTC, and in patients with MEN 2.

Prescribing, Dosing, and Administration

Semaglutide 2.4 mg is administered subcutaneously once weekly (**Table 9.2**). Injections (in the abdomen, thigh, or upper arm) should be given on the same day of the week and at any time of day, with or without meals.[29] Use of semaglutide with insulin or insulin secretagogues can increase the risk of hypoglycemia; the doses of the concomitant medications may need to be reduced or discontinued. Semaglutide is available in five dosage strengths for the treatment of obesity: 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg, and 2.4 mg.

Per the package insert, treatment should be initiated at a 0.25 mg weekly dose and the dosage should be escalated every four weeks to 0.5 mg, 1.0 mg, and 1.7 mg before reaching the final maintenance dose of 1.7 mg or 2.4 mg at week 13 or week 17, respectively. For pediatric patients, only the 2.4 mg dose is approved for maintenance. If patients do not tolerate a dose, escalation can be delayed for 4 weeks or the dose may be reduced. If the patient does not tolerate the final 2.4 mg dose, the dose can be decreased to 1.7 mg. In clinical practice, the lowest effective dose is often used. If a dose is missed, semaglutide should either be immediately administered (when the next dose is scheduled for >48 hours away) or skipped (when the next dose is scheduled for <48 hours away). In cases where more than 2 consecutive doses are missed, the package insert states that treatment can either be continued at the maintenance dose, or reinitiated with dose escalation. In clinical practice, re-initiating the dose escalation is often deemed the safer option.

Consider prescribing semaglutide 2.4 mg weekly for

appetite suppression and increased satiety. Also consider using it for patients with concomitant T2D.

Tirzepatide (Zepbound)

In 2023, tirzepatide became the newest pharmacological agent to receive FDA approval for chronic weight management. Tirzepatide is indicated in combination with a reduced-calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition.[44] Like liraglutide and semaglutide, tirzepatide is a synthetic peptide that acts an a GLP-1 receptor agonist.[45] However, unlike liraglutide and semaglutide, tirzepatide also acts as a GIP receptor agonist, making it a dual agonist, ie, a mimic of two incretin hormones; this dual mechanism likely increases its efficacy.

Owing to its elimination half-life of 5 days, tirzepatide is administered once weekly, as a subcutaneous injection. It is available in the following dosage forms (in a single-dose pen): 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg per 0.5 mL. It is also available, under a different brand name, for the treatment of T2D, for which it received approval in 2022.[46]

Efficacy

The efficacy of tirzepatide was assessed in the SURMOUNT clinical trial program, which includes 7 phase 3 studies published to date: SURMOUNT-1, -2, -3, -4, the two SURMOUNT-OSA trials, and SUMMIT.[47] Each of the first 4 SURMOUNT trials was double-blind and placebo-controlled, and all had percentage change in body weight from randomization to the end of treatment as a primary endpoint. SURMOUNT-1 and -2 were fixed-dose studies, while SURMOUNT-3 and -4 were maximum tolerated dose (MTD) studies. The approval of tirzepatide for chronic weight management was based on results from SURMOUNT-1 and -2.44 With a reported weight loss differential of up to 17.8% compared to the placebo,[40] tirzepatide is the most effective of the currently approved anti-obesity drugs. The efficacy of tirzepatide in the treatment of sleep apnea, a common comorbidity of obesity, was assessed in the two SURMOUNT-OSA trials.

The SUMMIT trial tested the efficacy of tirzepatide for the treatment for HFpEF.

SURMOUNT-1

SURMOUNT-1 was a 72-week trial designed to test the weight loss efficacy of tirzepatide in patients with overweight or obesity but no T2D.[48] A total of 2539 adult patients with either BMI ≥30 or BMI ≥27 with at least one weight-related comorbid condition (eg, hypertension, dyslipidemia, obstructive sleep apnea, or CVD) were randomized (1:1:1:1) to receive a weekly subcutaneous dose of tirzepatide 5 mg, 10 mg, 15 mg, or a matching placebo. Patients with T2D were excluded. Percent change in weight from baseline and proportion of patients achieving a weight loss of ≥5% were the co-primary endpoints. Efficacy was assessed using two estimands: the treatment regimen estimand (TRE; assessing efficacy in all randomized patients regardless of treatment discontinuation) and the efficacy estimand (assessing the treatment effect for randomized participants provided that the treatment was administered as intended).

At week 72, percent weight change in all tirzepatide dose groups was greater than that for placebo, for both the TRE and the efficacy estimand (tirzepatide 5 mg: -15.0%; tirzepatide 10 mg: -19.5%; tirzepatide 15 mg: -20.9%; placebo: -3.1%; P <0.001 for all comparisons to the placebo for the treatment efficacy estimand) (**Figure 9.19A-B**).[48] More patients in each tirzepatide group achieved the other co-primary endpoint of ≥5% weight loss compared to the placebo group, for both the TRE (tirzepatide 5 mg: 85.1%; tirzepatide 10 mg: 88.9%; tirzepatide 15 mg: 90.9%; placebo: 34.5%; P <0.001 for all comparisons to the placebo) and the efficacy estimand (tirzepatide 5 mg: 89.4%; tirzepatide 10 mg: 96.2%; tirzepatide 15 mg: 96.3%; placebo: 27.9%) (**Figure 9.19C-D**). Significantly more patients in the tirzepatide groups also achieved the secondary endpoints of ≥10%, ≥15%, and ≥20% weight loss (P <0.001 for all comparisons to the placebo), and numerically more patients achieved the exploratory endpoint of ≥25% weight loss (statistical significance not assessed) (**Figure 9.19C-D**).

A long-term extension study of SURMOUNT-1 examined the efficacy of tirzepatide in delaying progres-

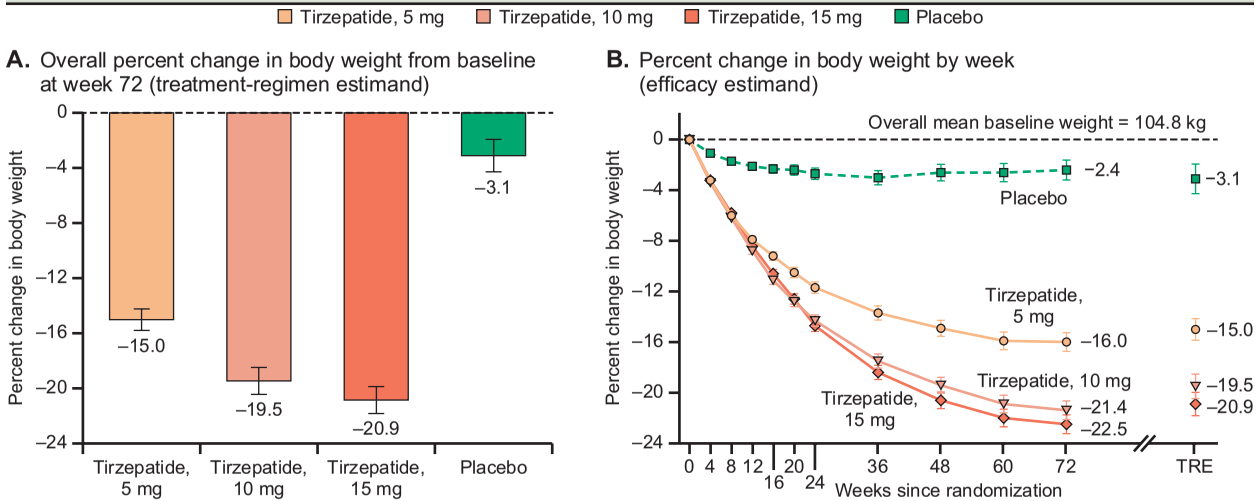
sion to T2D among patients who had both prediabetes and obesity (n = 1032 at baseline).[49] The patients in this analysis received a dose of tirzepatide or placebo for 176 weeks (including the initial 72-week period), followed by an off-treatment period of 17 weeks. The three key endpoints of the analysis included the percent change in body weight from baseline to week 176, onset of T2D during the on-treatment (176-week) period and onset of T2D during the entire 193-week period. At all doses, tirzepatide demonstrated statistical superiority (P <0.001) to the placebo for all three key endpoints. At week 176, the mean percent change in body weight was -12.3%, -18.7%, and -19.7% with tirzepatide (5, 10, and 15 mg, respectively), compared to -1.3% with placebo. During the 176-week period, progression to T2D was observed in 1.3% of patients in the pooled tirzepatide group, compared to 13.3% of patients in the placebo group; in the entire 196-week period, prediabetes progressed to T2D in 2.4% and 13.7% of patients in the tirzepatide and placebo group, respectively.

SURMOUNT-2

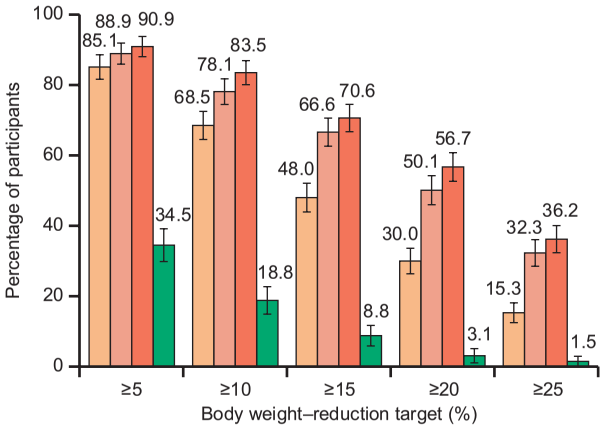
The SURMOUNT-2 trial assessed the efficacy of tirzepatide in a patient population with T2D and overweight or obesity.[50] Eligible adult patients (BMI ≥27, glycated hemoglobin 7-10% [53-86 mmol/mol]) (n = 938) were randomized (1:1:1) to receive tirzepatide 10 mg, 15 mg, or a matching placebo as a subcutaneous once-weekly injection for 72 weeks. The co-primary endpoints, percent change in body weight from baseline and proportion of patients achieving ≥5% weight loss, were identical to those of SURMOUNT-1, as were the two estimands: the TRE (which included all patients who were randomized) and the efficacy estimand (which included randomized patients who remained on the study treatment for the entire efficacy assessment duration of the trial).

Patients in both tirzepatide groups achieved significantly greater percent weight change at week 72 compared to those in the placebo group for the TRE (tirzepatide 10 mg: -12.8%; tirzepatide 15 mg: -14.7%; placebo: -3.2%; P <0.0001 for both comparisons) (**Figure 9.20A**) and the efficacy estimand (tirzepatide

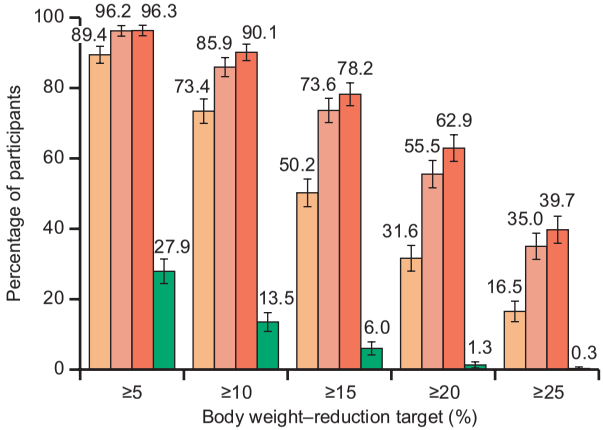
FIGURE 9.19 — SURMOUNT-1: Change in Body Weight from Baseline and Proportion of Patients Achieving ≥5%, ≥10%, ≥15%, ≥20%, and ≥25% Weight Loss



C. Participants who met weight-reduction targets (treatment-regimen estimand)

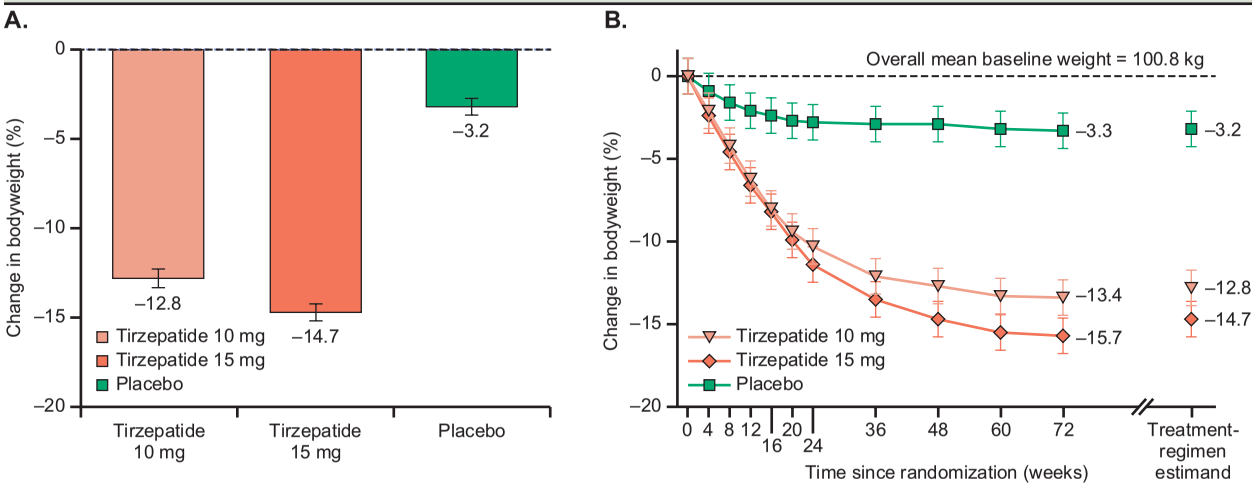


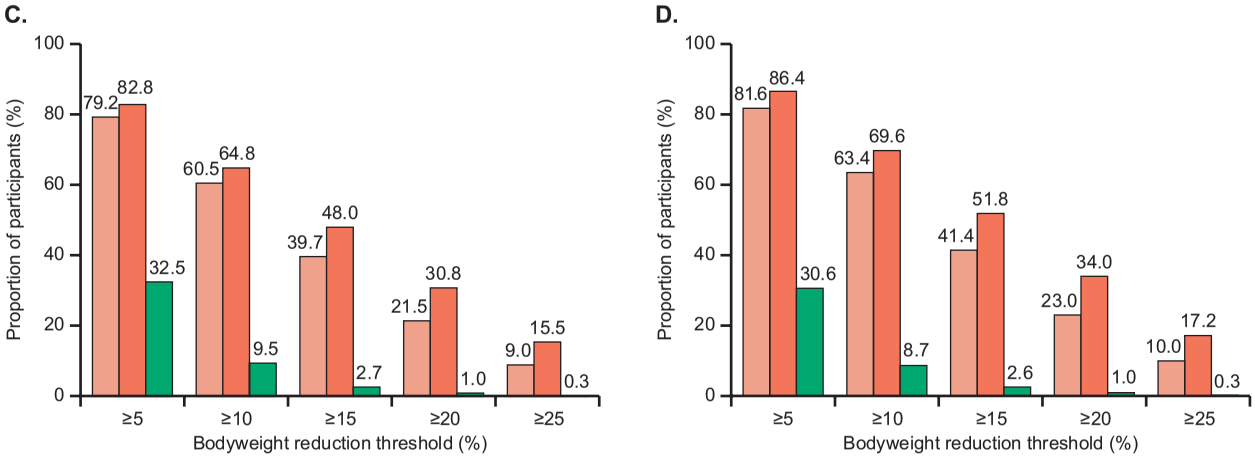
D. Participants who met weight-reduction targets (efficacy estimand)



Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

FIGURE 9.20 — SURMOUNT-2: Change in Body Weight from Baseline and Proportion of Patients Achieving ≥5%, ≥10%, ≥15%, ≥20%, and ≥25% Weight Loss





Efficacy results for the treatment regimen estimand (panels A and C) and the efficacy estimand (panels B and D).

Garvey WT, et al. *Lancet*. 2023;402(10402):613-626.

10 mg: -13.4%; tirzepatide 15 mg: -15.7%; placebo: -3.2%; P <0.0001 for both comparisons) (**Figure 9.20B**).[50] Compared to patients in the placebo group, more patients in both tirzepatide groups achieved ≥5% body weight loss for both the TRE (tirzepatide 10 mg: 79.2%; tirzepatide 15 mg: 82.8%; placebo: 32.5%; P <0.0001 for both comparisons) (**Figure 9.20C**) and the efficacy estimand (tirzepatide 10 mg: 81.6%; tirzepatide 15 mg: 86.4%; placebo: 30.6%; P <0.0001 for both comparisons) (**Figure 9.20D**). SURMOUNT-2 also met all of its key secondary endpoints, with more patients in both tirzepatide groups achieving ≥10%, ≥15%, and ≥20% body weight loss compared to patients in the placebo group, for both estimands (**Figure 9.19C-D**). Both doses of tirzepatide also resulted in a greater proportion of patients achieving the secondary endpoint of ≥25% weight reduction compared to the placebo for both estimands (**Figure 9.20C-D**).

SURMOUNT-3

The SURMOUNT-3 trial tested the efficacy of tirzepatide in adult patients with BMI ≥27 and without T2D who achieved ≥5% weight loss reduction after an intensive 12-week lifestyle intervention lead-in program.[51] A total of 579 patients were randomized (1:1) to either the MTD (10 mg or 15 mg) of tirzepatide or a matching placebo, given by once-weekly subcutaneous injection for 72 weeks. The co-primary endpoints were percent change from baseline in body weight and proportion of patients achieving ≥5% additional weight loss (ie, beyond that already achieved by the lifestyle intervention). Efficacy was assessed by the TRE (all randomized participants, regardless of whether they adhered to treatment) and the efficacy estimand (randomized participants who completed the planned treatment course).

At week 72, significantly greater percent weight change was achieved by patients in the tirzepatide group (-18.4% for the TRE and -21.1% for the efficacy estimand) than in the placebo group (2.5% for the TRE and 3.3% for the efficacy estimand; P <0.001 against tirzepatide for both estimands) (**Figure 9.21A-B**). Significantly more patients achieved the co-primary endpoint of ≥5% body weight reduction with tirzepatide MTD (87.5% for

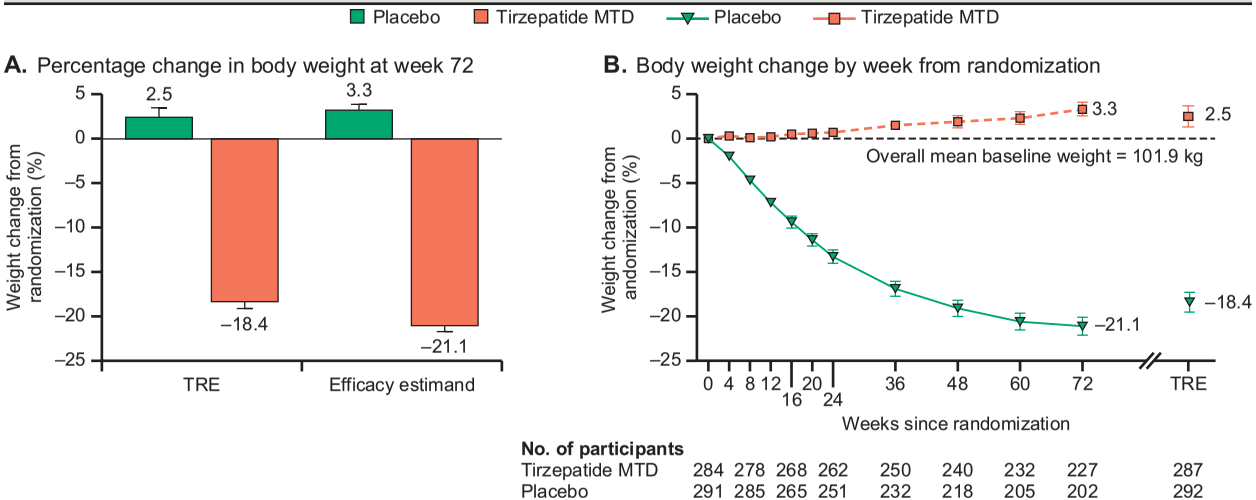
the TRE and 94.4% for the efficacy estimand) than with placebo (16.5% for the TRE and 10.7% for the efficacy estimand; P <0.001 for both comparisons against tirzepatide) (**Figure 9.21C-D**). Tirzepatide proved superior to the placebo with regard to the proportion of patients achieving the key secondary endpoints of ≥10%, ≥15%, and ≥20% weight loss, as well as the exploratory endpoint of ≥25% weight loss (P <0.001 for all comparisons for both estimands) (**Figure 9.21C-D**).

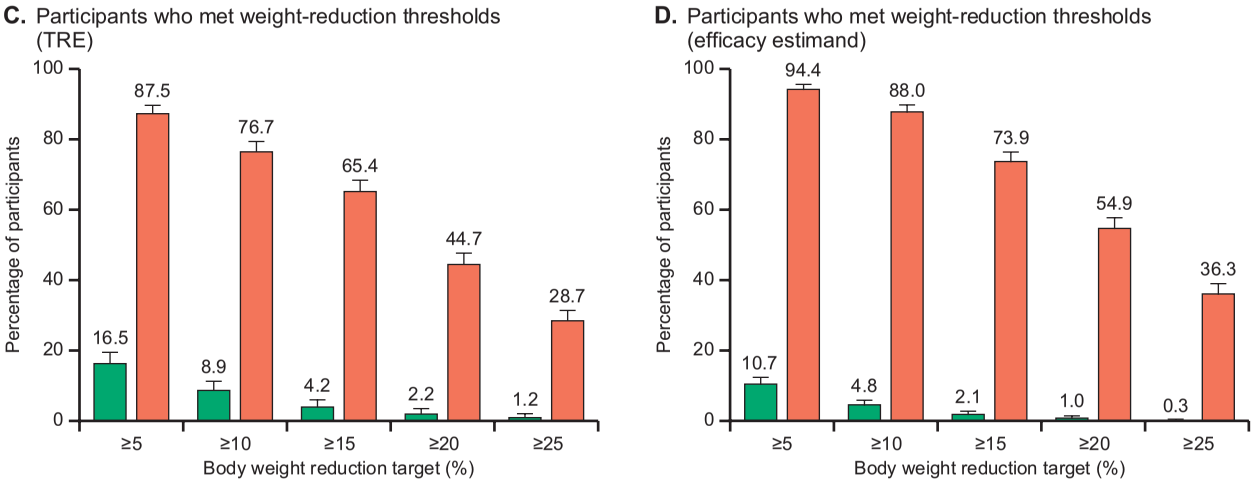
SURMOUNT-4

The fourth study of the program, SURMOUNT-4, was designed to evaluate the efficacy of tirzepatide in weight loss maintenance in adult patients with a BMI ≥30 or ≥27 with an associated complication, but no T2D.[47] A total of 783 patients underwent a 36-week open-label lead-in period on tirzepatide MTD (10 mg or 15 mg), followed by randomization to either continued tirzepatide MTD or a placebo for a 52-week double-blind treatment period.[52] The primary endpoint was percent change in body weight from randomization (week 36) to the end of the trial (week 88).

At the end of the 36 week open-label lead-in period on tirzepatide 10 mg or 15 mg, subjects experienced an average weight reduction of -20.9%.[52] After randomization, for the TRE, patients in the tirzepatide group had a mean weight change of -5.5%, while those in the placebo group experienced, on average, a weight regain of 14.0% (P <0.001) (**Figure 9.22A**). Similarly, for the efficacy estimand, patients randomized to continue tirzepatide had a mean additional body weight change of -6.7%, compared to 14.8% for patients in the placebo group (P <0.001). For the TRE, in the continued tirzepatide group, 89.5% of patients maintained at least 80% of their initial weight loss, compared to only 16.6% of patients in the placebo group who maintained at least 80% of their initial weight loss (**Figure 9.22B**). Across the entire trial (week 0 to 88) for the TRE, significantly more patients in the tirzepatide group achieved a body weight loss of ≥5% (97.3% vs 70.3% for the placebo; P <0.001), ≥10% (92.1% vs 46.2% for the placebo; P <0.001), ≥15% (84.1% vs 25.9% for the placebo; P <0.001), and ≥20% (69.5% vs 12.6% for the placebo; P <0.001) (**Figure 9.22C**). Finally,

FIGURE 9.21 — SURMOUNT-3: Change in Body Weight from Baseline and Proportion of Patients Achieving ≥5%, ≥10%, ≥15%, ≥20%, and ≥25% Weight Loss

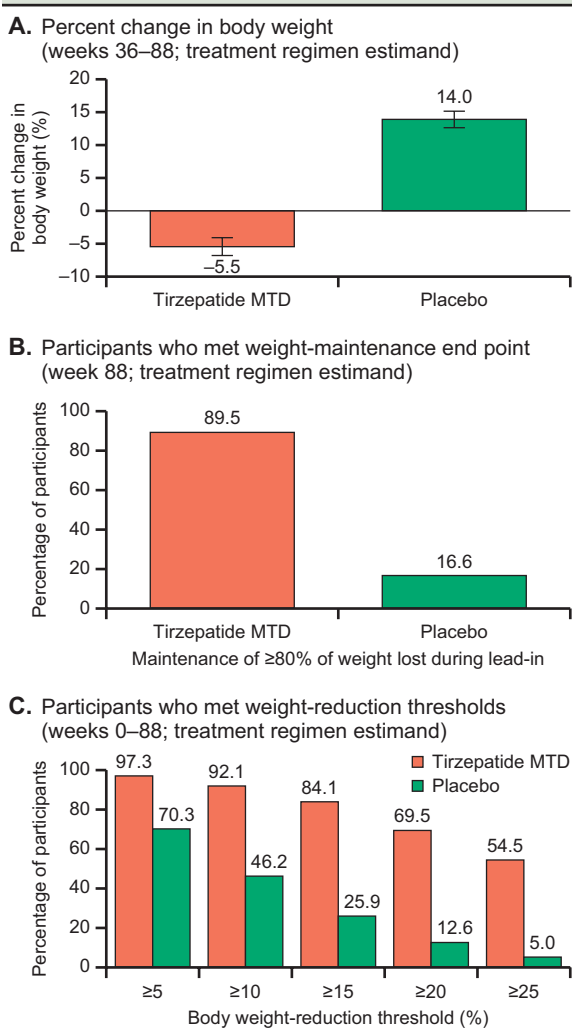




MTD, maximum tolerated dose; TRE, treatment regimen estimand.

Wadden TA, et al. *Nat Med*. 2023;29(11):2909-2918.

FIGURE 9.22 — SURMOUNT-4: Percent Change in Body Weight (Week 36 to 88), Proportion of Patients Maintaining ≥80% Weight Loss, and Proportion of Patients Achieving ≥5%, ≥10%, ≥15%, ≥20%, and ≥25% Weight Loss



Aronne LJ, et al. *JAMA*. Published online December 11, 2023. doi:10.1001/jama.2023.24945.

for the TRE, significantly more patients treated with tirzepatide (54.5%) achieved the exploratory endpoint of ≥25% weight loss, compared to those who received the placebo (5.0%; P <0.001) (**Figure 9.22C**). Therefore, withdrawing treatment of tirzepatide led to weight regain, whereas continued treatment led to additional weight loss.

SURMOUNT-OSA

The SURMOUNT-OSA trials were two phase 3, double-blind, randomized controlled trials which tested the efficacy of tirzepatide for the treatment of sleep apnea, a condition associated with increased risk of MACE and etiologically linked to obesity.[53] Trial 1 enrolled patients who were not on positive airway pressure (PAP) therapy while Trial 2 enrolled patients on PAP therapy; they were otherwise identical in design. A total of 234 (Trial 1) and 235 (Trial 2) patients were randomized (1:1) to either the maximum tolerated dose of tirzepatide (10 or 15 mg) or a matching placebo for 52 weeks. The primary endpoint was the change from baseline in the apnea-hypopnea index (AHI), defined as the number of apnea or hypopnea episodes during an hour of sleep time. Other key endpoints included the percent change in AHI and body weight, changes in hypoxic burden, patient-reported sleep impairment/disturbance, high-sensitivity CRP (hsCRP) concentration, and systolic blood pressure. All endpoints were assessed at week 52, with the exception of blood pressure (which was assessed at week 48).

Among patients not on PAP therapy (Trial 1), the mean change in AHI at week 52 was -25.3 and -5.3 events/hour with tirzepatide and placebo respectively (P <0.001).[53] Tirzepatide treatment also resulted in significant (P <0.001) reduction in AHI events (-29.3 events/hour) in the PAP therapy group (Trial 2) compared to the placebo (-5.5 events/hour). In both trials, tirzepatide treatment also resulted in significant improvements compared to the placebo in the key secondary endpoints (P <0.001 for all except the change in hsCRP concentration in Trial 1 [P = 0.004] and the change in systolic blood pressure at week 48 in Trial 2 [P = 0.02]).

SUMMIT

SUMMIT was a phase 3, double-blind, randomized controlled trial which assessed the efficacy of tirzepatide for the treatment of HFpEF.[54] In total, 731 patients with HFpEF (an EF of ≥50%) and obesity (BMI ≥30) were randomized (1:1) to receive tirzepatide (up to 15 mg) subcutaneously once per week or a matching placebo, for ≥52 weeks. There were two primary endpoints: 1) a composite of adjudicated death from CV causes or a worsening HF event resulting in hospitalization, intravenous drug treatment in an urgent care setting, or intensification of oral diuretic therapy; and 2) the change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), a patient reported outcome instrument with scores ranging from 0 to 100 (with higher scores indicative of higher quality of life). The key secondary endpoints included change in 6-minute walk distance, percent change in body weight, and percent change in hsCRP.

A total of 36 composite primary endpoint events (adjudicated CV-related deaths or worsening HF-related events) occurred in the tirzepatide group (9.9%), significantly ($P = 0.026$) fewer than the 56 events that occurred in the placebo group (15.3%; hazard ratio 0.62).[54] At week 52, the change from baseline in KCCQ-CSS was significantly ($P < 0.001$) greater in the tirzepatide group (19.5), compared to the placebo group (12.7; difference of 6.9 points). Tirzepatide treatment also resulted in significant improvements in weight change (-13.9% vs -2.2% with tirzepatide and placebo, respectively), percent change in hsCRP (-38.8% vs -5.9%), and change in 6-minute walk distance (26.0 meters vs 10.1 meters ($P < 0.001$ for all comparisons.

Safety

Overall, tirzepatide was well tolerated in the SURMOUNT clinical trial program. The safety profile of tirzepatide in the SURMOUNT program was similar to that observed in the SURPASS program, which assessed the efficacy of tirzepatide for glycemic control and chronic weight management in patients with T2D.[48] As expected for a dual incretin agonist, gastrointestinal-related AEs were the most common type of AE in SURMOUNT-1,

-2, and -3, and occurred more commonly in patients taking tirzepatide. The pooled frequency of adverse events in SURMOUNT-1 and -2 is shown in **Table 9.12**.[44] The three most common AEs in SURMOUNT-3 were nausea (tirzepatide: 39.7%; placebo: 14.0%), diarrhea (tirzepatide: 31.0%; placebo: 9.2%), and constipation (tirzepatide: 23.0%; placebo: 6.8%).[51]

In all treatment groups in the first three SURMOUNT trials, the majority (≥90%) of adverse events were mild to moderate in intensity. The safety findings from SURMOUNT-4 were consistent with this, with AEs and serious AEs generally balanced across treatment groups, except for GI AEs which were numerically more common with tirzepatide. Across SURMOUNT-1 and -2, treatment discontinuation due to an AE occurred in 4.8%, 6.3%, and 6.7% of patients receiving tirzepatide 5 mg, 10 mg, and 15 mg, respectively, and 3.4% of patients receiving placebo.[44] In SURMOUNT-3, 10.5% and 2.1% of patients in the tirzepatide and placebo group, respectively, discontinued treatment due to an AE.[51] In SURMOUNT-4, the proportions of patients in the tirzepatide and placebo group who discontinued treatment due to an AE were 1.8% and 0.9%, respectively.[52] The long-term safety data from the SURMOUNT-1 analysis of patients with pre-diabetes were consistent with those of other trials of tirzepatide, and no new safety signals were identified.[49] The safety profile of tirzepatide in SURMOUNT-OSA was also similar to that observed in previous trials.[53] Consistent with prior studies, GI AEs were more common with tirzepatide than with placebo in SUMMIT, but serious AEs occurred with similar frequency in the two groups.[54]

The prescribing information for tirzepatide contains a black box warning about thyroid C-cell tumors, based on data from rats with unclear significance to humans.[44] Like liraglutide and semaglutide, tirzepatide is currently contraindicated for patients with either a personal or family history of MTC and for patients with MEN 2.

Tirzepatide slows gastric emptying and therefore can alter the absorption of other oral medications. Of particular importance, patients who are on concomitant oral contraceptives should either switch to non-oral

contraceptives or should be counseled to use a barrier method of contraception for 4 weeks after initiating tirzepatide and for 4 weeks after any dose escalation.[44]

Dosing, Administration, and Prescribing

Tirzepatide is administered once weekly by subcutaneous injection in the abdomen, thigh, or upper arm (**Table 9.2**). It can be injected either by healthcare professionals or by patients, once trained in the proper injection technique. Injection sites should be rotated with each dose. Tirzepatide can be administered at any time of day, with or without meals. The use of tirzepatide with insulin or an insulin secretagogue may increase the risk of hypoglycemia; therefore, lowering the dose of insulin or insulin secretagogue should be considered. Tirzepatide is available in pre-filled, single-dose pens of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg.

The recommended starting dose is 2.5 mg once weekly, increased after 4 weeks to 5 mg once weekly. The recommended maintenance dose is 5 mg, 10 mg, or 15 mg once weekly, depending on the treatment response and tolerability, with 15 mg being the maximum recommended weekly dose. Dosage should be increased in 2.5 mg increments every 4 weeks until the individualized maintenance dose is reached. A missed dose should be taken as soon as possible within 4 days or 96 hours of the scheduled dose; if more time elapsed since the originally scheduled dose, the dose should be skipped and the regimen continued from the next scheduled dose. If required, the day of administration can be changed, provided that at least 3 days or 72 hours elapsed between two doses.

Consider prescribing tirzepatide 5 mg, 10 mg, or 15 mg weekly for appetite suppression and increased satiety. Also consider using it for patients with concomitant T2D.

Summary

Successful treatment of obesity requires a multidisciplinary approach and multimodal therapy including dietary and behavioral strategies. Since not all patients respond to lifestyle modification alone, pharmacologic treatment options can be pursued. There are seven FDA-approved agents currently available in the United States. Effective pharmacotherapy may require either single or

multiple agents, and attention to patient medical history is critical to determining the appropriate choice of agent or agents. Patients should be monitored at least monthly for the first three months of treatment, and then at least every three months. The efficacy of the medication should be re-evaluated at each appointment, and behavioral interventions should be reinforced.

Antiobesity pharmacotherapy is intended for long-term use, as obesity is a chronic disease. Continued use of the medication to promote maintenance of weight loss is recommended to help offset the reduction in energy expenditure and the increase in appetite that occurs with weight loss. The future of obesity treatment will likely consist of multiple combinations of agents in conjunction with behavioral approaches in order to achieve clinically significant weight loss. Weight maintenance and relapse prevention justifies a long-term approach requiring chronic treatment and follow-up.

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Bariatric Interventions

Introduction

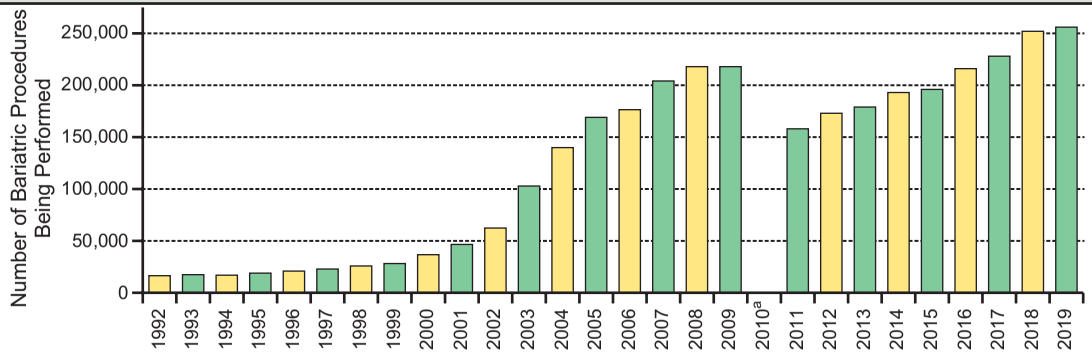
Bariatric intervention has evolved rapidly since its introduction in the 1950s. In the United States, the number of bariatric procedures has increased exponentially from the early 1990s until 2008. After a brief decrease, likely caused by the great recession (2007-2009) during which many patients may have deferred or delayed elective procedures, the numbers continued to increase, reaching an all-time peak of 256,000 in 2019 (**Figure 10.1**).[1-5] The rate of increase was lower in the period between 2011 and 2019 compared to the pre-recession exponential increase; this may be due to a shift in the general perception of bariatric intervention from being a "cure" to being the first step that requires continuing commitment to major changes in lifestyle in order to maintain weight loss. Because of a lack of referrals and stigma, only a small percentage (~1%) of all eligible people receive bariatric surgery.

The most plausible explanation for the observed historical trends, however, is that bariatric intervention has gone through a period of slow acceptance by the medical and lay community and is now an established option for weight loss in patients who qualify. With the introduction of minimally invasive (laparoscopic) surgery and reversible endoscopic procedures, as well as a continuously improving interventional safety profile, the number of bariatric interventions may continue to increase. The introduction of transient bariatric devices, such as intragastric hydrogels, provides an option for patients unable or unwilling to undergo endoscopic or surgical procedures.

Bariatric Devices and Endoscopic Procedures

In recent decades, a number of devices and endoscopic procedures have been developed. Implantable devices which reduce the need for invasive bariatric

FIGURE 10.1 — Number of Bariatric Procedures Performed in the United States From 1992 to 2019



The exponential growth of weight-loss surgeries has ended. Though numbers have experienced a decrease because of the great recession, the number of procedures is now linearly increasing.

[a] Data for 2010 were not available.

Adapted from: Elliott VS. Bariatric surgery maintains, doesn't gain. American Medical News Web site. http://www.amednews.com/article/20120423/business/304239976/4/. Accessed March 28, 2022; and ASMBS website. Metabolic & Bariatric Surgery Fact Sheet. https://asmbs.org/app/uploads/2021/07/Metabolic-Bariatric-Surgery-Fact-Sheet-2021.pdf. Accessed March 28, 2022.

surgery are therapeutic alternatives. They include gastric balloons (introduced in 1985), EndoBarrier (2007), endoscopic sleeve gastroplasty (2008), and aspiration therapy (2013), to name just a few approaches.[6] Most recently (2019), an orally-administered hydrogel capsule received FDA approval, and may represent an attractive option for patients unable to undergo other bariatric or endoscopic procedures.

Intragastric Balloons

Intragastric balloons (IGBs) are one of the most well-established bariatric procedures. An empty balloon is introduced into the stomach either endoscopically or by swallowing a capsule and then inflated with air or saline to varying volumes. This both reduces the stomach volume and alters stomach motility, resulting in a feeling of satiety which then leads to weight loss. The use of IGBs is indicated for 6 to 12 months, and they have to be removed after that period. Intragastric balloons are approved (in conjunction with diet and exercise) for use in patients with a BMI of 30-40; they thus represent an option for patients whose BMI (30-35) excludes them from bariatric surgery, but not for people with a BMI above 40.

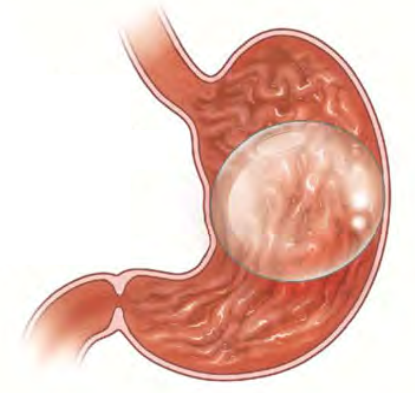
There were initially three FDA-approved IGBs on the market: the ReShape Integrated Dual Balloon System, the Orbera Intragastric Balloon System (**Figure 10.2A**), and the Obalon Balloon system (**Figure 10.2B**). Reshape and Orbera are saline-filled balloons while Obalon is gas-filled. The Reshape system is now being phased out, leaving the other two FDA-approved systems available.

The estimated weight loss with Orbera is 8.5% at 3 months, 11.8% 6 months, and 13.3% at 9 months.[7] The most common complication was early balloon removal, with the top three causes being vomiting, patient request, and nausea. Orbera has also been studied as a bridge to bariatric surgery in order to achieve pre-operative weight loss of 10% in patients with class III obesity.[8]

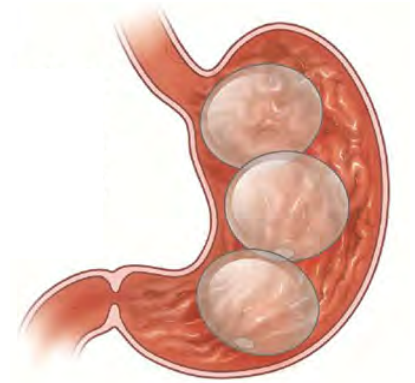
In the SMART trial, the Obalon balloon system demonstrated a total body weight loss (TBWL) of 6.6%, with a weight loss maintenance rate of 88.5% at 48 weeks. Most of the reported adverse events were mild, and serious adverse events were rare.[9] The Obalon

FIGURE 10.2 — Intragastric Balloons

A. Orbera Intragastric Baloon System



B. Obalon Baloon System



Balloons are introduced into the stomach either endoscopically or by swallowing a capsule and then inflated with air or saline to the desired volume, reducing gastric volume and altering stomach motility, and leading to increased satiety. A, the Orbera balloon system. B, the Obalon balloon system.

Sullivan S, et al. *Gastroenterology*. 2017;152(7):1791-1801.

Navigation System received FDA approval in December 2018, eliminating the need for radiography to confirm balloon positioning and instead utilizing magnetic resonance to provide a real-time image of the balloon on computer screen; this reduced both procedure costs and

radiation exposure.

Another study compared fluid-filled IGBs with the gas-filled IGBs, revealing that gas-filled IGBs had lower meta-analytic rates of nausea (55.10 vs. 72.99%) and vomiting (16.2 vs. 76.95%).[10] Gas-filled balloons may be better tolerated compared with the fluid-filled balloons and have not been associated with pancreatitis.

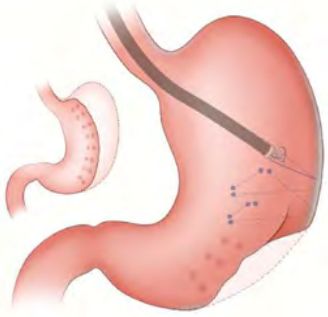
Weight regain is a concern after the balloon has been removed; therefore, the procedure should be combined with lifestyle changes and possibly pharmacotherapy to help maximize weight loss maintenance success rates.

Endoscopic Sleeve Gastroplasty (ESG)

Endoscopic sleeve gastroplasty is a minimally invasive technique intended to reduce the size of gastric reservoir. It utilizes a full thickness endoscopic suturing device to stitch together the anterior and posterior stomach walls and achieve a tubular structure (**Figure 10.3**).[11-14] Successful ESG decreases gastric capacity up to 70%.[11-13]

The mechanisms of ESG weight loss include delayed gastric emptying, increased early satiation, and alternation of the gut and metabolic hormones: ghrelin and insulin levels decrease and insulin secretion patterns improve.[15,16] The gastric fundus and neuronal innervation are left intact, so stasis and delayed transition of food

FIGURE 10.3 — Endoscopic Sleeve Gastroplasty



Endoscopic sleeve gastroplasty uses an endoscopic suturing device to stitch together the anterior and posterior stomach walls and create a tubular structure.

Sullivan S, et al. *Gastroenterology*. 2017;152(7):1791-1801.

induce early satiety through the stomach-brain signaling pathway.[17,18]

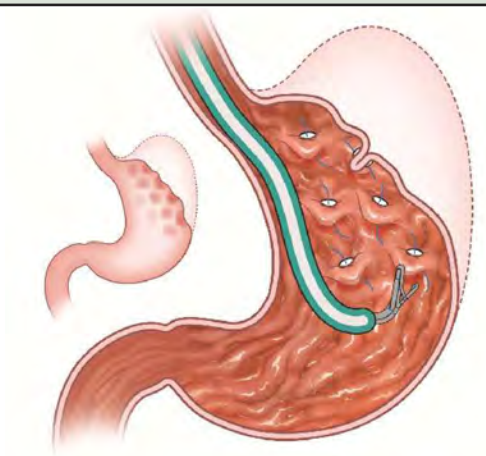
ESG showed better results than both high intensity diet and lifestyle therapy (HIDLT) and intragastric balloon insertion in TBWL (ESG vs HIDLT: 20.6% vs 14.3%; ESG vs intragastric balloon: 20.6% vs 13.9%).[19] A number of studies reported a TBWL of 14.5% to 20% with ESG in a timeframe of 6-12 months.[12,20-22] ESG is safe in patients with class I-III obesity, although one study reported better %BMI loss in patients with class I obesity (BMI under 35).[23] Available data also show that ESG may be an effective long-term weight loss strategy, with 90% of patients maintaining a TBWL of 5% and 61% a TBWL of 10% 5 years after the procedure.[24] ESG has demonstrated significant improvements in obesity-related comorbidities (decreases in A1C, systolic blood pressure, insulin resistance, triglycerides, and ALT) and health-related quality of life.[25-28]

Compared to laparoscopic sleeve gastrectomy (the most common bariatric surgery),[6] ESG is less effective in terms of %TBWL, but has a better safety profile, shorter procedure time, shorter hospital stay, and lower incidence of new-onset GERD.[19,29] Incidence of severe adverse events is low with ESG (1%) and mild events like nausea, vomiting, and abdominal pain typically improve after a few days with postoperative care.[29] Importantly, ESG can be reversed if patients do not respond well, though this is almost vanishingly rare (<0.01%).[31]

Primary Obesity Surgery Endolumenal (POSE)

Primary obesity surgery endolumenal is a minimally invasive procedure that modifies the gastric anatomy using a platform which consists of a flexible tube, control handle for maneuverability, an endoscope, four working channels, and specialized instruments for grasping tissue and placing anchors.[32] The platform folds stomach tissue in the fundus and distal body using a suture and the specialized tissue anchors, thus preventing fundal accommodation and inducing antral dysmotility (**Figure 10.4**). This in turn triggers earlier and prolonged gastric distention, which helps patients feel full sooner and eat less.[32] POSE is intended for patients who have not previously had any other bariatric procedures and may

FIGURE 10.4 —Primary Obesity Surgery Endolumenal



Primary obesity surgery endolumenal is a minimally invasive procedure that folds stomach tissue in the fundus and distal body using a suture and specialized tissue anchors, preventing fundal accommodation and inducing antral dysmotility, which leads to increased satiety.

Sullivan S, et al. *Gastroenterology*. 2017;152(7):1791-1801.

be an effective weight loss option for patients with class I and II obesity. Patients with class III obesity can be considered for this procedure if they agree to comply with postoperative care. The overall goal of POSE is to treat early stages of obesity and associated comorbidities and prevent disease progression.

One study of POSE efficacy demonstrated a 45% reduction in excess weight 1 year after the procedure (excess weight being the difference between the actual weight of the patient and their "ideal" weight - the weight at BMI of 25), and an average TBWL of 15%.[33] Patients reported a 50% reduction in hunger and 60% reduction in stomach capacity after the procedure.[33] Another trial noted that patients who had the best results at 1 year (TBWL ≥15%) were younger and had higher initial BMIs.[34] Variables that affect weight loss include age, weight before surgery, overall condition of patient's health, commitment to lifestyle changes, and follow-up care.[34]

The overall frequency of adverse events with POSE is 1%, with the most common serious adverse events being postoperative bleeding, perforation of the stomach, pneumothorax, and perihepatic/perisplenic abscess.[33] No serious long-term adverse events associated with the anchors have been reported.

POSE provides individuals with an alternative option to achieve long-term weight loss and improved health related quality of life without large expenses, long hospital stays, and high safety risks. If optimal weight loss is not achieved, POSE does not preclude other bariatric procedures.

Orally-Administered Gastric Hydrogel

Approved by the FDA in April 2019, Plenity (referred to as Gelesis100 in clinical studies) is a novel alternative to endoscopic and surgical bariatric procedures. Plenity is an oral, nonsystemic, superabsorbent hydrogel capsule composed of encapsulated cellulose and citric acid. The orally administered capsule disintegrates in the stomach, releasing the hydrogel particles, which hydrate up to 100 times their initial weight and mix with ingested food to create a larger volume with higher elasticity and viscosity which helps make patients feel fuller (**Figure 10.5**). The fiber is not absorbed systemically and once it reaches the colon, the hydrogel is broken down and the water is reabsorbed while the remaining fiber particles are eliminated with feces. Plenity works by promoting the feeling of fullness and satiety. It is indicated for adult patients with overweight or obesity with a BMI of 25 to 40 in conjunction with reduced calorie diet and exercise.[35] It is the only intervention approved for patients with a BMI of 25-27.

The efficacy of Plenity was assessed in a 24-week Gelesis Loss of Weight Trial (GLOW) – a randomized, double-blind, placebo-controlled study in adults with BMI of 27 to 40, with or without T2D. A 24-week extension to the study (GLOW-EX) examined the effectiveness of Plenity in maintaining weight loss achieved after 6 months for an additional 6 months, as well as the safety of long-term exposure to Plenity. The co-primary efficacy end points were percent change in body weight from baseline and percent of patients who lost ≥5%

body weight from baseline. Plenity was safe and effective at promoting weight loss in adults with overweight or obesity with or without T2D.[36]

In the GLOW trial, patients self-administered three capsules containing either Plenity 2.25 g or a placebo with 500 mL of water 20 to 30 minutes before lunch and dinner (twice daily). Mean weight loss from the baseline was 6.4% in the treatment group compared with 4.4% in the placebo group (P = 0.0007; **Figure 10.6A**). Among the participants, 32 subjects in the treatment group and 36 subject in the placebo group had prediabetes or drug-naïve T2D. In participants with these conditions, the mean weight loss from baseline were 8.1% and 5.6% for the treatment and placebo groups, respectively. Overall, in the Plenity group, 59% of patients achieved a weight loss of ≥5% compared to 42% in the placebo group (P <0.001; **Figure 10.6B**), and 27% of Plenity-taking patients achieved a weight loss of ≥10%, compared to 15% in the placebo group (P <0.05; **Figure 10.6B**).[36]

In GLOW-EX, continuation of treatment combined with lifestyle modifications was offered to 52 eligible participants who had completed the GLOW study and demonstrated a weight loss of ≥3% from the baseline. Of those, 39 enrolled in GLOW-EX for further 24 weeks of treatment. After 48 weeks, the Plenity treatment group had a mean weight loss of 7.6% compared to 7.1% in the initial 24-week GLOW trial. Patients from the placebo group who were switched to Plenity in GLOW-EX had a mean weight loss of 9.4%, compared to 7.1% in the initial 24-week GLOW trial. These results suggest that Plenity is effective at maintaining weight loss beyond the initial 6 months when combined with diet and exercise.[36]

Plenity was well tolerated in the GLOW study, with a favorable safety profile. The incidence of adverse events was comparable between the Plenity and the placebo groups (~70%). The most common adverse events in both groups were gastrointestinal related, with a lower incidence of infections and infestations, and musculoskeletal and connective tissue disorders. Overall, gastrointestinal-related AEs were significantly different between groups (P = 0.0248). However, none of the individual gastrointestinal AEs showed statistical significance.

FIGURE 10.5 — Plenity

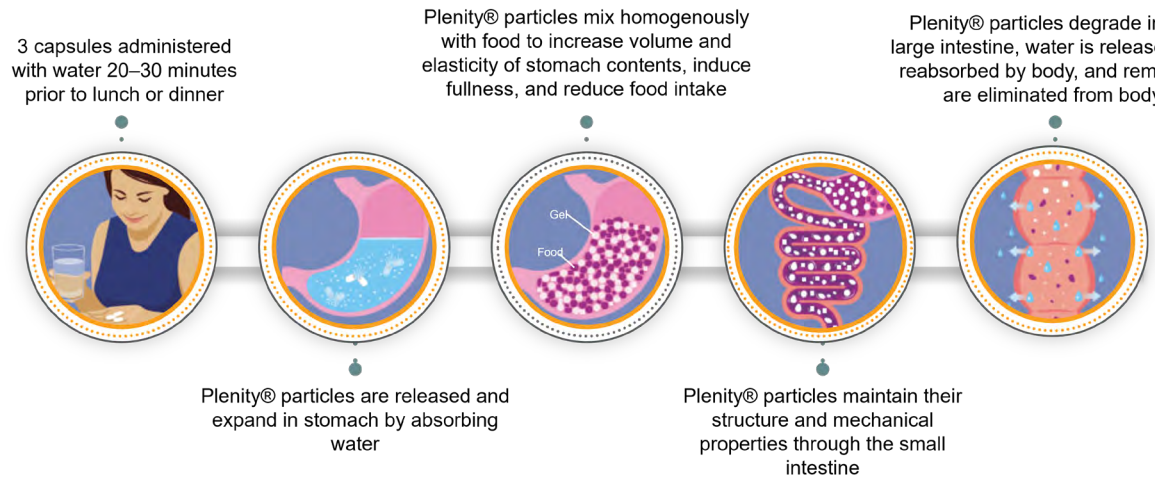
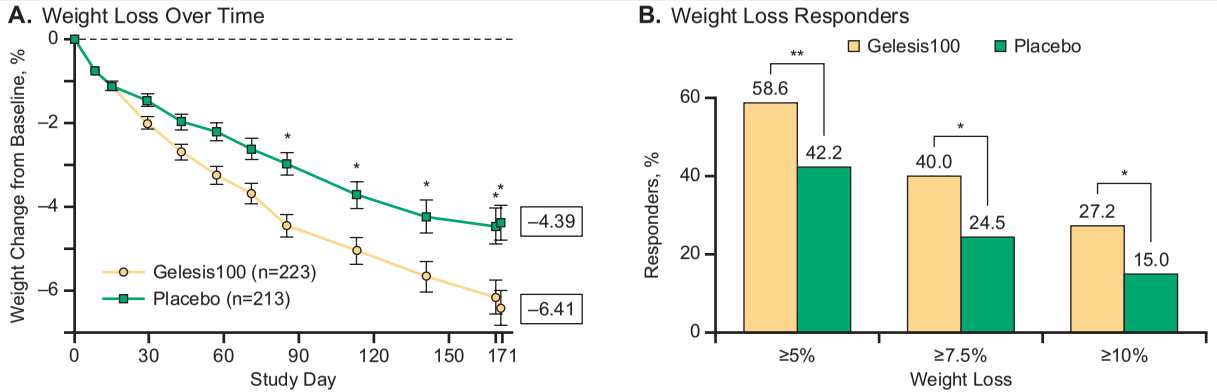


Figure from Gelesis, Inc. Used with permission.

FIGURE 10.6 — GLOW: Change in Body Weight from Baseline and Proportion of Patients Achieving ≥5%, ≥7.5%, and ≥10% Weight Loss



Greenway FL, et al. *Obesity (Silver Spring)*. 2019;27(2):205-216.

The safety results from GLOW-EX were consistent with those from GLOW.[37] Given the indication of Plenity for diabetic patients, another study was conducted to assess whether single-dose co-administration of Plenity and metformin has any effect on the PK parameters or safety compared to metformin co-administration with food. This trial concluded that the effect of Plenity on the pharmacokinetics of metformin was similar to the effect of food, and that Plenity is safe to co-administer with metformin for patients who have diabetes.[37]

Aspiration Therapy (AT)

Aspiration therapy is an endoscopic procedure available for people with a BMI of 35-55 that uses an FDA-approved device called AspireAssist to drain gastric contents (**Figure 10.7**).[38] Aspire Assist consists of:[39]

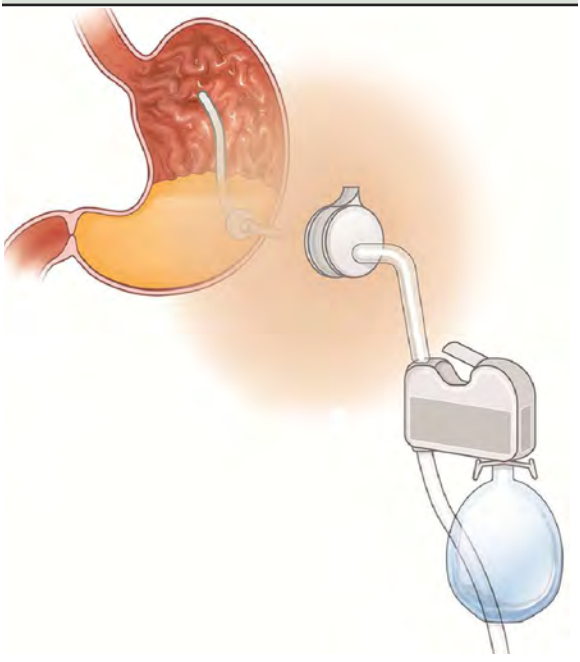
- An endoscopic gastronomy tube (A-tube) with a fenestrated intragastric drainage catheter
- A flange (Skin-Port) connected to the external end of the A-tube and closed unless aspirating, to prevent gastric leakage
- A detachable connector, connected to the skin tube when aspirating, used for drainage of gastric contents
- A two-way syphon allowing gastric draining and infusion of water into the stomach
- A 600 mL reservoir
- A drain tube, allowing the disposal of aspirated gastric content.

Patients undergoing AT aspirate approximately 30% of the ingested calories, 30 minutes after meals.[39] After 5-6 weeks (115 uses), the connector locks and can no longer be used, so patients are required to see a healthcare practitioner who will provide a new connector.[39]

Aspiration therapy is used alongside non-high-intensity lifestyle therapy (LT). Patients should be counseled by a healthcare practitioner about LT when they come to exchange the connector.[39]

The observed TBWL at 1 year is around 17-19%, with 80% of weight loss coming from aspiration of calories[39,40] and the remaining 20% from reduced food intake. Since food particles have to be 5 mm or smaller to

FIGURE 10.7 — Aspiration Therapy



Patients can use the AspireAssist device to aspirate ~30% of the ingested calories after each meal.

Sullivan S, et al. *Gastroenterology*. 2017;152(7):1791-1801.

fit through the A-tube, this may result in longer chewing time and reduced calorie consumption. Increased water consumption to allow liquid gastric contents to flow out of the A-tube may also increase satiety. The visibility of the gastric aspirate may play a role as well, as patients report that less healthy food options have an unappealing appearance after aspiration, potentially reducing consumption of such foods.[39]

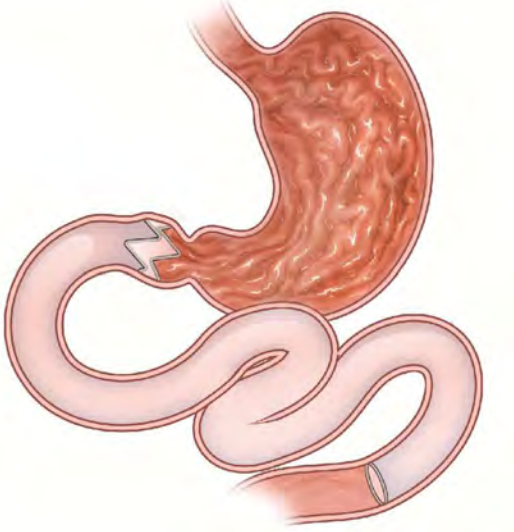
AT is associated with significant improvements in hypertension, hyperlipidemia, T2D, and non-alcoholic fatty liver disease. This improvement in metabolic functions is likely related to the amount and type of weight loss following AT.[41]

The disadvantages of AT include the visibility of the catheter and the time and effort required to aspirate. The safety profile is acceptable, with a serious adverse event incidence of 4.1%, the most common being buried bumper.

EndoBarrier

EndoBarrier is an implantable duodenal-jejunal bypass sleeve shown to be effective at reducing excess weight and minimizing CVD risk factors (**Figure 10.8**). It is a fluoropolymer sleeve that is reversibly fixated to the duodenal bulb and extends 80 cm into the small bowel, terminating in the proximal jejunum. This endoscopically inserted device aids weight loss through induction of malabsorption and activating hormonal triggers. Studies using the EndoBarrier found that patients were able to achieve between 11.9% and 23.6% excess weight loss within 12 weeks. A longer trial found that patients

FIGURE 10.8 — EndoBarrier



EndoBarrier is a fluoropolymer sleeve reversibly fixated to the duodenal bulb, extending 80 cm into the small intestine and terminating in the proximal jejunum.

Sullivan S, et al. *Gastroenterology*. 2017;152(7):1791-1801.

were able to achieve 47% mean excess weight loss in 52-weeks.[42] In addition to weight loss, one study found that this procedure resulted in statistically significant reductions in fasting blood glucose (-30.3 ± 10.2 mg/dL), fasting insulin (-7.3 ± 2.6 μU/mL), and A1C (-2.1 ± 0.3%) compared with baseline.[43] The EndoBarrier may also have a positive impact on CVD risk factors, including a reduction in lipid levels and blood pressure.

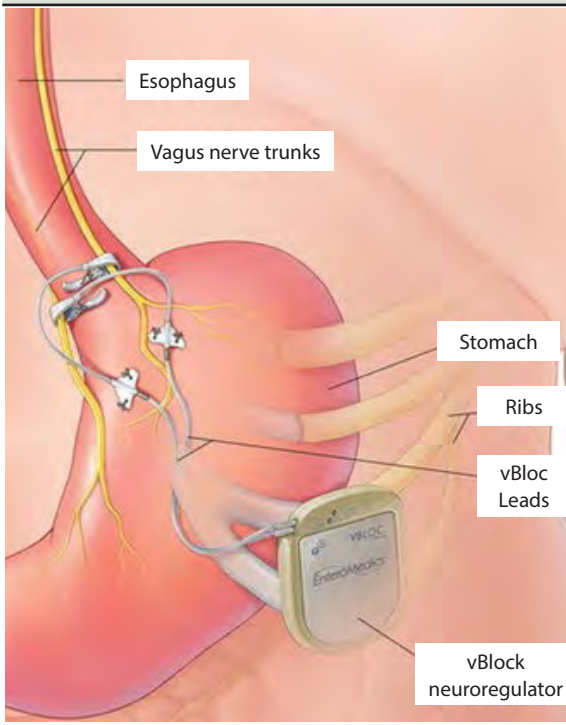
vBloc

The vBloc (Maestro Rechargeable System; marketed by ReShape Lifesciences) is a laparoscopically-implantable device which is capable of delivering low-energy electrical pulses to the intra-abdominal vagal trunks (**Figure 10.9**).[44] The role of the vagus nerve in the regulation of metabolism, appetite/satiety, and autonomic control of the upper GI tract provided the rationale for developing a therapy that can intermittently deliver a vagal block and reduce the feeling of hunger. The vBloc is indicated in patients with a BMI of 40 to 45, or a BMI of 35 to 39.9 and at least one obesity-related co-morbid condition, and who have not achieved the goal weight loss on at least one supervised weight management program in the past five years.

The efficacy of vBloc was assessed in ReCharge, a multicenter, randomized, double-blind trial that enrolled 239 patients to receive either a vBloc device capable of delivering electric pulses or a sham device that was not; the patients in the pulse-capable group received at least 12 hours of vagal block therapy per day.[44,45] Patients in the vagal block therapy group demonstrated greater TBWL at 12 months (10% vs 6% with sham; $P<0.001$) and 18 months (9% vs 4% with sham; $P<0.001$) following implantation. Twenty-four months after implantation, patients who continued vagal block therapy maintained a similar TBWL (8%). The vBloc demonstrated a favorable safety profile, with 94% of reported AEs being of mild or moderate intensity.[44]

The vBloc device thus represents a reasonable and safe option for patients with class III obesity who are hesitant to undergo procedures which modify GI anatomy. While the vBloc has been FDA approved, it is not currently commercially available.

FIGURE 10.9 — vBloc



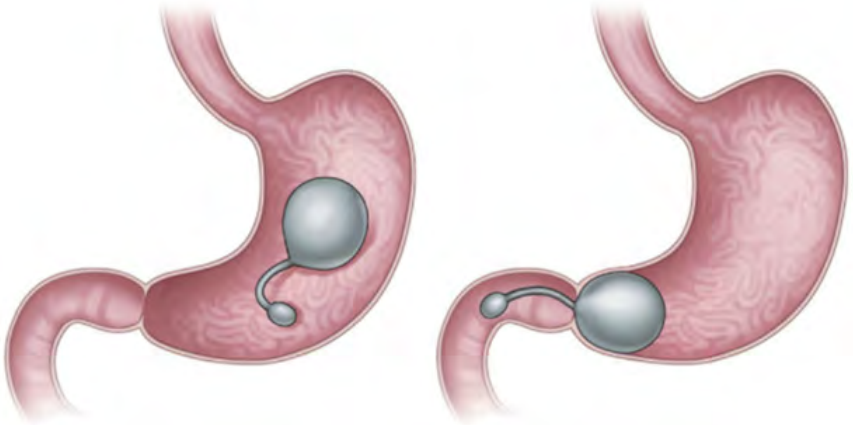
The vBloc is a laparoscopically-implantable device which delivers ~12 hours of electric pulses to the intraabdominal vagal nerve trunks, decreasing the feeling of hunger.

From Enteromedics, Inc.

Transpyloric Shuttle

The TransPyloric Shuttle (TPS; developed by BARONova) is a device composed of a two silicon-based balloons connected by a catheter (**Figure 10.10**). The TPS is endoscopically introduced into the stomach where is self-assembles, with the smaller balloon positioned in the duodenum and the larger balloon positioned in the pylorus.[46] Properly positioned, the TPS results in more rapid filling and slower gastric emptying. It is indicated for adult patients who have not achieved the desired weight loss with medical strategies, and who have a BMI

FIGURE 10.10 — TransPyloric Shuttle



The TPS consists of two balloons connected by a catheter: the smaller oval balloon is positioned in the duodenum and the larger in the pylorus, providing more rapid filling and slower gastric emptying.

Choi YI, et al. *Clin Endosc*. 2018;51(5):420-424.

of 35-40, or 30-34.9 with an associated comorbidity. The TPS can remain in the stomach for up to 12 months. In a randomized controlled trial in 302 patients, the TPS group demonstrated a significantly greater TBWL (9.5%) compared to the control group (2.3%; $P<0.0001$).[47]

Conclusion

Non-surgical endobariatric interventions, including endoscopic procedures and orally-administered intragastric hydrogels, represent a significant leap in bariatric management. Their favorable safety profile and greater reversibility make them an attractive option to patients who qualify and can help bridge the "treatment gap" for patients who do not qualify for or are not interested in bariatric surgery.

Candidates and Qualifications for Bariatric Surgery

Surgical bariatric procedures currently represent the most successful treatment for obesity, but only 1% of the eligible population opts for surgical treatment.[48] The 2019 joint guidelines by the American Association of Clinical Endocrinologists (AACE), The Obesity Society (TOS), American Society for Metabolic & Bariatric Surgery (ASMBS), Obesity Medicine Association (OMA), and American Society of Anaesthesiologists (ASA) present the following eligibility criteria for bariatric surgery:[49]

- Patients with a BMI ≥40 without co-existing medical problems and for whom bariatric procedures would not be associated with excessive risk

According to the AACE/TOS/ASMBS/OMA/ASA guidelines, bariatric surgery may also be considered in:

- Patients with a BMI of ≥35 and at least one obesity-related comorbidity, including T2D, insulin resistance, prediabetes, metabolic syndrome, poorly-controlled hypertension, nonalcoholic steatohepatitis, obstructive sleep apnea, osteoarthritis of the knee or hip, and urinary stress incontinence
- Patients with a BMI of ≥35 and any of the following, though the evidence is less clear: obesity hypoventilation syndrome and Pickwickian syndrome (after

a careful evaluation of operative risk), idiopathic intracranial hypertension, GERD, severe venous stasis disease, impaired mobility due to obesity, and considerably impaired quality of life

- Patients with a BMI of 30-34.9 and T2D with inadequate glycemic control despite optimal lifestyle and medical therapy

The guidelines also state that the BMI eligibility criteria should be adjusted for ethnicity, and that bariatric procedures should be considered when there are significant obesity-related complications that cannot be prevented or treated with the amount of weight loss achieved on lifestyle change and medical therapy only.

As discussed in *Chapter 1*, the rates of overweight and obesity continue to rise among children and adolescents. Recent data has demonstrated the safety and efficacy of bariatric surgery in adolescent patients; intervening early can reduce the risk of persistent obesity. The 2018 ASMBS guidelines present the following indications and contraindications for bariatric surgery in adolescents:[50]

- *Indications*:
  - BMI ≥35 or 120% of the 95th percentile, with clinically significant co-morbid conditions, including obstructive sleep apnea (AHI >5), T2D, IIH, NASH, Blount's disease, SCFE, GERD, or hypertension
  - BMI ≥40 or 140% of the 95th percentile
- *Contraindications*:
  - A medically correctable cause of obesity
  - An ongoing substance abuse problem (within the preceding year)
  - A medical, psychiatric, psychosocial, or cognitive condition that prevents adherence to postoperative dietary and medication regimens
  - Current or planned pregnancy within 12 to 18 months of the procedure

The ASMBS guidelines also state that before bariatric surgery is attempted, a multidisciplinary healthcare team

must decide whether the patient and his/her family members are both able and motivated to adhere to recommended pre- and postoperative treatments.[50]

Patients considering bariatric surgery need to understand the procedure and its potential benefits and risks, and be willing to accept the responsibility of long-term compliance to lifestyle changes and medical follow-up. Answers to the following questions may help patients decide whether weight-loss surgery is right for them.[1,5,51,52]

Is the patient[5,51]:

- Unlikely to lose weight or keep it off over the long-term using other methods?
- Well informed about the surgery and treatment effects?
- Aware of the risks and benefits of surgery?
- Ready to lose weight and improve his or her health?
- Aware of how life may change after the surgery? (For example, patients need to adjust to side effects, such as the need to chew food well and the loss of ability to eat large meals.)
- Aware of the limits on food choices, and occasional failures?
- Committed to lifelong healthy eating and physical activity, medical follow-up, and the need to take extra vitamins and minerals?

Bariatric Surgical Procedures

Currently, the following five bariatric procedures are the most commonly used in the United States:[2,3,5,51]

- Roux-en-Y gastric bypass (RYGB)
- Laparoscopic sleeve gastrectomy (LSG)
- Biliopancreatic diversion with or without duodenal switch (BPD or BPD/DS)
- Single Anastomosis Duodeno-Ileal Switch (SADI-S)
- Adjustable gastric banding (AGB).

LSG is the most commonly performed procedure in the United States as of 2019, accounting for 61.4% of bariatric surgeries performed. It is followed by RYGB

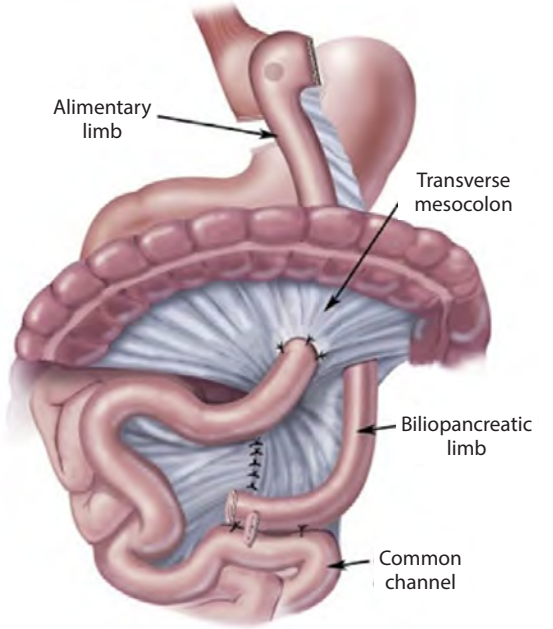
(17.0%). LSG has become very popular due to the simplicity of the procedure, the durability of weight loss, and the potential that side effects such as vitamin and mineral deficiencies are less common than with RYGB. Initially, these procedures were performed using open surgical techniques; however, there has been an overwhelming trend toward the use of laparoscopic technologies. For example, the proportion of laparoscopic bariatric operations increased from 20.1% in 2003 to 90.2% in 2008.[2]

Although the mechanisms by which bariatric surgery causes weight loss have not been completely elucidated, the three generally accepted weight loss mechanisms are restriction, malabsorption, and hormonal changes. The active mechanism depends on the type of intervention; some procedures can have a restrictive effect on the amount of food (thus the total number of calories consumed), while others involve a combination of restriction plus the bypass of portions of the stomach and small intestine, resulting in changes in the gut biome and hormone milieu. These changes alter appetite, satiety, and possibly even metabolism, leading to weight loss.

Roux-En-Y Gastric Bypass (RYGB)

RYGB (often simply called "gastric bypass") is generally considered the gold standard of weight loss surgery and is the second most commonly performed bariatric procedure worldwide as of 2019, having been overtaken by LSG as in the United States.[53] There are two major steps in this procedure (**Figure 10.11**).[1,5,51,52] In the first step, the top of the stomach is divided from the rest of the stomach to create a small stomach pouch (~30 mL in volume). Next, the proximal portion of the small intestine is divided (30-40 cm from the junction between the duodenum and jejunum), and the distal end is brought up and connected to the newly created small stomach pouch. The procedure is completed by connecting the top portion of the small intestine to the rest of the small intestine (100-150 cm further down) so that the stomach acids and digestive enzymes from the bypassed stomach and first portion of small intestine will eventually mix with the food.[54] The RYGB is generally considered a nonreversible procedure but can reversed in "emergency" situations.

FIGURE 10.11 — Roux-en-Y Gastric Bypass



The RYGB surgery restricts food intake and also decreases how food is absorbed. A new stomach pouch is created from which food flows directly into the small intestine, bypassing the stomach, duodenum, and the upper intestine.

Mehta M, et al. *Endocr Pract*. 2021;27(6):626-635.

RYGB leads to weight loss through restrictive, malabsorptive, and hormonal changes. First, the newly created stomach pouch is considerably smaller and facilitates significantly smaller meals, which translates into fewer calories consumed. Most importantly, the rerouting of the food stream produces changes in gut hormones that promote satiety and suppress hunger. The concept that RYGB is a strictly malabsorptive procedure has been disproven due to the discovery that there are changes in the gut microbiome and hormone milieu that occur after RYGB, including reduced ghrelin levels and increased nutrient-stimulated PYY and GLP-1 levels.[55]

The potential advantages and disadvantages of RYGB according to the American Society for Metabolic and Bariatric Surgery are listed in **Table 10.1**.

Laparoscopic Sleeve Gastrectomy (LSG)

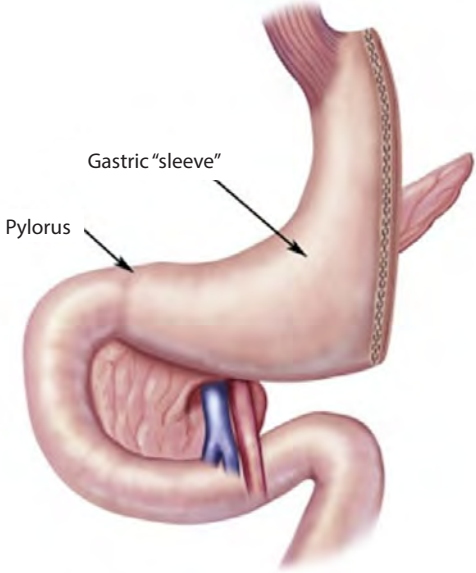
LSG (often simply called the "sleeve") is a procedure that permanently removes ~80% of the stomach. (**Figure 10.12**) The remaining stomach is a tubular pouch that resembles a banana. LSG was originally performed as a modification to another bariatric procedure (BPD/DS), and then later as the first part of a two-stage gastric bypass operation on patients with a BMI >55 for whom the risk of performing gastric bypass surgery was deemed too great. The initial weight loss in these patients was so successful that it began to be investigated as a stand-alone procedure.

Since the new stomach pouch holds a considerably smaller volume than the normal stomach, there is a significantly reduced amount of food (and thus calories) that can be consumed. In addition, like RYGB, LSG alters the gut microbiome and the gut hormone milieux.

TABLE 10.1 — RYGB: Potential Advantages and Disadvantages

Advantages
■ 60% to 80% long-term excess weight loss
■ 20% to 30% total body weight loss
■ Restricts amount of food that can be consumed
■ May lead to conditions that increase energy expenditure
■ Produces favorable changes in gut hormones that reduce appetite and enhance satiety
■ Associated with maintenance of >50% excess weight loss
■ Greater incidence of diabetes remission compared with other bariatric procedures
Disadvantages
■ Long-term vitamin/mineral deficiencies, particularly in vitamin B12, iron, calcium, and folate
■ Requires adherence to dietary recommendations, life-long vitamin/mineral supplementation, and follow-up compliance

FIGURE 10.12 — Laparoscopic Sleeve Gastrectomy



The LSG procedure removes most of the stomach, restricting food intake by decreasing the amount of food that can be ingested.

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Ghrelin levels are reduced to a greater extent than after RYGB (since the primary location of ghrelin production - the gastric fundus - is removed), while GLP-1 and PYY are increased, though to a smaller degree than following RYGB. These changes result in reduced hunger, increased satiety, and improved blood sugar control.

The potential advantages and disadvantages of LSG according to the American Society for Metabolic and Bariatric Surgery are listed in **Table 10.2**.

Biliopancreatic Diversion With Duodenal Switch (BPD/DS)

BPD/DS is a two-step procedure. First, a smaller, tubular stomach pouch is created by removing a portion of the stomach, very similar to the sleeve gastrectomy (**Figure 10.13**). Next, a large portion of the small intestine is bypassed. The duodenum is divided just past the

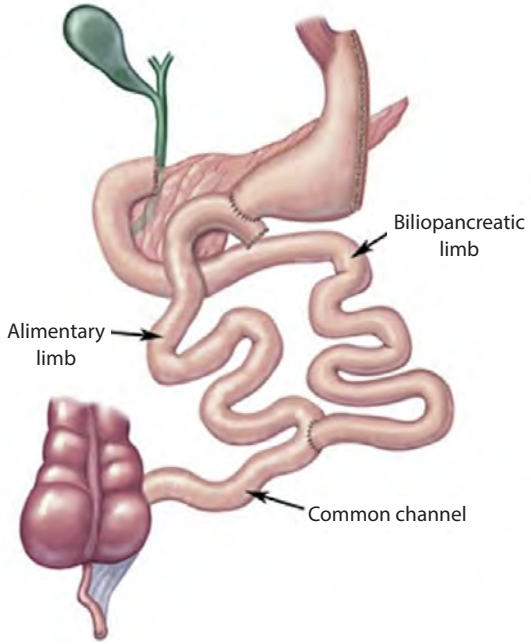
TABLE 10.2 — LSG: Potential Advantages and Disadvantages

Advantages
■ Restricts the amount of food passing into the stomach
■ Induces rapid and significant excess weight loss similar to that with RYGB (>50% during 3-5+ year maintenance)
■ 20% to 30% total body weight loss
■ Requires no foreign objects (as in AGB) and no bypass or re-routing of the food stream (as in RYGB)
■ Requires a relatively short hospital stay (~2 days)
■ Causes changes in gut hormones that suppress hunger, reduce appetite, and improve satiety
Disadvantages
■ A nonreversible procedure
■ The potential for long-term vitamin deficiencies—less than RYGB but greater than AGB
■ A higher early complication rate than the AGB

outlet of the stomach. A segment of the distal small intestine is then brought up and connected to the outlet of the newly created stomach. Therefore, when the person eats, the food goes through a newly created tubular stomach pouch and empties directly into the last segment of the small intestine. Roughly three fourths of the small intestine is bypassed by the food stream. The bypassed small intestine, which carries the bile and pancreatic enzymes that are necessary for the breakdown and absorption of protein and fat, is reconnected to the last portion of the small intestine so that they can eventually mix with the food stream. Currently, the BPD/DS is not used very frequently in the United States, although there are a few states in which it is currently performed.

Unlike the other procedures, there is a significant amount of small bowel that is bypassed. Additionally, the food does not mix with the bile and pancreatic enzymes until very far down (100 cm from the end of the small intestine).[54] This results in a significant decrease in the absorption of calories and nutrients (particularly protein and fat) as well as nutrients and vitamins dependent on fat for absorption (fat soluble vitamins and nutrients).

FIGURE 10.13 — Biliopancreatic Diversion With Duodenal Switch



Biliopancreatic diversion with duodenal switch involves three features: removal of a large part of the stomach (see LSG), a duodenal switch that re-routes food away from much of the small intestine, and a change in how bile and other digestive juices affect how the body digests food and absorbs calories.

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Lastly, the BPD/DS, similar to the gastric bypass and sleeve gastrectomy, affects gut hormones in a manner that impacts hunger and satiety as well as blood sugar control.

The potential advantages and disadvantages of BPD/DS according to the American Society for Metabolic and Bariatric Surgery are listed in **Table 10.3**.

Single Anastomosis Duodeno-Ileal Switch (SADI-S)

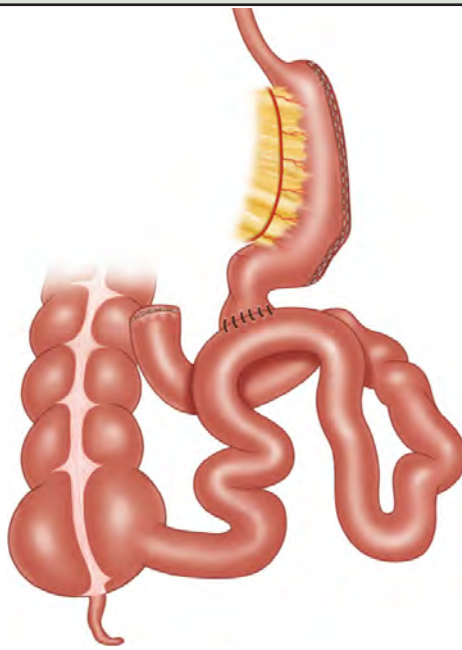
SADI-S was developed in 2007 as an attempt to simplify the BPD/DS procedure, primarily by reducing the number of anastomoses (surgical connections between

TABLE 10.3 — BPD/DS: Potential Advantages and Disadvantages

Advantages
■ Greater weight loss than RYGB, LSG, or AGB (60% to 70% excess weight loss or greater, at 5-year follow-up)
■ 25% to 45% total body weight loss
■ ≥70% reduction of fat absorption
■ Favorable changes in gut hormones to reduce appetite and improve satiety
■ Most effective against diabetes compared with RYGB, LSG, and AGB
■ Allows patients to eventually eat near "normal" meals
Disadvantages
■ Higher complication rates and risk for mortality than AGB, LSG, and RYGB
■ Longer hospital stay than the AGB or LSG
■ Greater potential for protein deficiencies and long-term deficiencies in vitamins and minerals (iron, calcium, zinc, fat-soluble vitamins such as vitamin D)
■ Requires compliance with follow-up care and strict adherence to dietary and vitamin supplementation guidelines

elements of the GI tract). SADI-S consists of a sleeve gastrectomy combined with an end-to-side duodeno-ileal diversion which creates a 200-300 cm channel from the pylorus to the cecum (**Figure 10.14**).[56,57] Compared to BPD/DS, SADI-S reduces operation time and the overall complication rate. Postoperative complications are rare. In patients with a shorter (200 cm) common limb between the stomach and the large intestine, nutritional issues such as undernutrition and diarrhea may be present; a common limb of 250-300cm is now the standard.[56,57] Because of a good record of weight loss (TBWL at 1 year ranged from 21.5% to 41.2% in one meta-analysis)[57] and relatively reduced technical complexity, SADI-S is becoming more widely used.

FIGURE 10.14 — Single Anastomosis Duodeno-Ileal Switch (SADI-S)



SADI-S is a procedure that combines a sleeve gastrectomy and an end-to-side duodeno-ileal diversion which creates a 200-300 cm channel from the pylorus to the ileocecal valve.

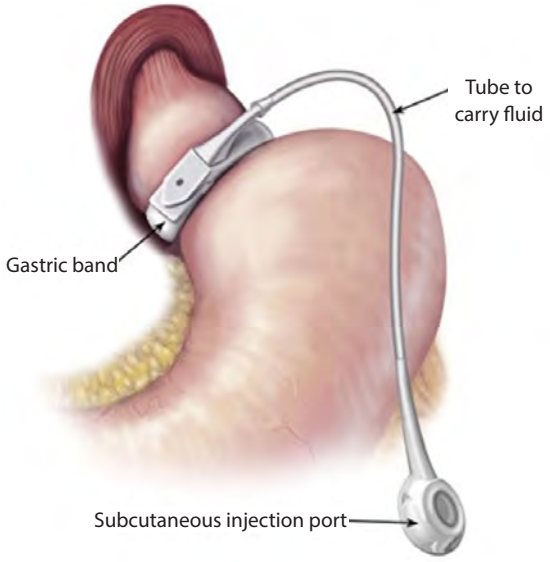
Ruano A, et al. In: Lutfi, R, Palermo M, Cadière GB, eds. *Global Bariatric Surgery*. Springer, Cham.2018.

Adjustable Gastric Band (AGB)

AGB (often simply called the "lap band") is a laparoscopic procedure in which an inflatable band is placed around the upper portion of the stomach, creating a small pouch above the band, and the rest of the stomach below the band (**Figure 10.15**).

The common explanation of how this device works is that with the smaller stomach pouch, eating just a small amount of food will satisfy hunger and promote the feeling of fullness. The size of the stomach opening can be adjusted by filling the band with sterile saline, which is injected through a subcutaneous port. The size of the

FIGURE 10.15 — Adjustable Gastric Band



AGB surgery restricts food intake by placing a small band around the top of the stomach, enabling restriction of the size of the opening from the throat to the stomach. This opening can be adjusted by the surgeon utilizing a circular balloon inside the band. The balloon can be deflated or inflated using saline solution as needed to accommodate the patient's needs via an access port.

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opening is gradually reduced over time with repeated adjustments or "fill" until a so-called "sweet spot" is achieved where restriction of the size causes decreased food intake but no regurgitation or obstruction.

The notion that the band is a restrictive procedure (works by restricting how much food can be consumed per meal and by restricting the emptying of the food through the band) has been challenged by studies that show the food passes rather quickly through the band, and that absence of hunger or feeling of being satisfied was not related to food remaining in the pouch above the band. What is known is that there is no malabsorption; the food is digested and absorbed as it would be normally. The clinical impact of the band seems to be that it

reduces hunger, which helps the patients to decrease the amount of calories that are consumed.

AGB used to be one of the most common bariatric surgeries, but has declined precipitously: in 2011, it accounted for 35.4% of all bariatric procedures, but constituted less than 1% of bariatric surgeries in 2019. The primary reasons for this shift away from AGB is a high complication and removal rate.

The potential advantages and disadvantages of AGB according to the American Society for Metabolic and Bariatric Surgery are listed in **Table 10.4**.

Clinical Experience

While there are considerable and increasing clinical trial data on the clinical efficacy and safety of bariatric surgery, the quality of the studies varies considerably due to the difficulties implicit in performing high quality, randomized, controlled trials of surgeries. As a result, most of the data come from studies with less rigorous designs. Nevertheless, the efficacy of the various bariatric procedures is supported by systematic reviews and meta-analyses, as well as the results of individual studies.

Systematic Reviews and Meta-analyses

One early analysis of 147 studies concluded that surgery resulted in a weight loss of 20 to 30 kg, which was maintained for up to 10 years and was accompanied by improvements in some comorbid conditions.[58] One large, matched cohort analysis reported greater weight loss with surgery than with medical treatment in individuals with an average BMI ≥40. For BMIs of 35 to 39, data from case series strongly supported superiority of surgery but was not considered to be conclusive.

A subsequent systematic review included three randomized controlled trials (RCTs) and three cohort studies that compared surgery with nonsurgical interventions, and 20 RCTs that compared different surgical procedures.[1] Overall, bariatric surgery was a more effective intervention for weight loss than nonsurgical options. RYGB was more effective for weight loss than LSG and AGB. All comparisons of open vs laparoscopic surgeries found similar weight losses in each group. Comorbidities

TABLE 10.4 — AGB: Potential Advantages and Disadvantages

Advantages
■ Induces excess weight loss of approximately 40% to 50%
■ 20% to 25% total body weight loss
■ No cutting of the stomach or rerouting of the intestines
■ Requires a shorter hospital stay, usually <24 hours, with some centers discharging the patient the same day as surgery
■ Reversible and adjustable
■ The lowest rate of early postoperative complications and mortality among the approved bariatric procedures
■ Lowest risk for vitamin/mineral deficiencies
Disadvantages
■ Slower and less early weight loss than other surgical procedures
■ Greater percentage of patients failing to lose at least 50% of excess body weight compared with the other surgeries commonly performed
■ Requires a foreign device to remain in the body
■ Possible band slippage or band erosion into the stomach in a small percentage of patients
■ Can have mechanical problems with the band, tube, or port in a small percentage of patients
■ Can result in dilation of the esophagus if the patient overeats
■ Requires strict adherence to the postoperative diet and to postoperative follow-up visits
■ Highest rate of re-operation

after surgery improved in all groups, but with no significant differences between different surgical interventions.

Another systematic review analyzed the results of 14 trials (one randomized trial) of at least 1 year of follow-up that compared RYGB and AGB.[59] Excess body weight loss at 1 year was consistently greater for RYGB than with AGB (median difference, 26%; P <0.001). Resolution of comorbidities also was greater after RYGB. In the highest-

quality study, excess body weight loss was 76% with RYGB vs 48% with AGB. Both operating room time and length of hospitalization were shorter for those undergoing AGB and perioperative complications were more common with RYGB (9% vs 5%). However, long-term reoperation rates were lower after RYGB (16% vs 24%).

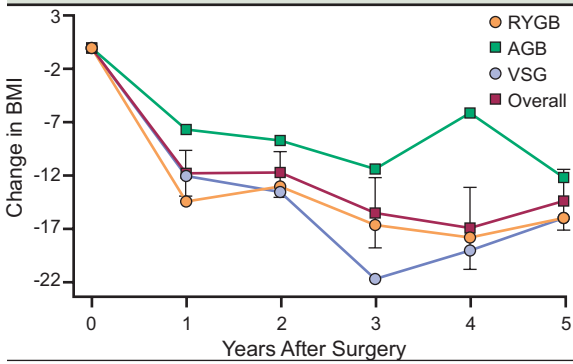
In one systematic review and meta-analysis, Chang and associates analyzed data from 37 randomized clinical trials and 127 observational studies published from 2003 to 2012. A total of 161,756 patients with a mean age of 44.5 years and mean BMI of 45.6 were included.[60] As shown in **Figure 10.16**, RYGB was more effective for weight loss than AGB.

Although data were limited for LSG, it appeared to be more effective for weight loss than AGB and comparable to RYGB.

Individual Studies

O'Brien and colleagues reported the 15-year follow-up data from their prospective longitudinal cohort study of AGB that enrolled 3227 patients with a mean BMI of 43.8.[61] Seven hundred fourteen patients completed ≥10 years of follow-up. Among patients who were at ≥10 years post procedure, the mean excess weight loss was 47.0%. This weight loss occurred regardless of whether

FIGURE 10.16 — Meta-analysis of Postoperative Change in BMI Over 5 Years[a]



[a] Based on 37 studies published between 2003 and 2012.

Chang SH, et al. *JAMA Surg*. 2014;149(3):275-287.

any revisional procedures were needed. These results were compared with a systematic review of the literature that reported weight loss at ≥10 years after other bariatric procedures. In this review, there was ≥50% excess weight loss with all current procedures (**Table 10.5**).

The weighted mean excess weight loss with AGB was 54.2% and 54.0% with RYGB. Revisional procedures were performed for proximal enlargement (26%), erosion (3.4%), and port and tubing problems (21%). The band was explanted in 5.6%. Although this was a single-center study, the results support the long-term durability of weight loss with bariatric surgery, specifically laparoscopic ABG.

The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium reported the 3-year follow-up results of a multicenter observational cohort study in 2458 adults who underwent first-time bariatric surgical procedures between 2006 and 2009 and then followed up until September 2012.[62] At baseline, 79% were women, median BMI was 45.9, and median weight was 129 kg. RYGB was the initial procedure in 1738 participants; AGB was the initial procedure in 610 participants, while 110 underwent other procedures. At baseline, 774 (33%) participants had T2D, 1252 (63%) had dyslipidemia, and 1601 (68%) had hypertension. Three years after surgery, median actual weight loss was 41 kg in RYGB

TABLE 10.5 — Pooled Data From Systematic Review

Procedure	No. Reports	Mean % EWL	Range % EWL	Revision Range
RYGB	9	54.0	28-68	8-39
AGB	7	54.2	33-64	8-60
Gastroplasty	5	52.9	-10 to 62	10-40
BPD/DS	3	73.3	70-75	—

NOTE: In this analysis, the primary efficacy endpoint was change in % EWL. Percent total body weight losses (%TBWL) were not reported. However, %TBWL can be estimated from %EWL by assuming that %TBWL is numerically about one-half the numerical value of the %EWL. Thus, if the %EWL is 50% then the %TBWL would be ~25%.

O'Brien PE, et al. *Ann Surg*. 2013;257:87-94.

recipients, corresponding to a percentage of baseline weight loss of 31.5%. In AGB recipients, actual weight loss was 20 kg corresponding to 15.9% baseline weight loss. The majority of weight loss was evident 1 year after surgery for both procedures. Among participants who had T2D at baseline, 216 (67.5%) RYGB recipients and 28 (28.6%) LAGB recipients experienced partial remission at 3 years. The incidence of T2D was 0.9% after RYGB and 3.2% after LAGB. Dyslipidemia resolved in 237 (61.9%) RYGB recipients and 39 (27.1%) in AGB recipients; remission of hypertension occurred in 269 (38.2%) of RYGB recipients and in 43 (17.4%) of AGB recipients.

In a 7-year follow-up published by the LABS Consortium in 2018, mean weight loss (from baseline weight) was 28.4% in the RYGB group and 14.9% in the AGB group, with a mean regain of 3.9% and 1.4% mean weight regain between years 3 and 7 in the RYGB and AGB groups, respectively.[63] The prevalence of dyslipidemia was lower than at baseline in both groups, while diabetes and hypertension were lower in the RYGB group only. Of the patients with diabetes at baseline, 60.2% in the RYGB group and 20.3% in the AGB group experienced remission 7 years after surgery.

Although many studies of short-term to mid-term outcomes of LAGB have been published, long-term outcomes reports with a follow-up of ≥10 years are still scarce. One study assessed the long-term results of AGB in 60 consecutive patients (44 women, 16 men) who were treated for class III obesity by AGB between 1996 and 1999.[64] The median age of the patients at the time of operation was 45 years and their median preoperative BMI was 45. All patients were instructed to adhere to a strict follow-up program. Complete data on all 60 patients could be assessed; thus, the overall rate of follow-up was 100%. After a median follow-up of 14.1 years, the mean BMI decreased from 45 to 36, with a mean 49% excess weight loss (EWL). At 15 years of follow-up, 48% of bands had been removed. In those patients with the band still in place at 14 years, 40% had >50% EWL while 20% had <25% EWL.

The efficacy and complications of LSG were assessed in a prospective cohort of 68 patients who underwent

LSG either as primary bariatric procedure (n = 41) or as a redo operation after failed AGB (n = 27) between August 2004 and December 2007.[65] At the time of LSG, the mean BMI was 43, the mean age was 43.1 years, and 78% were female. The follow-up rate was 100% at 1 year postoperatively, 97% after 2 years, and 91% after 5 years; the mean follow-up time was 5.9 years. The average EWL was 61.5% after 1 year, 61.1% after 2 years, and 57.4% after 5 years. Comorbidities improved considerably. For example, remission of T2D was achieved in 85% of cases. Complications included: one leak (1.5%), two incisional hernias (2.9%), and new-onset gastroesophageal reflux in 11 patients (16.2%). Reoperation due to insufficient weight loss was necessary in eight patients (11.8%).

A retrospective cohort analysis compared clinical outcomes in 190 consecutive patients who underwent primary BPD/DS between 2005 and 2010, of whom 178 (93.7%) were available for follow-up. These patients were matched with 139 patients who underwent primary RYGB in the same medical center during the same period.[66] While percentage changes from baseline in each group were significant, there was no significant difference in percent total weight loss between groups. T2D, hypertension, and hyperlipidemia all improved significantly within each group, although the improvements were significantly higher in the BPD/DS group. Loose stools and bloating symptoms were more frequently reported among BPD/DS patients. With the exception of increased emergency department visits among BPD/DS patients (P <0.01), overall complication rates were not significantly different between BPD/DS and RYGB. There was no difference in mortality rates between the groups.

In an Israeli trial of 8385 patients with obesity who underwent bariatric surgery (AGB, RYGB, or LSG) and 25,155 matched controls who received usual care (non-surgical, including dietary and behavioral counseling), the all-cause mortality over a course of ~4.5 years was lower in the surgery group (1.3% overall; 1.7% for AGB, 1.3% for RYGB, 0.8% for LSG) than in the non-surgery group (2.3%; adjusted hazard ratio = 2.02). These results underscore the benefit of bariatric surgery to overall health beyond weight loss.[67]

The Swedish Obese Subjects Study

The Swedish Obese Subjects (SOS) study is an ongoing, nonrandomized, prospective, controlled study conducted at 25 public surgical departments and 480 primary health care centers in Sweden that included 2010 participants with obesity who underwent bariatric surgery and 2037 contemporaneously matched participants with obesity who received usual care. Participants were followed up for a median of 14.7 years. The objectives of the SOS study were to determine the long-term effects of weight-loss surgery on "hard" clinical endpoints, including overall mortality, CV events, incidence of diabetes, and stroke.[68] Of the patients who had surgery, 13% underwent a bypass procedure, 19% underwent a banding procedure, while 68% had vertical banded gastroplasty.

In the surgery group, the mean changes in body weight after 2, 10, 15, and 20 years were -23%, -17%, -16% and -18% while the mean changes in the usual care group were 0%, 1%, -1%, and -1%. Compared with usual care, bariatric surgery was associated with a long-term reduction in overall mortality (adjusted HR = 0.71, $P = 0.01$).[68] Bariatric surgery also was associated with a reduced number of CV deaths (28 events among 2010 patients in the surgery group vs 49 events among 2037 patients in the control group (HR = 0.47; $P = 0.002$). The number of total first time (fatal or nonfatal) CV events (myocardial infarction or stroke, whichever came first) was also lower in the surgery group (199 events among 2010 patients) than in the control group (234 events among 2037 patients; HR = 0.67; $P < 0.001$).[69] Perhaps the most striking finding was that during the follow-up period, the incidence of T2D was substantially lower than in the usual care group (6.8 cases per 1000 person-years vs 28.4 cases per 1000 person-years, respectively (HR = 0.17; $P = 0.54$).[70]

Safety

Operative (30-day) mortality for bariatric surgery has been reported to range from 0.1% to 2%.[3,52,59] These rates depend on several factors: complexity of the operation, patient comorbidities, and experience of the surgeon and the center. AGB typically has the lowest mortality rate of 0.1%, whereas the rate with RYGB or VSB is

~0.5%. Higher mortality rates have been correlated with visceral obesity, sex, BMI ≥50, diabetes mellitus, sleep apnea, and older age.

In the meta-analysis of 147 studies discussed above, the overall rate of AEs in bariatric surgery was 20%. Laparoscopic approaches resulted in fewer wound complications than open procedures.[58]

Early general complications include thromboembolism (1%), pulmonary or respiratory insufficiency (<%), hemorrhage (1%), peritonitis (1%), and wound infection (2%). The increased use of laparoscopy has been instrumental in decreasing these rates. GI obstructions are of most concern among long-term complications. The cause of the obstruction typically depends on the type of bariatric procedure. For example, gastric obstruction associated with AGB may be due to food entrapment at the narrowed banded area, from overinflation of the band, or from band "slippage," which causes pouching over the band. Symptoms can be resolved by loosening the band but in certain circumstances, surgical repositioning of the band is necessary. Gastric obstruction associated with RYGB or LSG may be caused by stenosis of the gastric outlet secondary to scar tissue and may be treated with endoscopic dilation.[59] Intestinal obstruction can occur after gastric bypass or other malabsorptive procedures and typically requires urgent surgical intervention.

Topart and colleagues retrospectively reviewed their 2-year, single institution bariatric surgery experience to compare the 30-day morbidity and 90-day mortality rates with LSG (n = 88), RYGB (n = 360), and BPD-DS (n = 59).[71] Thirty-day morbidities were significantly more frequent with LSG and BPD-DS than with RYGB. The global complication rate was significantly higher after BPD-DS (P = 0.0017) compared with RYGB, however, there was no difference between RYGB and LSG. Compared with RYGB, bleeding was more frequent, after comparison with BPD-DS and LSG.

In the meta-analysis by Chang and colleagues (discussed above), the overall complication rate was 17% in RCTs (**Table 10.6**).[60] This pattern persisted across all of the surgical procedures. In RCTs, complications rates were relatively low for LSG (13%) and AGB (13%)

TABLE 10.6 — Estimated Rates (%) of Surgical Risks and Complications[a]

	RYGB	AGB	LSG	Overall
Mortality ≤30 days	0.08	0.11	0.50	0.08
Mortality >30 days	0.39	0.14	0.60	0.31
Complication rates	21.00	13.00	13.00	17.00
Reoperation rates	2.56	12.23	9.05	6.95

[a] Based on meta-analysis of 64 studies published between 2003 and 2012.

Chang SH, et al. JAMA Surg. 2014;149*3):275-287.

compared with VGB (21%). Reoperation rates were not as high as complication rates. In RCTs, RYGB appeared to have the lowest reoperation rate (3%) followed by LSG (9%).

Surgery as Diabetes Treatment

Weight loss has long been regarded as the first approach to prevent T2D in high-risk subjects and to manage the metabolic derangements of established T2D. The attractiveness of weight control as a therapeutic intervention and the limited efficacy of producing medically induced weight loss has led to increased interest in the effect of surgically produced weight loss to correct the metabolic abnormalities in patients with established T2D and to prevent or remit T2D in high-risk individuals.[3,72-74]

Although the results of clinical trials so far have been promising, there still is a lack of consensus regarding the minimum BMI requirement and uncertainties regarding the comparative effectiveness of different bariatric procedures, especially in the long term. For example, in one literature review, bariatric surgery in T2D patients with a BMI of ≥35 resulted in a 56% EWL and remission of T2D in 57% to 95% of patients, depending on the type of surgery and the definition of diabetes resolution.[73] Four other reviews reported similar benefits of surgery in adults with T2D or other metabolic conditions and a BMI of 30.0 to 34.9.[72,74-76] In many trials, there also were significant benefits in other comorbidities.

Several trials also reported beneficial effects of bariatric surgery in patients with T2D. However, it is

difficult to compare the studies due to the difference in type of procedures used as well as different definitions of remission of diabetes. A randomized, non-blinded, single-center trial evaluated the efficacy of intensive medical therapy alone vs medical therapy plus RYGB or LSG in 150 patients with obesity and uncontrolled T2D.[77] The mean age of the patients was 49 years, and 66% were women. The average baseline A1C was 9.2%. The primary end point was the proportion of patients with an A1C level of 6% or less 12 months after treatment. Of the 150 patients, 93% completed 12 months of follow-up. The proportion of patients with the primary end point was 12% in the medical-therapy group vs 42% in the RYGB group ($P = 0.002$) and 37% in the LSG group ($P = 0.008$).

Glycemic control improved in all three groups, with a mean A1C level of 7.5% in the medical-therapy group, 6.4% in the RYGB group ($P < 0.001$), and 6.6% in the LSG group ($P = 0.003$). The index for homeostasis model assessment of insulin resistance (HOMA-IR) improved significantly after both bariatric procedures. Weight loss was greater in the RYGB and LSG groups (-29.4 kg and -25.1 kg, respectively; $P < 0.001$ for both comparisons) than in the medical-therapy group (-5.4 kg; $P < 0.001$ for both comparisons). In addition, use of drugs to lower glucose, lipid, and BP levels decreased significantly after both surgical procedures but increased in patients receiving medical therapy only. Four patients underwent reoperation. There were no deaths or life-threatening complications.

Another single-center, non-blinded, randomized, controlled trial in 60 adult patients compared the effects of bariatric surgery vs conventional medical therapy for T2D in patients with BMI ≥35 and a history of T2D for at least 5 years and a baseline A1C level of ≥7.0%.[78] Patients were randomly assigned to receive conventional medical therapy or undergo either RYGB or BPD. The primary end point was the rate of T2D remission at 2 years (defined as a fasting glucose level of <100 mg per deciliter [5.6 mmol/l per liter] and an A1C level of <6.5% in the absence of pharmacologic therapy). At 2 years, no patients in the medical-therapy group experienced T2D remission compared with 75% of those in

the RYGB group and 95% of those in the BPD group (P <0.001 for both comparisons).

Age, sex, baseline BMI, duration of T2D, and weight changes were not significant predictors of T2D remission at 2 years or of improvement in glycemia at 1 and 3 months. At 2 years, the average baseline A1C level (8.65%) had decreased in all groups, but patients in the two surgical groups had the greatest degree of improvement in average A1C levels, 7.69% in the medical-therapy group, 6.35% in the RYGB group, and 4.95% in the BPD group.

An analysis of clinical outcomes in 217 patients with T2D who underwent bariatric surgery (RYGB [n = 162]; AGB [n = 32]; LSG [n = 23]) between 2004 and 2007 and had at least 5-year follow-up assessed the effects of bariatric surgery on long-term T2D remission rates.[79] Overall, RYGB resulted in the greatest short-term and long-term reductions in total and EWL weight loss (**Table 10.7**). Complete remission was defined as A1C <6% and FBG <100 mg/dL off diabetic medications. At a median follow-up of 6 years after surgery a mean EWL of 55% was associated with mean reductions in A1C from 7.5% to 6.5% (P = 0.001) and FBG from 155.9 to 114.8 (P <0.001). Long-term complete and partial remission rates were 24% and 26%, respectively, whereas 34% of patients improved (>1% decrease in A1C without remission) from baseline and 16% remained unchanged. Shorter duration of T2D (P <0.001) and higher long-term EWL (P = 0.006) predicted long-term remission. Recurrence of T2D after initial remission occurred in 19% of patients and was associated with longer T2D duration (P = 0.03), less EWL (P = 0.02), and weight regain (P = 0.015).

On the basis of evidence available, the IDF issued a position statement stating that bariatric surgery can be considered an appropriate treatment for individuals with a BMI of ≥35 or greater and T2D who have not achieved recommended treatment targets with medical therapies, especially in the presence of other major comorbidities.[80]

TABLE 10.7 — Short-Term and Long-Term Weight Loss With RYGB, AGB, or LSG

	Whole Cohort	RYGB	LSG	*P*1 Value (RYGB vs LSG)	AGB	*P*2 Value (LSG vs AGB)
Total Weight Loss (%)						
Short-term	27.6	30.9	21.2	<0.001	16.5	0.068
Long-term	25.4	28.1	22.2	0.015	13.2	0.002
EWL (%)						
Short-term	60.3	66.8	49.7	0.029	37.0	0.112
Long-term	54.9	6.5	49.5	0.47	29.5	0.004

Short-term: 1 to 2 years after surgery.

Long-term: ≥5 years after surgery.

*P*1: gastric bypass vs sleeve gastrectomy.

*P*2: sleeve gastrectomy vs gastric banding.

Brethauer SA, et al. *Ann Surg*. 2013;258:628-636.

Bariatric Surgery and Obstructive Sleep Apnea

Obesity, older age, male sex, and heredity are well-established risk factors for OSA, with obesity being the single most important modifiable risk factor.[81] If untreated, OSA is associated with increased risk of diabetes, CV disease, driving accidents, and all-cause mortality.[82] However, few studies have compared the effect of surgical and conservative weight loss strategies on OSA in patients with obesity.

A one-year study in a total of 133 patients with class III obesity (70% females) were treated with either a 1-year ILI program (n = 59) or bariatric surgery (RYGB) (n = 74) and underwent repeated sleep recordings with a portable somnograph.[83] At baseline, participants had a mean age of 44.7 years, a mean BMI of 45.1, and an AHI of 17.1 events/hour. Eighty-four patients (63%) had a diagnosis of OSA. The average weight loss was 8% in the ILI-group and 30% in the RYGB-group (P <0.001). The mean AHI decreased in both treatment groups, although significantly more in the RYGB group (group difference 7.2; P = 0.017) and 66% of RYGB-treated patients experienced remission of OSA compared with 40% of the ILI-patients (P = 0.028).

At follow-up, after adjusting for age, gender, and baseline AHI, the RYGB-patients had significantly lower adjusted odds for OSA than the ILI-patients (OR 0.33; P = 0.0150). However, after further adjustment for BMI change, the treatment group difference was no longer statistically significant (OR 1.31; P = 0.709). The authors concluded this study demonstrates that RYGB was more effective than ILI at reducing the prevalence and severity of OSA. However, further analysis also suggests that weight loss, rather than the surgical procedure per se, explains the beneficial effects bariatric surgery in individuals with obesity.

Many studies have reported significant improvement of OSA in patients with obesity after bariatric surgery. It also has been noted that weight loss following surgery often is rapid in the first few months but often can take at least 1 year to reach the maximum effect. In order to assess the time course of the benefits of bariatric surgery,

one study compared the effects of bariatric surgery on its effects at two postoperative intervals.[84]

Patients who had been diagnosed with OSA preoperatively were invited to undergo PSG at least 6 months postoperatively and again at least 12 months postoperatively if OSA persisted. At a mean of 7.7 months after surgery, 110 patients completed a first postoperative PSG. At that time, the mean AHI had decreased significantly from 39.5/hr to 15.6/hr. In 26% of patients, the AHI was reduced to <5/hr. Fifty patients underwent a first PSG at a mean of 7.1 months and a second PSG at a mean 16.9 months after surgery. The mean AHI decreased significantly from a baseline of 49.1/hr to 2.7/hr and 17.4/h following bariatric surgery. Thus, while the beneficial effects of bariatric surgery occur early in the postoperative period, they continue at a slower rate. Therefore, the authors suggest that follow-up PSG after surgery should be considered to check for residual disease and possible retitration of continuous positive airway pressure.

Bariatric Surgery in Adolescents

As noted in *Chapter 1*, the most recent (2017-2018) national data on obesity prevalence indicate that about 19.3% US children and adolescents had obesity, presenting a major current and future health problem as many of these individuals age and become adults with obesity and longstanding comorbidities.[85] Weight-loss surgery is used to treat selected adolescents with obesity, although with very limited data regarding the safety of currently used, minimally invasive procedures.

An ongoing prospective, multisite observational study (Teen-LABS) assessed the preoperative clinical characteristics and perioperative safety outcomes in 242 adolescent patients with class III obesity aged 19 years or younger who underwent weight-loss surgery from February 28, 2007 through December 30, 2011. The mean age of participants was 17.1 years and the median BMI was 50.5. At baseline, 51% demonstrated four or more major comorbid conditions.[86] The procedures included RYGP, LSG, and AGB in 66%, 28%, and 6% of patients, respectively. There were no deaths during the initial hospitalization or within 30 days of operation.

Major complications (eg, reoperation) occurred in 19 patients (8%). Minor complications (eg, readmission for dehydration) were noted in 36 patients (15%). All reoperations and 85% of readmissions were related the surgery itself. At this time, this study reported a favorable short-term complication profile, supporting the early postoperative safety of weight-loss surgery in selected adolescents with obesity. At the 3-year follow-up, mean weight was reduced by 27% in the patients who underwent gastric bypass and by 26% in those who underwent a sleeve gastrectomy. At this time point, high percentages of participants achieved a remission in T2D (95%), abnormal kidney function (86%), prediabetes (76%), elevated blood pressure (74%), and dyslipidemia (66%).[87] In a 5-year follow-up report, mean weight was 26% lower compared to baseline and remission rates of T2D and hypertension remained high (86% and 68%, respectively).[88]

A recent analysis of Teen-LABS data has revealed few differences in the post-surgical outcomes of younger (13-15 years of age) and older (16-19 years of age) adolescents, suggesting that younger age should not by itself be a criterion for not considering bariatric surgery.[89] This cohort is still being followed in order to provide longer-term data.

Postsurgical Care

It is important for patients to have long-term follow-up with their bariatric surgeon; after the first year the expectation is that patients will see their surgeon annually.

Follow-up of the patients with obesity who have had bariatric surgery can be divided into three categories: the issues of surgical complications and weight loss during the first year, the nutritional and metabolic concerns that typically arise after the first postoperative year, and the problem of weight maintenance over the longer term.[70,90,91]

Female patients should be advised that pregnancy is contraindicated for at least 18 months after surgery because of the rapid weight loss and nutritional requirements. In addition, all patients should be encouraged to stop both smoking and the use of alcohol.

Short-term complications of bariatric surgery include vomiting, wound infections, stomal stenosis (ie, narrowing of the gastrojejunostomy), marginal ulceration, and constipation.

Common long-term complications of bariatric surgery include cholelithiasis, dumping syndrome, persistent vomiting, and nutritional deficiencies.

Because bariatric surgery affects a number of metabolic and neuro-hormonal processes, it is the most successful intervention for lowering the body weight "set point".[92] However, a variable proportion of patients still experience some degree of weight regain - depending on the study population and surgery type, observed weight regain has ranged from <10% to >90%. Overall, it appears that a substantial minority (25-35%) of patients experience significant (at least 15%) weight regain following surgery.[92] Preoperative predictors of weight regain include a higher BMI and psychiatric comorbidities. Postoperatively, the most important factors are diet/exercise noncompliance, hormonal or metabolic imbalance, and psychiatric comorbidities. Behavioral support (dietary counseling/intervention, cognitive behavioral therapy) has been shown to be efficacious in counteracting weight regain. Pharmacological support may also be useful - significant postoperative weight-loss effects have been reported for orlistat, topiramate, phentermine/topiramate, and liraglutide.[93]

Table 10.8 provides a list and suggested schedule of laboratory tests useful for long-term follow-up of patients who have had bariatric surgery.

Summary

Bariatric surgery has evolved since the 1950s with the emergence of the jejunoileal bypass and now includes the RYGB, LSG, BPD/DS, SADI-S, and AGB. These procedures have been shown to produce significant and durable weight loss as well as reduction or resolution of the serious comorbidities associated with obesity including mortality. Comparative studies on surgical procedures vs control groups have suffered from the inability to conduct randomized controlled clinical trials; however, long-term studies have been published which clearly

TABLE 10.8 — Routine Postsurgical Laboratory Follow-Up of Individuals After Bariatric Surgery

Follow-up Period	Laboratory Tests
1 month	CBC, SMA 21 , B12, folic acid, iron studies, 25-Vitamin D, iPTH, thiamine
3 months	CBC, SMA 21 , B12 (MMA and HCy optional), folic acid, iron studies, 25-Vitamin D, iPTH, thiamine (copper, zinc, and selenium if clinically indicated)
6 months	CBC, SMA 21 , B12, folic acid, iron studies, 25-Vitamin D, iPTH, thiamine, lipids, 24-hr urinary calcium (at 6 months, then annually) (copper, zinc, and selenium if clinically indicated)
12 months	CBC, SMA 21 , B12, folic acid, iron studies, 25-Vitamin D, iPTH, thiamine, lipids (copper, zinc, and selenium if clinically indicated)
24 months	CBC, SMA 21 , B12, folic acid, iron studies, 25-Vitamin D, iPTH, thiamine, bone density (copper, zinc, and selenium if clinically indicated)
Annually	CBC, SMA 21 , B12, folic acid, iron studies, 25-Vitamin D, iPTH, thiamine (copper, zinc, and selenium if clinically indicated)

Mechanick JI, et al. *Surg Obes Relat Dis*. 2013;9:159-191.

show benefit. The introduction of endoscopic techniques and orally-administered devices in recent decades has revolutionized the field; while it is too early to say how such modalities will develop in the future, they are likely to complement traditional surgical interventions and pharmacotherapy in the management of obesity and its comorbidities. The exact mechanism of action of the durable weight loss in especially the combination procedures are still being researched, but a combination of restriction and change in gut hormone milieu seems to be partly if not completely responsible for the reduction in appetite and increase in satiety, and hence, weight loss. Despite the known benefits, only a small number of eligible patients undergo bariatric surgery every year. Physicians should consider discussing bariatric surgery and endobariatric procedures with patients who qualify.

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Abbreviations/Acronyms

5-HT	serotonin
A1C	glycosylated hemoglobin
AACE	American Association of Clinical Endocrinologists
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotropic hormone
ADAPT	Arthritis, Diet, and Activity Promotion Trial
ADMA	asymmetric dimethylarginine
AE	adverse event
AED	anti-epileptic drug
AGB	adjustable gastric banding
AgRP	agouti-related peptide
AHA	American Heart Association
AHEAD	[Look] Action for Health in Diabetes [study]
AHI	apnea-hypopnea index
AIDS	acquired immunodeficiency syndrome
αMSH	alpha melanocyte-stimulating hormone
AMA	American Medical Association
AP	acute pancreatitis
ARB	angiotensin receptor blocker
ARC	arcuate nucleus
ASP	acylation-stimulating protein
ATP	Adult Treatment Panel
BDI	Beck Depression Inventory
BIA	bioelectrical impedance analysis
BID	twice daily
BMI	body mass index (measured in kg/m^2)
BMOD	behavior modification
BP	blood pressure
BPD	biliopancreatic diversion
BPD/DS	biliopancreatic diversion without duodenal switch
bpm	beats per minute
BUN	blood urea nitrogen
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults [study]
CART	cocaine- and amphetamine-regulated

	transcript
CCB	calcium channel blocker
CCK	cholecystokinin
CGS	Clinical Guidelines Subcommittee
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CMDS	cardiometabolic disease staging system
CNS	central nervous system
COR	Contrave Obesity Research [study]
COR-BMOD	Contrave Obesity Research with Behavior Modification
COR-II	Contrave Obesity Research-II [study]
CRF	chronic renal failure
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
CT	computed tomography
CV	cardiovascular
CVD	cardiovascular disease
DA	dopamine
DBP	diastolic blood pressure
DMPA	depot medroxyprogesterone acetate
DPP	Diabetes Prevention Program
DPPOS	Diabetes Prevention Program Outcomes Study
DSE	diabetes support and education
EGF	epidermal growth factor
EOSS	Edmonton Obesity Staging System
EPIC	European Prospective Investigation into Cancer and Nutrition [study]
ER	extended-release
EWL	excessive weight loss
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGP	food guide pyramid
GABA	gamma aminobutyric acid
GES	gastric electrical stimulation
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide 1
h	hour(s)
HDL-c	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HO	hypothalamic obesity
HOMA-IR	homeostasis model assessment of insulin resistance

HR	hazard ratio
HRT	hormone replacement therapy
IDF	International Diabetes Foundation
IFG	impaired fasting glucose
IGF-1	insulin-like growth factor-1
IGFBP	insulin-like growth factor-binding protein
IGT	impaired glucose tolerance
IL	interleukin
ILI	intensive lifestyle intervention
LABS	Longitudinal Assessment of Bariatric Surgery
lb	pound(s)
LCD	low calorie diet
LOCF	last observation carried forward
LSG	laparoscopic sleeve gastrectomy
MAOI	monoamine oxidase inhibitor
MC4R	melanocortin 4 receptor
MDD	major depressive disorder
MHO	metabolically healthy obesity
MI	myocardial infarction
mITT	modified intent-to-treat
mo	month(s)
MRI	magnetic resonance imaging
NAc	nucleus accumbens
NAFLD	nonalcoholic fatty liver disease
nal/bup SR	naltrexone SR/bupropion SR [Contrave]
NASH	nonalcoholic steatohepatitis
NE	norepinephrine
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NMS	neuroleptic malignant syndrome
NSAID	nonsteroidal anti-inflammatory drug
NYP	neuropeptide Y
OA	osteoarthritis
OR	odds ratio
OSA	obstructive sleep apnea
OTC	over-the-counter [drug]
OXM	oxyntomodulin
PAI-1	plasminogen activator inhibitor-1
PCOS	polycystic ovarian syndrome
PCP	primary care physician
PfC	prefrontal cortex
phen/top ER	phentermine/topiramate ER [Qsymia]
PMR	partial meal replacement
POMC	proopiomelanocortin [neuron]

PSG	polysomnography
PSMF	protein-sparing modified fast
PVN	paraventricular
PYY	peptide YY
QD	once daily
RCT	randomized controlled trial
REE	resting energy expenditure
RR	relative risk
RYGB	Rou-en-Y gastric bypass
SBP	systolic blood pressure
SGLT2	sodium glucose cotransporter 2
SHBG	sex hormone-binding globulin
SOS	Swedish Obese Subjects [study]
SSRI	selective serotonin reuptake inhibitor
T1D	type 1 diabetes
T2D	type 2 diabetes
TCA	tricyclic antidepressant
TEAE	treatment-emergent adverse events
TEE	total energy expenditure
TGF-β	transforming growth factor-beta
TNF-α	tumor necrosis factor-alpha
TOS	The Obesity Society
TSH	thyroid-stimulating hormone
TZD	thiazolidinediones
VLCD	very low calorie diet
VSG	vertical sleep gastrectomy
VTA	ventral tegmental area
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
y	year(s)

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